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

Amino Acids from Methyl Formamidomalonate

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Phenylalanine, tyrosine, norleucine, and aspartic acid have been prepared from methyl formamidomalonate. Its alkylated products have higher melting points and are more easily hydrolyzed than corresponding ethyl acetamidomalonates.

One of the classical methods of producing α-amino acids is to make an α-haloacid and then treat it with concentrated ammonium hydroxide. This method has sometimes proved unsatisfactory because of the lengthy procedure involved in the isolation of a product free from ammonium halide.

Goldeckemeyer[2] condensed an α-haloester (ethyl chloroacetate) with potassium phthalimide and then hydrolyzed with concentrated hydrochloric acid at 200° in a sealed tube.

The next advancement was made by Sorensen[3] who condensed potassium phthalimide with ethyl bromomalonate. The resulting ethyl phthalimidomalonate was then alkylated and upon hydrolysis as before gave an amino acid. The malonic acid was decarboxylated during the hydrolysis. This method eliminated the need of a variety of α-haloacids or their esters and substituted the use of readily available alkyl halides.

Thirty-seven years later Redemann and Dunn[4] used ethyl benzamidomalonate as a reagent for the preparation of amino acids; thus, the ease of hydrolysis and decarboxylation was improved. Ethyl acetamidomalonate was prepared by Cerchez[5] in 1931, but he did not use it to prepare amino acids. Its use for this purpose was suggested by M. Tishler.[6] The acetamido group is more easily hydrolyzed than the benzamido group, but the ultimate in an acyl group appeared when Galat[7] used ethyl formamidomalonate in 1947. The acyl group cannot be eliminated without exposing the nitrogen atom to competing alkylation.[4] The sole remaining simplification is the use of methyl formamidomalonate. This compound was reported by Conrad and Schulze[8] in 1909, but its use to prepare amino acids was not reported until Hellmann and Lingens[9] used it to prepare precursers for tryptophan and glutamic acid.

Methyl formamidomalonate appeared to us to have two advantages over ethyl formamidomalonate. The first of these is that methyl esters generally have higher melting points than the corresponding ethyl esters. This has also been pointed out by Hellmann and Lingens. Secondly, methyl esters hydrolyze more readily than ethyl esters. The working time from alkyl halide to amino acid is then less because of greater ease in getting a crystalline intermediate and in carrying out its cleavage. This aids in the preparation of unsaturated amino acids where γ-δ unsaturated alkyl malonates on acid cleavage give lactones.[10] Although methyl esters are less hindered than ethyl esters, alkylation with secondary C_4 halides was not successful with methyl formamidomalonate.

(1) Taken mainly from the master's thesis of S. Minkowitz, University of Colorado, 1950.
(2) C. Goldeckemeyer, *Ber.*, 21, 2684 (1888).
(3) S. P. L. Sorensen, *Z. Physiol. Chem.*, 44, 448 (1905).
(4) C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, 130, 341 (1939).
(5) V. Cerchez, *Bull. soc. chim. France*, (4), 49, 45 (1931).
(6) H. R. Snyder, E. E. Howe, G. W. Cannon and M. A. Nyman, *J. Am. Chem. Soc.*, 65, 2213 (1943), ref. 7.
(7) A. Galat, *J. Am. Chem. Soc.*, 69, 965 (1947).
(8) N. Conrad and A. Schulze, *Ber.*, 42, 729 (1909).
(9) H. Hellmann and F. Lingens, *Z. physiol. Chem.*, 297, 283 (1954).
(10) H. L. Goering, S. J. Cristol and K. Dittmer, *J. Am. Chem. Soc.*, 70, 3311 (1948).

To see how the melting points varied with structure, the following table was completed by synthesizing the unknown compounds:

Compound	M.P.	M.P. of *n*-Butyl	Derivative
Ethyl acetamidomalonate	97°[11]	42°[10]	oil[12]
Methyl acetamidomalonate	128.5°[9]	100°	
Ethyl formamidomalonate	48°[3]	83°[13]	
Methyl formamidomalonate	85°[3]	109.5°	

Since the condensation of ethyl acetamidomalonate with ethyl bromoacetate gave an oil,[14] a similar reaction was tried with methyl formamidomalonate. The product was readily crystallized and melted at 94°. The yield was 80%. Galat condensed ethyl formamidomalonate with ethyl chloroacetate and obtained a brown syrup containing some crystals. This was hydrolyzed to aspartic acid with a yield of 55%.[7]

The rate of hydrolysis in base is twice as great for methyl esters as for the corresponding ethyl esters.[15] In acid hydrolysis the difference is not so large, but the methyl esters still hydrolyze at a slightly faster rate.

As was expected, the hydrolysis of our methyl esters occurred quite rapidly. The esters were placed in constant boiling hydrobromic acid and were heated under a reflux condenser. From the top of the condenser a drying tube containing sodium hydroxide was led to a solution of silver nitrate. The end of a hydrolysis or cleavage of an ether group was found by noting when fresh silver nitrate no longer gave a silver bromide precipitate. Corresponding ethyl esters required three to four hours before the test was negative. Aspartic acid was synthesized from ethyl carbethoxymethylacetamidomalonate by refluxing with 7 hr. constant-boiling hydrochloric acid.[14] The ethyl carboethoxyformamidomalonate was heated for 3 hr.[7] Our methyl carbethoxymethylformamidomalonate hydrolyzed completely in 60 minutes. Albertson and Archer[16] synthesized phenylalanine by condensing ethyl acetamidomalonate with benzyl chloride and then heating the intermediate under reflux with constant-boiling hydrobromic acid for 7.5 hr. The melting point of this ethyl acetamidobenzylmalonate was 104° and the overall yield was 60%. We found that methyl benzylformamidomalonate melted at 153°, its hydrolysis took 60 minutes, and the overall yield was 73%.

To check further the speed of hydrolysis, tyrosine was synthesized by chloromethylating anisole, condensing it with methyl formamidomalonate and then heating with hydrobromic acid. In this preparation an ether cleavage was involved as well as hydrolysis and decarboxylation, but again the silver nitrate test was negative at the end of 60 minutes. Formamido compounds dissolve in hot hydrobromic acid in a few minutes as the formyl group comes off readily to form an amine salt. This rapid solution facilitates hydrolysis of the ester groups above that which would be found for acetamido or benzamidomalonates. As the average atmospheric pressure at the University of Colorado is about 630 mm. of mercury, solutions come to a boil at lower temperatures. As a result the length of time needed for hydrolysis may be less elsewhere.

EXPERIMENTAL

Methyl malonate. Methyl malonate is available commercially but is considerably more expensive than ethyl malonate. Therefore, some was prepared by ester interchange between ethyl malonate and methanol,[17] and by use of cyanoacetic acid and methanol following Ross and Bibbins[18] procedure for ethyl malonate.

Methyl formamidomalonate. Methyl formamidomalonate was prepared by a modification of Galat's preparation of ethyl acetamidomalonate.[7] The product was crystallized from aqueous methanol and obtained in a 41% yield, m.p. 83–84°. The subsequent preparation reported by Hellmann and Lingens[9] appears much superior to ours and they report a 96% overall yield and a melting point of 85.5°.

Methyl acetamidomalonate. An almost quantitative yield is reported by Hellmann and Lingens for methyl acetamidomalonate melting at 128.5°. Our material melted at 128°.

Ethyl formamidomalonate. This was prepared by Galat's method.[7] Subsequently Shaw and Nolan[11] have published an improved method.

Alkylations of methyl formamidomalonate. The alkylations followed a procedure of Albertson.[11] Ten g. of methyl formamidomalonate, 50 ml. of absolute methanol, 5.4 g. of sodium methoxide, and 9 g. of *n*-butyl bromide were heated under a reflux condenser for 12 hr. Then 50 ml. of water was added. Chloroform extraction gave 5 g. of crude material. Treatment with decolorizing charcoal and crystallization from methanol gave 1.75 g. of starting material and a 37% yield of methyl *n*-butylformamidomalonate, m.p. 108–109°. Aqueous methanol was used to prepare an analytical sample, m.p. 109.5°.

Anal. Calcd. for $C_{10}H_{17}NO_5$: N, 6.06. Found: 5.88; 5.98.

In a similar fashion 10.8 g. of ethyl bromoacetate gave after crystallization from aqueous methanol 7 g. of methyl carbethoxymethylformamidomalonate, m.p. 87–90° (47%). Further recrystallizations raised the melting point to 93–94°.

Anal. Calcd. for $C_{10}H_{15}NO_7$: N, 5.36. Found: N, 5.53; 5.47.

Anisole was chloromethylated as directed by Quelet and Allard.[19] Ten g. of *p*-methoxybenzyl chloride and 8.5 g. of methyl formamidomalonate gave 6.6 g. of crude methyl *p*-

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(12) N. F. Albertson, *J. Am. Chem. Soc.*, **68**, 450 (1946).

(13) J. S. Meek and J. W. Rowe, *J. Am. Chem. Soc.*, **77**, 6675 (1955).

(14) H. Goering, Ph.D. thesis, University of Colorado, 1948.

(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, 1940, p. 211–213.

(16) N. F. Albertson and S. Archer, *J. Am. Chem. Soc.*, **67**, 308 (1945).

(17) M. Reimer and H. R. Doanes, *J. Am. Chem. Soc.*, **43**, 945 (1921).

(18) A. A. Ross and F. E. Bibbins, Ind. and Eng. Chem., 29, 1341 (1937).

(19) R. Quelet and J. Allard, *Bull. soc. chim. France*, (5), **3**, 1794 (1936).

methoxybenzylformamidomalonate, m.p. 102–106°. In addition 1.9 g. of methyl formamidomalonate was recovered. Crystallization from methanol and benzene raised the melting point to 120–120.5°.

Anal. Calcd. for $C_{14}H_{17}NO_6$: N, 4.84. Found: N, 4.72.

Ten g. of methyl formamidomalonate and 5.5 g. of benzyl chloride gave 13 g. (75%) of crude product, m.p. 148–150°. Crystallization from aqueous methanol raised the melting point of the methyl benzylformamidomalonate to 153–154°.

Anal. Calcd. for $C_{13}H_{15}NO_5$: N, 5.29. Found: N, 5.16.

Alkylation of ethyl formamidomalonate with n-butyl bromide. Ten g. of ethyl formamidomalonate, 3.4 g. of sodium ethoxide and 9 g. of *n*-butyl bromide were heated for 8 hr. in absolute ethanol. One crystallization from aqueous ethanol gave 7.9 g. (62%) of ethyl *n*-butylformamidomalonate, m.p. 79–81°. Further recrystallization raised the melting point to 81.0–81.8°. This compound has also been prepared in this laboratory by hydrogenation of ethyl allylcarbinylformamidomalonate.[13] Previously conflicting melting points of 101°[20] and 77–80°[21] have been reported.

Anal. Calcd. for $C_{12}H_{21}NO_5$: N, 5.21. Found: N, 5.51, 5.44.

Alkylation of methyl acetamidomalonate with n-butyl bromide. One g. of methyl acetamidomalonate and 1 g. of *n*-butyl bromide were placed in 5 ml. of absolute methanol to which 0.5 g. of sodium had been added. The mixture was heated under a reflux condenser for 4 hr. and was allowed to stand overnight. Five ml. of water was added, and then a chloroform extraction gave 280 mg. of long cylindrical needles, m.p. 96–98°. The analytical sample of methyl *n*-butylacetamidomalonate was prepared by dissolving the product in benzene and diluting with petroleum ether. The melting point was 99–100° and the analysis was performed by Galbraith Laboratories.

Anal. Calcd. for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81. Found: C, 53.67; H, 7.65.

Hydrolysis with hydrobromic acid. The malonates were refluxed with constant boiling hydrobromic acid and the vapors were passed through a tower of sodium hydroxide pellets and then into a 4% alcoholic solution of silver nitrate. The rate of hydrolysis was followed by observing the appearance of silver bromide. When the hydrolysis was completed, there was no further precipitate of silver bromide.

It took from 3 to 4 hr. to hydrolyze ethyl *n*-butylacetamidomalonate, ethyl *n*-octylacetamidomalonate, and ethyl *n*-butylformamidomalonate. Complete hydrolysis for the methyl formamidomalonate intermediates took place in an hour for all the compounds studied.

Two hundred mg. of *p*-methoxybenzylformamidomalonate was refluxed with 50 ml. of constant boiling hydrobromic acid. Complete hydrolysis took place in 1 hr. but was continued for an additional 0.5 hr. The hydrobromic acid was removed *in vacuo* and the residue purified on an ion exchange column containing the Duolite resin A2. One hundred ten mg. of *dl*-tyrosine was obtained, yield 98%, m.p. 295–298° dec.; reported m.p. 290–295° dec.[22]

Identification of the tyrosine was obtained by making the *N*-benzoyl-*dl*-tyrosine, m.p. 196–198°; reported 195–197°.[22]

One g. of methyl carboethoxmethylformamidomalonate was refluxed with 50 ml. of constant boiling hydrobromic acid. Hydrolysis was complete in an hour but was continued for another 0.5 hr., yield 80%, m.p. 300–303° dec.; reported, above 300°.[7] Identification of the *dl*-aspartic acid was obtained by a spot test developed by Inukai, Tsurumi, and Sakai.[23]

Four hundred seventy mg. of methyl *n*-butylformamidomalonate was refluxed with 50 ml. of constant boiling hydrobromic acid, hydrolysis was complete in 1 hr. The hydrobromic acid was removed *in vacuo* and the residue purified on an ion exchange column containing the Duolite resin A2, yield 85%, m.p. 274–276°.

Identification of the norleucine was obtained by preparing the *N*-formylnorleucine, m.p. 109–111°, reported 113–115°.[24]

The hydrolysis of methyl benzylformamidomalonate was complete in an hour. The yield was practically quantitative and the product melted at 269–272° with decomposition, reported 271–273°;[25] 257° dec.[16]

Identification of the phenylalanine was obtained by preparing the *N*-benzoyl-*dl*-phenylalanine, m.p. 187–188°; reported 187–188°.[26]

BOULDER, COLO.

(20) J. Capkova-Jirku, J. V. Kostir and M. Vondracek, *Chem. Listy*, **44**, 114 (1950); *Chem. Abstr.*, **45**, 7962 (1951).

(21) British Patent **621,706**. (*Chem. Abstr.*, **44**, 2017 (1950).

(22) E. Fischer, *Ber.*, **32**, 3638 (1899).

(23) F. Inukai, M. Tsurumi and S. Sakai, 49, 111, *Bull., Inst. Phys. Chem. Research (Tokyo)*, 22, 919 (1943). [*Chem. Abstr.*, **41**, 5916 (1947)].

(24) D. Marko, *Ann.*, **362**, 333 (1908).

(25) S. P. L. Sorensen, *Chem. Zentral.*, **74**, 11, 33 (1903).

(26) E. Fischer and A. Mouneyrat, *Ber.*, **33**, 2383 (1900).

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Synthesis of (+)(S)-3-Methyl-1-pentene

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(+)(S)-3-Methyl-1-pentene (*i.e.*, L-3-methyl-1-pentene) having an optical purity of at least 86% has been prepared in five steps starting from (−)(S)-2-methyl-1-butanol with an over-all yield of 18% and a maximum per cent of racemization of 12.6%. The optical purity of the (+)(S)-3-methyl-1-pentene was calculated by regenerating the (+)(S)-3-methyl-1-pentanol by addition of the olefin to diisobutylaluminum monohydride and by oxidation followed by hydrolysis of the trialkylaluminum thus obtained.

The preparation and the determination of optical purity of aliphatic olefins do not seem to have been investigated extensively. No data have been found in the literature (up to 1957) on the simplest optically active α-olefin, 3-methyl-1-pentene. For the mixture of 4-methyl-hexenes prepared by dehydration of the optically active 4-methyl-2-hexanol over alumina, α_D^{26} (l = 1) +13.7° is reported.[1] For 5-methyl-1-heptene, two very different values (+6.84°[2] and +10.2°[3]) have been reported for the

(1) G. S. Gordon III and R. L. Burwell, Jr., *J. Am. Chem. Soc.*, **71**, 2355 (1949).

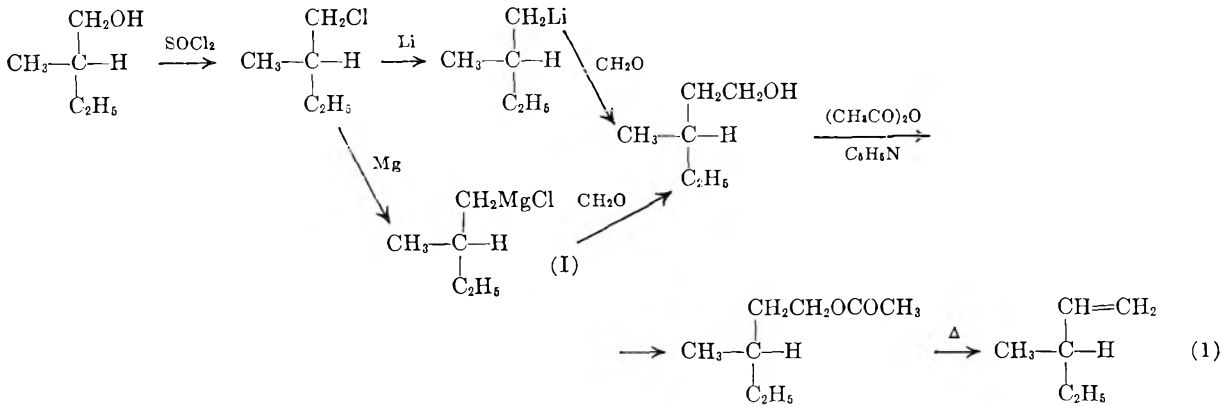
(2) R. L. Burwell, Jr., and G. S. Gordon III, *J. Am. Chem. Soc.*, **70**, 3129 (1948).

specific rotation. Because we needed an optically active α-olefin having a known optical purity for a systematic investigation of some aspects of the chemical reactivity of α-olefins, we have investigated the preparation of the (+)(S)-3-methyl-1-pentene[4] (*i.e.*, L-3-methyl-1-pentene).

The racemic 3-methyl-1-pentene has been prepared by Boord and Schmitt[5] in five steps starting from 2-bromobutane and acetaldehyde. We have preferred to start from (−)(S)-2-methyl-1-butanol which is more readily available[6] than the optically active *sec*-butyl alcohol whose preparation requires the tedious resolution of the racemic 2-butanol. Starting from (−)(S)-2-methyl-1-butanol of known optical purity the 3-methyl-1-pentene was obtained through the following steps (Scheme 1):

In Table II some data on the physical properties of 3-methyl-1-pentanol have been collected.

Conflicting data are reported in the literature for the refractive index and density of the 3-methyl-1-pentanol. Because our data on the density were higher than the data reported by Hovorka *et al.*,[8] we purified the alcohol through its acetate. The purified alcohol had n_D^{25} in close agreement with the data of Hovorka; however, the density, although lower than that of the unpurified alcohol, was still definitely higher than that reported by Hovorka. The density found for a sample of racemic 3-methyl-1-pentanol prepared starting with racemic *sec*-butyl alcohol according to the method proposed by Huston and Agett,[9] was in agreement with that found by us for the optically active alcohol (Table II).



(1)

Preparation and purification of (+)(S)-3-methyl-1-pentanol. From the (−)(S)-2-methyl-1-butanol, the (+)(S)-1-chloro-2-methyl-butane was prepared by the method of McKenzie and Clough.[7]

To obtain the 3-methyl-1-pentanol, two different methods were tested: the first through the (+)-(S)-2-methyl-butyllithium and the other through the (+)(S)-2-methylbutylmagnesium chloride. As is shown in Table I, relatively low yields were obtained in the preparation of the organolithium compound but good yields were achieved in its reaction with formaldehyde. On the other hand, carrying out the synthesis through the Grignard compound resulted in high yields in the preparation of the organomagnesium compound but in lower yields in the reaction between it and formaldehyde.

The per cent of racemization observed in the preparation of 3-methyl-1-pentanol (Table III) was calculated by comparing the optical purity of the starting (−)(S)-2-methyl-1-butanol with the optical purity of the (+)(S)-3-methyl-1-pentanol, assuming for the specific optical activity of the optically pure alcohols the values given by Marckwald and McKenzie[10] and Hardin.[11,12] Racemization occurs to a small extent (1–3%) in the preparation of 1-chloro-2-methyl-butane as well as in the prepara-

(3) S. F. Velick and J. English, Jr., *J. Biol. Chem.*, **160**, 476 (1948).

(4) We have adopted the nomenclature proposed by Cahn, Ingold, and Prelog [*Experientia*, **12**, 81 (1956)], and although it is not required by the nomenclature adopted, we have added (+) and (−) before the prefixes (S) and (R) to indicate the sign of the rotation according with Beilstein's *Handbuch der Organischen Chemie*, Band I, Drittes Erganzunswerk, Springer-Verlag, Berlin (1958).

(5) C. G. Schmitt and C. E. Boord, *J. Am. Chem. Soc.*, **54**, 751 (1932).

(6) F. C. Whitmore and H. J. Olewine, *J. Am. Chem. Soc.*, **60**, 2569 (1938).

(7) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **103**, 698 (1913).

(8) F. Hovorka, H. P. Lankelma, and I. Schneider, *J. Am. Chem. Soc.*, **62**, 1096 (1940).

(9) R. C. Huston and A. H. Agett, *J. Org. Chem.*, **6**, 123 (1941).

(10) W. Marckwald and A. McKenzie, *Ber.*, **34**, 495 (1901).

(11) D. Hardin, *J. Chim. Phys.*, **6**, 587 (1908).

(12) For the specific rotation of the optically (+)(S)-3-methyl-1-pentanol we have chosen the value of +8.77° found by Hardin for the product obtained from Roman Camomile oil, which is in fair agreement with the maximum value calculated by Levene and Marker [*J. Biol. Chem.*, **91**, 77 (1931)]. We have not considered the maximum value calculated by Mosher and La Combe from the fraction having the highest optical activity obtained by rectification of a mixture of 26% of 4-methyl-1-pentanol with 74% of (+)(S)-3-methyl-1-pentanol; in fact on the basis of our experimental results, we think that a separation between 3-methyl-1-pentanol and 4-methyl-1-pentanol takes place during the rectification and must be considered in the calculations made by Mosher and La Combe, *J. Am. Chem. Soc.*, **72**, 4991 (1950).

TABLE I

YIELDS IN THE PREPARATION OF (+)(S)-3-METHYL-1-PENTENE FROM (−)(S)-2-METHYL-1-BUTANOL

	Yield, %
$CH_3CH_2CH(CH_3)CH_2OH$[a] $\longrightarrow$ $CH_3CH_2CH(CH_3)CH_2Cl$	80
$CH_3CH_2CH(CH_3)CH_2Cl \xrightarrow{Mg} CH_3CH_2CH(CH_3)CH_2MgCl$	90[b]
$CH_3CH_2CH(CH_3)CH_2MgCl \xrightarrow{CH_2O} CH_3CH_2CH(CH_3)CH_2CH_2OH$	40[c]
$CH_3CH_2CH(CH_3)CH_2Cl \xrightarrow{Li} CH_3CH_2CH(CH_3)CH_2Li$	56[d]
$CH_3CH_2CH(CH_3)CH_2Li \xrightarrow{CH_2O} CH_3CH_2CH(CH_3)CH_2CH_2OH$	60[e]
$CH_3CH_2CH(CH_3)CH_2CH_2OH \longrightarrow CH_3CH_2CH(CH_3)CH_2CH_2OCOCH_3$	90–95
$CH_3CH_2CH(CH_3)CH_2CH_2OCOCH_3 \xrightarrow{\Delta} CH_3CH_2CH(CH_3)CH{=}CH_2$	70

[a] The (−)(S)-2-methyl-1-butanol had an optical purity of 97.4%, calculated on the basis of the pure (−)(S)-2-methyl-1-butanol $[\alpha]_D^{20}$ −5.9°.[10] [b] Calculated following the procedure of Gilman, Wilkinson, Fishel and Meyers, (*J. Am. Chem. Soc.*, **45**, 150 (1923). [c] Calculated on the rectified 3-methyl-1-pentanol. [d] Calculated following the procedure of Ziegler (*Ann.*, **473**, 21 (1923)). [e] Calculated on the distilled 3-methyl-1-pentanol.

TABLE II

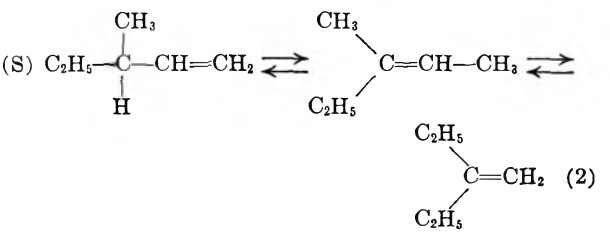
PHYSICAL PROPERTIES OF 3-METHYL-1-PENTANOL

	Literature	Rectified (+)(S)-3-Methyl-1-pentanol	Purified[a] (+)(S)-3-Methyl-1-pentanol	Racemic 3-Methyl-1-pentanol	Purified[a] Racemic 3-Methyl-1-pentanol
Boiling point, °C.	152.44[8] 151–152[9] 151.2–152[12]	99–100 (100 mm.) 152–152.5	65 (18 mm.)	64 (18 mm.) 152.5	64 (19 mm.)
n_D^{25}	1.4178[b] 1.4169[8]	1.4172	1.4170	1.4180	1.4172
n_D^{20}	1.4182 1.4195[12]	1.4192	1.4191	1.4196	1.4192
d_4^{25}	0.8156[b] 0.8187[8]	0.8227	0.8218	0.8230	0.8217
$d_4^{19.5}$		0.8263	0.8260		

[a] Purification through the acetate. [b] P. A. Levene and A. Rothen, *J. Biol. Chem.*, **116**, 217 (1936).

tion of the organometallic compound. Since racemization up to 8–10% is reported by Whitmore[13] in the preparation of the Grignard compound (I), we must conclude that practically no racemization occurs in the reaction between the Grignard compound and formaldehyde.

Preparation of (+)(S)-3-methyl-1-pentene. Many methods have been proposed for preparing the α-olefins from the corresponding alcohols without the formation of other isomeric olefins. In our case a highly specific dehydration method was needed as any double bond shift in the (+)(S)-3-methyl-1-pentene would cause a racemization (Scheme 2):



(2)

Since we needed relatively large quantities of the optically active olefins for our investigations, we chose for the olefin preparation the pyrolysis of the

(13) F. C. Whitmore and J. H. Olewine, *J. Am. Chem. Soc.*, 60, 2570 (1938).

TABLE III

RACEMIZATION IN THE PREPARATION OF (+)(S)-3-METHYL-1-PENTANOL FROM (−)(S)-2-METHYL-1-BUTANOL, $[\alpha]_D^{16}$ −5.75°, OPTICAL PURITY,[a] 97.4%

	$[\alpha]_D^t$	t, °C.	Optical Purity,[b] %	Racemization, %
(+)(S)-3-methyl-1-pentanol[c]	+7.89°	19	90[d]	7.6
(+)(S)-3-methyl-1-pentanol[e]	+8.24°	19.5	94	3.5
(+)(S)-3-methyl-1-pentanol[e]	+8.16°	19	93	4.5

[a] Calculated taking for the pure (−)(S)-2-methyl-1-butanol $[\alpha]_D^{20}$ −5.9°.[10] [b] Calculated taking for the pure (+)(S)-3-methyl-1-pentanol $[\alpha]_D^{20}$ +8.77°.[11] [c] Obtained through the lithium compound. [d] Calculated on unredistilled (+)(S)-3-methyl-1-pentanol. [e] Obtained through the Grignard reagent.

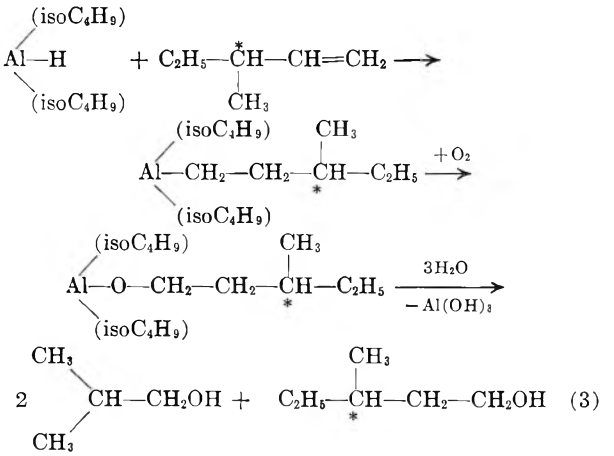
(+)(S)-3-methyl-1-pentyl acetate[14] which involves only two steps starting from (+)(S)-3-methyl-1-pentanol rather than the pyrolysis of the quaternary ammonium bases[15] or of the amine oxides[16] which involves many more reaction steps starting from the same alcohol.

(+)(S)-3-Methyl-1-pentyl acetate was prepared by cautiously heating the alcohol with an excess of acetic anhydride in the presence of pyridine. The acetate was pyrolized. The best yield of (+)(S)-3-methyl-1-pentene was obtained by pyrolizing the acetate of a slow nitrogen stream at 500° (Table I).

Better conversions could have been achieved in the acetate preparation, but we preferred to carry out the reaction under very mild conditions in order to avoid possible racemization.

The yield obtained in the pyrolysis is in the range reported in the literature for the other olefins; the formation of lower boiling highly refractive compounds (probably pentadienes) could not be completely avoided and two fractionations were necessary in order to obtain a product having physical constants in agreement with the literature data. Since we started from 2-methyl-1-butanol containing not more than 3% of 3-methyl-1-butanol, the 3-methyl-1-pentene obtained was actually a mixture of the 3-methyl-1-pentene with small quantities of 4-methyl-1-pentene (probably not more than 3% if no enrichment of the products deriving from 3-methyl-1-butanol took place during the preparation steps). The two isomeric olefins have very close physical properties and therefore the physical properties of the mixture agree very well with the data reported for 3-methyl-1-pentene.[17,18]

The eventual racemization occurring in the preparation of the (+)(S)-3-methyl-1-pentyl acetate was calculated by saponifying the acetate and determining the optical activity of recovered 3-methyl-1-pentanol. The racemization in the pyrolysis of the (+)(S)-3-methyl-1-pentyl acetate was estimated by regenerating the (+)(S)-3-methyl-1-pentanol from (+)(S)-3-methyl-1-pentene. The alcohol was obtained by reacting the olefin with diisobutylaluminum monohydride,[19] oxidizing the trialkylaluminum thus obtained with oxygen, and hydrolyzing the resultant aluminum alcoholate with water (Scheme 3).



The racemization data reported in Table IV are the upper limits for the racemization occurring in the pyrolysis of the (+)(S)-3-methyl-1-pentyl acetate since they include the eventual racemization occurring in the regeneration of the 3-methyl-1-pentanol.

Conclusions. The probable isomeric composition of the 3-methyl-1-pentene obtained is: 91.7% of (+)(S)-3-methyl-1-pentene, 5.7% of (−)(R)-3-methyl-1-pentene, and 2.6% of 4-methyl-1-pentene deriving from 3-methyl-1-butanol present in the starting product. The specific rotation found for the mixture, $[\alpha]_D^{17}$ +32.86°, is remarkably

(14) J. P. Wibaut and A. J. van Pelt, *Rec. trav. chim.*, **57**, 1055 (1938); A. J. van Pelt and J. P. Wibaut, *Rec. trav. chim.*, **60**, 55 (1941); J. P. Wibaut, A. J. van Pelt, Jr., A. Dias Santilhano, and W. Beuskens, *Rec. trav. chim.*, **61**, 265 (1942); J. P. W. Houtman, J. van Steenis, and P. M. Heertjes, *Rec. trav. chim.*, **65**, 781 (1946); W. J. Bailey and C. King, *J. Am. Chem. Soc.*, **77**, 75 (1955); W. J. Bailey, J. J. Hewitt, and C. King, *J. Am. Chem. Soc.*, **77**, 357 (1955).

(15) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 997 (1927); C. K. Ingold and C. C. Norrey Vass, *J. Chem. Soc.*, 3125 (1928); M. J. Schlatter, *J. Am. Chem. Soc.*, **63**, 1733 (1941); P. G. Stevens and H. J. Richmond, *J. Am. Chem. Soc.*, **63**, 3132 (1941).

(16) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3929 (1949); A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Am. Chem. Soc.*, **75**, 3212 (1953); paper presented before 124th Meeting American Chemical Society, Chicago, Ill., September 1953, p. 11F of Abstracts; D. J. Cram, *J. Am. Chem. Soc.*, **76**, 5740 (1954).

(17) C. E. Boord, A. L. Henne, G. W. Greenlee, W. L. Perilstein, and J. M. Derfer, *Ind. Eng. Chem.*, **41**, 609 (1949).

(18) F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. H. Poulson, and G. C. Pimenkel, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, 1953, p. 55.

(19) K. Ziegler and H. G. Gellert, *Angew. Chem.*, **64**, 323 (1952); K. Ziegler, *Angew. Chem.*, **68**, 721 (1956).

TABLE IV

RACEMIZATION IN THE PREPARATION OF 3-METHYL-1-PENTENE FROM 3-METHYL-1-PENTANOL

	Starting Materials		Recovered (+)(S)-3-methyl-1-pentanol		Racemization, %
	$[\alpha]^t_D$	t, °C,	$[\alpha]^t_D$	t, °C.	
(+)(S)-3-methyl-1-pentanol → (+)(S)-3-methyl-1-pentyl acetate	+8.24°	18	+8.17°	20	0.85
(+)(S)-3-methyl-1-pentyl acetate → (+)(S)-3-methyl-1-pentene	+8.30°	18	+7.54°	19	7.70

higher than the values found in the literature for other aliphatic olefins. The relatively high specific rotation can be attributed both to the particular structure of the 3-methyl-1-pentene and to the low optical purity of some of the optically active α-olefins reported in the literature.

EXPERIMENTAL

(−)(S)-2-Methyl-1-butanol was obtained by rectification of fusel oil[6]: samples having b.p. 128–129°, n_D^{20} 1.4108, d_4^{16} 0.8216 (lit.[6] n_D^{20} 1.4109, d_4^{20} 0.8189), $[\alpha]_D^{16}$ −5.75° (97.4% optical purity) were used.

(+)(S)-1-Chloro-2-methylbutane was prepared[7] in 80% yield by treatment of the (−)(S)-2-methyl-1-butanol with thionyl chloride. The halogenated hydrocarbon obtained had b.p. 99–100°, n_D^{20} 1.4125–1.4127, d_4^{20} 0.8857 (lit.[13] n_D^{20} 1.4125, d_4^{20} 0.8852), $[\alpha]_D^{20}$ 1.60–1.64° (94–96% optical purity).

(+)(S)-3-Methyl-1-pentanol. A) *Through the organolithium compound.* (+)(S)-1-Chloro-2-methylbutane (72.4 g., 0.68 mole, $[\alpha]_D^{20}$ 1.63°, n_D^{20} 1.4127) was added to 14.1 g. (2.04 mole) of metallic lithium[20] suspended in 200 ml. of low-boiling petroleum ether (b.p. 40°, olefin-free) at 35–40° under a dry nitrogen atmosphere. The suspension was vigorously stirred for 2 hr. Acidimetric titration indicated a 60% yield of the lithium derivative. Formaldehyde gas (obtained from dry paraformaldehyde[21]) was swept into the organolithium compound solution which had been separated from the unreacted lithium. The complex thus obtained was hydrolyzed by water and extracted with ether. The ether extracts were separated, dried, and distilled from a Claisen flask at reduced pressure. The weight of (+)(S)-3-methyl-1-pentanol (b.p. 60–67° (23 mm.), n_D^{25} 1.4165) was 23.3 g. (33.6% yield based on the (+)(S)-1-chloro-2-methylbutane). In a repeated experiment the same yield was obtained; 23 g. of product having b.p. 60–67° (23 mm.) afforded on redistillation, 16 g. of (+)(S)-3-methyl-1-pentanol, b.p. 65–68° (20 mm.) n_D^{25} 1.4180, $[\alpha]_D^{19}$ +7.89° (90% optical purity).

(B) *Through the Grignard reagent.* An ethereal Grignard solution was prepared from 106.5 g. (1.0 mole) (+)(S)-1-chloro-2-methylbutane, $[\alpha]_D^{20}$ +1.64°, n_D^{20} 1.4126, and 24.3 g. (1.0 mole) magnesium in 1000 ml. of anhydrous ether under a dry nitrogen atmosphere. Titration indicated a 90% yield of the 2-methylbutylmagnesium chloride. The formaldehyde, from depolymerization of dry paraformaldehyde, was carried into the Grignard reagent by a slow current of dry nitrogen.[22] The complex was hydrolyzed by water and extracted with ether; the ether extracts were separated, dried, distilled, and finally rectified at reduced pressure. The weight of redistilled (+)(S)-3-methyl-1-pentanol, b.p. 99–100° (100 mm.), n_D^{25} 1.4172, $[\alpha]_D^{19.5}$ +8.24° (94% optical purity) was 36.7 g. (36% yield based on the (+)(S)-1-chloro-2-methylbutane).

% OH (determined by phthalation method[23]): 16.41. % OH (calculated for $C_6H_{14}O$) 16.66.

(+)(S)-3-Methyl-1-pentyl acetate. (+)(S)-3-Methyl-1-pentanol (46 g., 0.45 mole, $[\alpha]_D^{19.5}$ +8.24°, n_D^{25} 1.4172) was added to 35.6 g. (0.45 mole) of freshly distilled pyridine and 138 g. (1.35 moles) of redistilled acetic anhydride (b.p. 140°, n_D^{20} 1.3903). The mixture was refluxed very gently for 4 hr. and then cooled overnight; it was then worked up by neutralizing with sodium bicarbonate, washing with water until the ester layer was neutral to litmus, and finally drying with anhydrous sodium sulfate. Rectification at 102 mm. pressure afforded (+)(S)-3-methyl-1-pentyl acetate in 65–70% conversion (90–95% yield), b.p. 103–103.5° (102 mm.), n_D^{25} 1.4081 (lit.[24] n_D^{25} 1.4079), d_4^{19} 0.8790, $[\alpha]_D^{19}$ +8.30° (93.15% optical purity).

% Ester (determined by saponification[25]): 99.

(+)(S)-3-Methyl-1-pentene (by pyrolysis of (+)(S)-3-methyl-1-pentyl acetate). The apparatus used for the pyrolysis was similar to that described by Bailey *et al.*[14] (+)(S)-3-Methyl-1-pentyl acetate (100 g., 0.694 mole, $[\alpha]_D^{19}$ +8.30° n_D^{25} 1.4081) was pyrolyzed in a quartz tube at 500–510° with dropping rate of about 1.5–1.6 ml. per min. A slow stream (5.6 ml. per min.) of dried nitrogen was introduced through the top of the tube during the pyrolysis. Fractionation of the pyrolyzate (43.8 g.) yielded several fractions of crude olefin. The crude olefin was rectified and 37.0 g. of (+)(S)-3-methyl-1-pentene, b.p. 54–54.3° (765 mm.), n_D^{20} 1.3840–1.3842, $[\alpha]_D^{17}$ +32.86° (lit.[18] n_D^{20} 1.3842), d_4^{17} 0.6703 was obtained (70% yield). Ten g. of unpyrolyzed (+)(S)-3-methyl-1-pentyl acetate was recovered.

Regeneration of (+)(S)-3-methyl-1-pentanol from (+)(S)-3-methyl-1-pentene. Triisobutylaluminum[26] (45.8 g.) in 8.1 g. heptane was heated at 140–160° for 5 hr. A slow evolution of isobutylene took place, and from the isobutylene evolved, a conversion of 68% to diisobutyl monohydride was calculated. To the mixture of diisobutyl monohydride and triisobutylaluminum thus obtained, 4.7 g. (0.056 mole) of (+)(S)-3-methyl-1-pentene (n_D^{20} 1.3841, $[\alpha]_D^{17}$ +32.86°)

(20) H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, 62, 2333 (1940); H. Gilman, F. W. Moore, and O. Baine, *J. Am. Chem. Soc.*, 68, 721 (1941).

(21) The paraformaldehyde had been previously dried for 2 days over phosphorus pentoxide in a vacuum dessiccator.

(22) H. Gilman and W. Catlin, *Org. Syntheses*, Coll. Vol. I, 188 (1941).

(23) S. Siggia, *Quantitative Organic Analysis via Functional Groups*, 2nd ed., John Wiley and Sons, Inc., New York, 1954, p. 12.

(24) W. G. Young and I. D. Webb, *J. Am. Chem. Soc.*, 73, 780 (1951).

(25) S. Siggia, *Quantitative Organic Analysis via Functional Groups*, 2nd ed., John Wiley and Sons, Inc., New York, 1954, p. 46.

(26) Generously supplied by Montecatini Co.

was added. The mixture was heated at 80–90° for 2 hr. and the reaction product was cautiously oxidized at 0° by bubbling in oxygen while stirring, until no more oxygen was absorbed. The oxidized product was hydrolyzed with water and the gelatinous mass thus obtained was extracted many times by ether. The ethereal solution, dried over sodium sulfate, was distilled to eliminate the ether and then rectified to eliminate most of the isobutyl alcohol present (resulting from the oxidation of the $\rangle Al\text{-}CH_2\text{-}CH(CH_3)_2$ groups). The residue of the rectification was distilled and a fraction 99–100° (100 mm.), n_D^{20} 1.4170 (0.8713 g.) was separated which was practically pure 3-methyl-1-pentanol containing small quantities of 4-methyl-1-pentanol. This fraction solution has $[\alpha]_D^{25}$ +7.65° in petroleum ether. A solution of the same concentration of the starting 3-methyl-1-pentanol in petroleum ether has $[\alpha]_D^{25}$ +8.35°.

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PISA, ITALY

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Reduction of Polymers Using Complex Metal Hydrides

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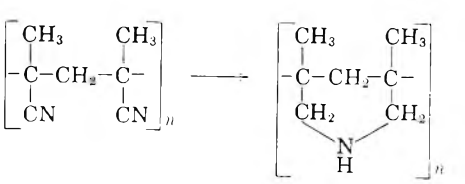
Polymeric nitriles, amides, imides, lactams, and oximes were reduced to the corresponding amines using lithium aluminum hydride. Polymeric hydrazides and hydrazones were reduced to hydrazines by the same procedure. Reduction of polymeric aldehydes and ketones gave alcohols.

Of the large number of publications that have appeared on the use of metal hydrides in reduction, only a few have been concerned with polymers. The reduction of poly(vinyl chloride) and poly(vinyl bromide) to polyethylene by lithium aluminum hydride in a hot (100°) tetrahydrofuran-decalin mixture was reported by Hahn and Muller.[1] Kern and Schulz[2] report the partial reduction of poly(acrolein oxime) by aqueous, alkaline sodium borohydride at 90°. The recent[3–5] publication of several additional papers concerned with the reduction by lithium aluminum hydride of specific polymers leads us to disclose similar, more general work which has been done at these Laboratories on the reduction of polymeric materials by complex metal hydrides. Polymers containing nitrile, amido, imido, oximino, lactam, hydrazide, hydrazone, and keto groups have been successfully reduced.

As with many other reactions of polymers, the proper choice of solvent is a major problem when reductions are carried out using complex metal hydrides. The requirements for the solvent in this case are quite stringent. Besides being a good solvent for both polymer and hydride, the medium must have a relatively high boiling point, as many reactions of polymers are exceedingly slow at ordinary temperatures. At these high temperatures, the solvent must be indefinitely stable to the hydride. Furthermore, because the addition complex formed between hydride and polymer is usually insoluble, the solvent must at least swell the complex so that reaction can go to completion.

N-Methylmorpholine met these requirements. It was also an excellent solvent for most of the reduced polymers, an advantage in that it enabled the use of a strong sodium hydroxide solution to hydrolyze the addition complex. The resulting strongly alkaline inorganic salts are insoluble in the amine, thereby simplifying isolation of the product. Tetrahydrofuran and the dimethyl ether of diethylene glycol (diglyme) were also useful on occasion.

Nitriles. The reduction of the styrene–methacrylonitrile copolymer was typical of the reduction procedures. Infrared analysis of this reduced polymer indicated the complete absence of nitrile groups. A Van Slyke nitrogen analysis indicated that about 70% of the nitrogen present was in the form of primary amino groups, while acetylation showed that the remaining 30% was in the form of secondary amino groups. As the nitrogen percentage was low, it may be assumed that ring closure had taken place, to some extent, with the loss of ammonia, giving a piperidine.



The mechanism of this closure is not known, although the formation of piperidines in the reduction of 1,5-dinitriles is quite common.

Another nitrile reduced was the methacrylonitrile–methyl methacrylate copolymer.

(1) W. Hahn and W. Muller, *Makromol. Chem.*, 16, 71 (1955).

(2) W. Kern and R. C. Schulz, *Angew. Chem.*, 69, 153 (1957).

(3) B. G. Rånby, Abstracts of Papers, Miami Meeting of American Chemical Society, April, 1957, p. 10-S.

(4) J. Petit and B. Houel, *Compt. rend.*, 246, 1427 (1958). B. Houel, *Compt. rend.*, 246, 2488 (1958).

(5) J. A. Blanchette and J. D. Cotman, *J. Org. Chem.*, 23,1117 (1958).

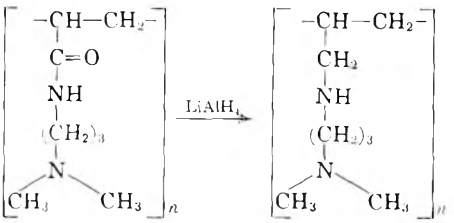
Neither poly(acrylonitrile) nor poly(methacrylonitrile) was soluble in *N*-methylmorpholine or any other useful solvent. The latter polymer was swelled by hot *N*-methylmorpholine, but attempted reduction was unsuccessful.

Attempted reduction of a styrene–fumaronitrile copolymer by using a mixture of the dimethyl ether of ethylene glycol (diglyme) and *N*-methylmorpholine as solvents was likewise unsuccessful.

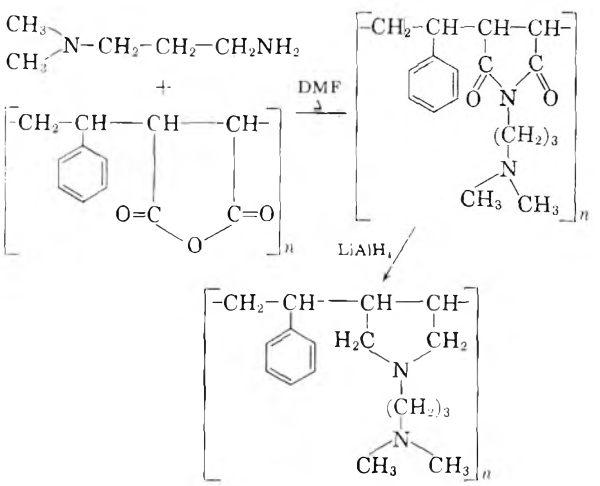
Attempts to reduce the methacrylonitrile–styrene copolymer with the sodium borohydride–aluminum chloride complex using diglyme as a solvent gave a small amount of partially reduced polymer. Most of the product was insoluble and probably crosslinked.

Diborane, likewise, gave a completely insoluble product.

Amides. Poly(*N*,*N*-dimethylacrylamide) was reduced in good yield to poly(*N*,*N*-dimethylallylamine) by lithium aluminum hydride in *N*-methylmorpholine. The resulting polymer was soluble in dilute acetic acid, methanol, and petroleum ether and was insoluble but swelled in acetone, dioxane, and dimethylformamide. Also reduced by this procedure was poly(γ - dimethylaminopropylacrylamide).



Imides. The imide produced in the reaction between γ-dimethylaminopropylamine and the styrene–maleic anhydride copolymer was reduced smoothly to the corresponding pyrrolidine polymer.

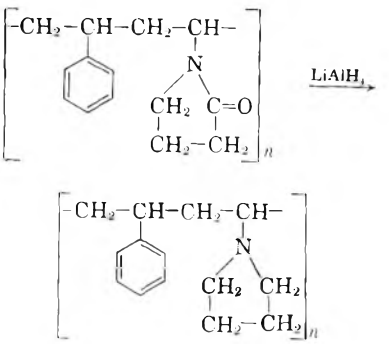


Oximes. Poly(methyl vinyl ketoxime) and the styrene–methyl vinyl ketoxime copolymer were reduced to the corresponding amines. The copolymer was reduced completely while the homopolymer contained a small amount of unreduced oxime. In both cases, a low nitrogen percentage in the product indicated piperidine formation.

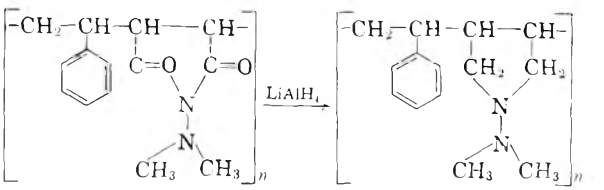
Attempted reduction of a styrene–methyl vinyl ketoxime copolymer with sodium borohydride in diglyme solution was completely unsuccessful. The starting material was recovered unchanged.

Lactams. Poly(vinylpyrrolidone) is dispersible in hot *N*-methylmorpholine although insoluble in the cold solvent. Reduction of the polymer gave a product which was initially soluble in *N*-methylmorpholine but which turned insoluble in the process of isolation and could not be purified.

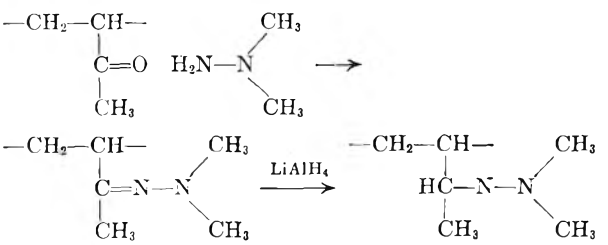
On the other hand, a styrene–vinylpyrrolidone copolymer was completely reduced by lithium aluminum hydride by the usual procedure.



Hydrazides. The reaction product between styrene–maleic anhydride copolymer and *N*,*N*-dimethylhydrazine was reduced to the corresponding substituted hydrazine by the usual procedure. It was readily soluble in dilute acetic acid while the starting material was not.



Hydrazones. The *N*,*N*-dimethylhydrazone of poly(methyl vinyl ketone) was also reduced by lithium aluminum hydride. However, the resulting polymer, initially soluble in water, became insoluble after standing for a short time. An aqueous



solution gelled within 3 hr., while an aqueous acetic acid solution, though more stable than the free base, also gelled in several days.

The *N*,*N*-dimethylhydrazone of the styrene–methacrolein copolymer was completely reduced to the corresponding hydrazine with lithium aluminum

TABLE I

	Reduced Polymer or Copolymer	Method of Preparation	Analysis C	Analysis H	Analysis N	*	Viscosity	**	Analysis C	Analysis H	Analysis N[a]	Percent Reduction
I	Methacrylonitrile–styrene	Copoly	84.2	8.1	8.2	50	0.30[c]	A	84.8	9.8	6.7[a] 4.8[b]	100
II	Methacrylonitrile–methyl methacrylate	Copoly	65.2	7.9	8.8	50	0.42[c]	B	68.8	11.8	8.6	100
III	*N,N*-Dimethylacrylamide	Poly	61.2	9.7	13.8	100	0.41[c]	C	70.3	12.7	16.4[f]	100
IV	γ-Dimethylaminopropylacrylamide	Poly	60.8	10.2	17.6	100	0.11[d]	C	68.1	12.7	18.6	100
V	γ-Dimethylaminopropylmaleimide–styrene	Der	70.6	7.8	9.4	48		A	78.6	10.1	10.3	100
VI	Methyl vinyl ketoxime	Der	54.6	8.1	15.9	95		A	69.5	10.9	15.6	65
								E	54.7	8.0	15.7	0
VII	Methyl vinyl ketoxime–styrene	Der	77.5	8.3	7.2	50		A	84.0	9.0	7.1	100
VIII	Vinylpyrrolidone	Poly	64.3	8.5	12.0	94	0.34[e]	D	63.5	10.3	11.3	
IX	Vinylpyrrolidone–styrene	Copoly	88.5	8.1	2.1	14	0.6[c]	A	89.8	8.8	2.0	100
X	γ-Dimethylaminomaleimide–styrene	Der	68.2	6.9	9.7	42		D	77.1	9.1	10.5	100
XI	Methyl vinyl ketone *N,N*-dimethylhydrazone	Der	65.4	10.4	20.9	85		A	65.7	11.1	20.3	60
XII	Methacrolein–styrene *N,N*-dimethylhydrazone	Der	78.3	9.4	11.4	42		A	79.7	10.1	9.0	100
XIII	Methyl vinyl ketone	Poly	68.3	8.5		100	0.43[c]	A&B	64.0	10.8[g]		95
								E	64.1	9.6		50
XIV	Methacrolein–styrene	Copoly	82.5	8.4		50	0.1[c]	E	81.4	8.9		95
XV	Methyl vinyl ketone–styrene	Copoly	82.6	8.7		50	0.21[c]	A	81.4	9.4[h]		100
								E	82.5	8.7[i]		75

* Percent reducible compound. ** Method of reduction.
[a] Dumas unless otherwise noted. [b] Van Slyke. [c] In acetone. [d] In methanol. [e] In water. [f] Methyl *p*-toluenesulfonate. *Anal.* C, 57.8; H, 7.8; N, 5.2; S, 11.6. [g] Acetate. *Anal.* C,6 2.8; H, 8.6; Acetyl, 37.4. [h] Viscosity, 0.19 (propanol). [i] Viscosity 0.23 (propanol).

hydride. It was soluble and stable in dilute acetic acid solution.

Carbonyl Compounds. Simple organic carbonyl compounds are reduced completely to the corresponding hydroxyl compounds with both sodium borohydride and lithium aluminum hydride. Polymeric carbonyl compounds are only partially reduced (40–60%) by sodium borohydride in diglyme at 60–90°. On the other hand, the more powerful lithium aluminum hydride in *N*-methylmorpholine at 115° effected complete reduction.

Poly(methyl vinyl ketone) and the styrene–methacrolein and styrene–methyl vinyl ketone copolymers were reduced by the method described.

The product from the lithium aluminum hydride reduction of poly(methyl vinyl ketone) exhibited inverse solubility in water.

EXPERIMENTAL

Starting Materials. *N*-Methylmorpholine and diglyme were purified by refluxing over sodium, then fractionating through a helix-packed column.

Lithium aluminum hydride (Metal Hydrides, Inc.) and sodium borohydride were used as purchased.

The analytical data for the intermediate polymers are given in the table. Those marked "poly" and "copoly" were obtained by either bulk or solution polymerization. Of the derived polymers (marked "Der"), the preparation of the *N,N*-dimethylaminomaleimide–styrene copolymer (X) was similar to that of the *N,N*-dimethylaminopropylmaleimide–styrene copolymer (V) described here. Poly(methyl vinyl ketoxime) (VI) and the methyl vinyl ketoxime–styrene copolymer (VII) were made by the method of Marvel.[6] The hydrazones XI and XII were made by tumbling a solution of the intermediate carbonyl polymers in *N,N*-dimethylhydrazine overnight.

Reductions. To conserve printing space, only the reduction procedure for the styrene–methacrylonitrile copolymer with lithium aluminum hydride (Method A) and of poly(methyl vinyl ketone) with sodium borohydride (Method E) will be described in detail.

The properties of some of the other polymers necessitated changes in the basic procedures. The methyl methacrylate–methacrylonitrile copolymer, insoluble in *N*-methylmorpholine, was dissolved in tetrahydrofuran and then diluted with *N*-methylmorpholine. Poly(methyl vinyl ketoxime) and

(6) C. S. Marvel and C. L. Levesque, *J. Am. Chem. Soc.*, 60, 280 (1938).

poly(vinyl pyrrolidone) were insoluble in the cold, but dissolved and melted respectively in boiling *N*-methylmorpholine to give reducible mixtures.

In those cases where the reduced polymer, after hydrolysis, was insoluble in *N*-methylmorpholine and precipitated from the solution, it was isolated by extraction of the filtered solids with another organic solvent, usually methanol, followed by precipitation or evaporation (Method B). Those reduced polymers not precipitated because of solubility in the common organic solvents were purified by repeated solution and evaporation of a suitable solvent (Method C). Reduced polymers insoluble in the common organic solvents were dissolved in dilute acetic acid, dialyzed, and isolated by evaporation of the solvent or precipitation with sodium hydroxide solution (Method D).

Analytical values given in the table are the averages of at least two determinations, each of which agreed within 0.4 unit. Since the differences in theoretical hydrogen percentages for the pure, unreduced, and reduced polymers are sometimes quite small and since secondary reactions further complicated the situation, the percentage reduction given in the table is sometimes only a rough estimate.

Reduction of the Styrene–Methacrylonitrile Copolymer. A solution of 25 g. (0.145 mole) of this interpolymer in 250 ml. of *N*-methylmorpholine was added, with stirring, over a period of 2 hr. to a suspension of 9.5 g. (0.25 mole) of lithium aluminum hydride in 500 ml. of *N*-methylmorpholine under nitrogen kept at 100–110°. After addition was over, the mixture was stirred for an additional 4 hr. under reflux. After the mixture had cooled, 20 ml. of water, 12 ml. of 25% sodium hydroxide solution, then 20 ml. more water were added dropwise, giving a granular precipitate. After the mixture had been stirred for an additional 3 hr., the precipitate was filtered and discarded. The filtrate was then evaporated down to 100 ml. on a steam-bath under vacuum. On pouring the residual solution into water, the reduced polymer precipitated as a friable powder. It was washed several times with water, filtered, and vacuum-dried. Yield, 19 g. of a white powder, soluble in methanol, dimethylformamide, and dilute acetic acid. It swelled but did not dissolve in acetone.

Anal. Calcd. for completely reduced copolymer: C, 82.8; H, 9.7; N, 8.0. Found: C, 84.8, 84.7; H, 9.9, 9.7; N (Dumas), 6.7, 6.7; N (Van Slyke), 4.8, 4.7.

Acetylation of Styrene–Methallylamine Copolymer. A solution of 5 g. of the styrene–methallylamine copolymer in 100 ml. of pyridine was treated with 50 ml. of acetic anhydride. The mixture was heated for 1 hr. on a steam-bath, then precipitated in water. It was dissolved in acetone and reprecipitated in water.

Anal. Calcd. for complete acetylation of reduced copolymer: acetyl, 16.7. Found: acetyl, 16.4, 16.6.

Preparation of the γ-Dimethylaminopropylmaleimide–Styrene Copolymer. Preparation of the Copolymer. A solution of 20.2 g. (0.1 mole) of a styrene–maleic anhydride copolymer (Monsanto Lytron 810) in 200 ml. of dimethylformamide was added dropwise to a stirred, heated (100°) solution of 14 g. (0.14 mole) of γ-dimethylaminopropylamine in 200 ml. of dimethylformamide over a period of 1.5 hr. The temperature was then raised gradually until 100 ml. of solvent had distilled off. During this time, the distillate temperature rose to 152°. The solution was then cooled and poured into water, giving a friable precipitate. This was washed with water, then vacuum-dried, giving 23 g. of a white, voluminous powder which was soluble in acetone and dilute acetic acid.

Preparation of the N,N-Dimethylhydrazone of Poly(methyl Vinyl Ketone). A mixture of 10 g. of poly(methyl vinyl ketone), 100 ml. of *N,N*-dimethylhydrazine, and 2 drops of glacial acetic acid was tumbled at room temperature overnight. Complete solution resulted. The polymer was precipitated in petroleum ether, redissolved in acetone, and reprecipitated in petroleum ether, giving a soft, water-soluble solid which hardened somewhat on drying. Yield, 7 g.

Reduction of Poly(methyl Vinyl Ketone) with Sodium Borohydride. A solution of 7 g. (0.1 mole) of poly(methyl vinyl ketone) in 100 ml. of anhydrous diglyme was added dropwise to a stirred solution of 3.8 g. (0.1 mole) of sodium borohydride in 150 ml. of diglyme, kept at 55° over a period of 0.5 hr. Following addition, the mixture was kept at 65° for 3 hr., then poured into one l. of water. The product was filtered and vacuum-dried. It was dissolved in tetrahydrofuran and precipitated in ether, giving 4.5 g. of a white powder.

ROCHESTER 4, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

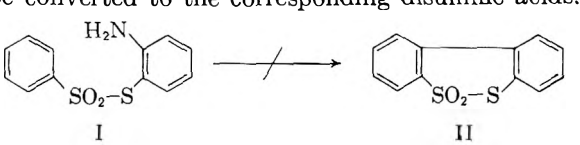
A Novel Displacement Reaction of the *N*-Nitroso Derivative of *N*-Acetyl-*o*-aminophenyl Benzenethiolsulfonate[1]

C. G. OVERBERGER, MICHAEL P. MAZZEO,[2] AND J. J. GODFREY

Received March 6, 1959

The preparation of *N*-acetyl-*o*-aminophenyl benzenethiolsulfonate is described. Decomposition of its *N*-nitroso derivative gave unexpectedly 1,2,3-benzothiadiazole and benzenesulfonic acid. A mechanism to account for this transformation is proposed.

The initial purpose of this work was to prepare unsymmetrically substituted biphenyl disulfinic acids in order to study the intramolecular reaction of the sulfinic acid groups with each other. One scheme proposed for this disulfinic acid synthesis involved preparation of unsymmetrically substituted biphenyl thiolsulfonates which could then be converted to the corresponding disulfinic acids.



I II

(1) This is the 31st in a series of papers concerned with azo compounds; for the previous paper in this series see C. G. Overberger, George Kesslin and Pao-tung Huang, *J. Am. Chem. Soc.*, **81**, 3779 (1959).

(2) This paper comprises portions of dissertations submitted by Michael P. Mazzeo in partial fulfillment of the requirements for the degree of Master of Science and John J. Godfrey in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

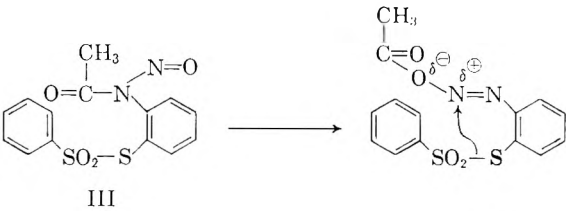
o-Aminophenyl benzenethiolsulfonate was prepared as a model intermediate for the study of the ring closure to give the known thiolsulfonate (II) of 2,2′-biphenyldisulfinic acid.[3] This paper describes the attempts to effect the conversion of I to II and the actual product isolated.

o-Aminophenyl benzenethiolsulfonate was prepared by the action of silver-*o*-aminothiophenolate on benzenesulfonyl iodide. The aminothiolsulfonate was then diazotized and decomposed by the method of Shetty[4] in the presence of powdered copper in an acidic medium. No biphenyl thiolsulfonate was isolated but only small traces of a white solid, identified as 1,2,3-benzothiadiazole. Strongly acidic conditions similar to the method of DeTar and Sagmanli[5] gave similar results. Cyclization was then attempted by means of the Gomberg-Bachman reaction.[6] Because thiolsulfonates are hydrolyzed with aqueous alkali, only enough aqueous sodium hydroxide was added to neutralize the acid present and form the diazohydroxide from the diazonium chloride. However, no biphenyl thiolsulfonate could be isolated from this reaction, but traces of impure 1,2,3-benzothiodiazole was detected.

Accordingly, the method using nitrosoacetylamines for the preparation of biaryl compounds was attempted. *o*-Aminophenyl benzenethiolsulfonate was first acetylated and then nitrosated by means of nitrosyl chloride according to the method of Heilbron[7] to give III. Decomposition of III in an aqueous sodium bicarbonate solution did not yield the expected biphenyl thiolsulfonate, but instead 1,2,3-benzothiadiazole (IV) and benzenesulfonic acid. In addition to these products, a small amount of *N*-acetyl-*o*-aminophenyl benzenethiolsulfonate, the denitrosated product, was isolated.

The formation of IV probably proceeds by way of an intramolecular displacement; a reaction which often occurs with an aromatic diazo compound having an appropriate ortho substituent. Some examples of this are the formation of benztriazole,[8] 1,2,3-benzothiadiazole[9] and indazole[10] from the corresponding *o*-aminothiol and methyl substituted compounds. The synthesis of hydroxy substituted benzo [c]pyridazines by the diazotization of an enolizable ortho amino ketone[11] is also analogous.

Whereas for the cases just cited the displaced group was a proton, the reaction reported here involves the elimination of a benzenesulfonium ion. The suggested path for this reaction, given below, is analogous to that described for the formation of indazole from *N*-nitroso-*N*-acetyl-*o*-toluidine[12] and for the previously mentioned hydroxy substituted benzo [c]pyridazines.[11]



The benzothiadiazole was identified by comparison of its infrared spectrum with a known sample of 1,2,3-benzothiadiazole prepared by the diazotization of *o*-aminobenzenethiol,[9] and further identified by a mixed melting point and the formation of the 4-nitro derivative.

EXPERIMENTAL[13]

o-Aminophenyl benzenethiolsulfonate. Benzenesulfonyl iodide was prepared by the method of Otto and Troeger[14] from the sodium salt of benzenesulfinic acid and iodine. Silver *o*-aminothiophenolate was prepared by a procedure similar to that described by Bulmer and Mann,[15] from the reaction of freshly distilled *o*-aminobenzenethiol with silver nitrate.

The procedure was related to that described by Gibson, Miller, and Smiles[16] for the preparation of thiolsulfonates,[5] although no detailed procedures were reported. To 200 ml. of anhydrous benzene cooled in an ice bath was added 13.4 g. (0.05 mole) of benzene sulfonyl iodide with stirring. To this, 12 g. (0.052 mole) of silver-*o*-aminothiophenolate was then added in small portions over a period of 20 min. and after the addition was complete the mixture was stirred an additional 20 min. The pale yellow thiolsulfonate solution was filtered free of silver iodide, the filtrate being collected in an ice cooled receiver. The benzene was then removed under vacuum without the use of heat—towards the end of the evaporation free iodine appeared in the vacuum traps due to the decomposition of unreacted benzenesulfonyl iodide. The yellow solid in the distilling flask was kept at 0.5 mm. pressure for an additional hour in order to ensure removal of all the benzene. The flask was then removed from the vacuum apparatus, 30 ml. of absolute ethanol was added, the contents were mixed thoroughly and placed in a refrigerator. This operation was performed in order to dissolve unreacted sulfonyl iodide and its decomposition products at the expense of some thiolsulfonate, since these contaminants render isolation of the thiolsulfonate diffi-

(3) H. J. Barber and S. Smiles, *J. Chem. Soc.*, 1141 (1928).
(4) G. Shetty, *Helv. Chim. Acta.*, **32**, 24 (1949).
(5) D. DeTar and S. Sagmanli, *J. Am. Chem. Soc.*, **72**, 965 (1950).
(6) W. E. Bachman and R. A. Hoffman, *Org. Reactions*, Vol. II, John Wiley and Sons, Inc., p. 225.
(7) H. France, M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 369 (1940).
(8) A. Ladenberg, *Ber.*, 9, 219 (1876).
(9) P. Jacobson, *Ber.*, **21**, 3104 (1888).
(10) P. Jacobson and L. Huber, *Ber.*, **41**, 669 (1908).
(11) K. Shofield and J. C. Simpson, *J. Chem. Soc.*, 1170 (1948).
(12) R. Husigen and H. Nakaten, *Ann.*, **586**, 84 (1954).
(13) All melting points are corrected.
(14) R. Otto and J. Troeger, *Ber.*, **24**, 485 (1891).
(15) G. Bulmer and F. G. Mann, *J. Chem. Soc.*, 680 (1945).
(16) D. T. Gibson, S. Smiles, and C. J. Miller, *J. Chem. Soc.*, 1827 (1925).

cult. The thiolsulfonate was then removed by filtration, washed with a minimum amount of cold ethanol and dried in a vacuum desiccator, to give 8.18 g. (61.7%) of *o*-aminophenyl benzenethiolsulfonate, m.p. 83°–83.5°.

Anal. Calcd. for $C_{12}H_{11}NO_2S_2$: C, 54.32; H, 4.18; N, 5.28; S, 24.16. Found: C, 54.68; H, 4.37; N, 5.58; S, 24.14.

N-Acetyl-o-aminophenyl benzenethiolsulfonate. In 95 ml. of acetic anhydride was dissolved 24.6 g. (0.093 mole) of *o*-aminophenyl benzenethiolsulfonate. The solution was kept at 50° for 30 min., cooled, and then poured into 200 ml. of ice water. An oil formed which soon solidified. The white solid was removed by filtration, washed with water, and recrystallized from an ethanol-water solution, white needles (94%), m.p. 114.6°–115.4°.

Anal. Calcd. for $C_{14}H_{13}NO_3S_2$: C, 54.88; H, 4.26; N, 4.56. Found: C, 54.93; H, 4.33; N, 4.49.

Preparation and decomposition of N-nitroso-N-acetyl-o-aminophenyl benzenethiolsulfonate. The procedure for the preparation of *N*-nitroso-*N*-acetyl-*o*-aminophenyl benzenethiolsulfonate was a general procedure described by France, Heilbron, and Hey[7] for *N*-acetyl derivatives, by the reaction of nitrosyl chloride with *N*-acetyl amines. This method led to the isolation of the crude *N*-nitroso compound in 85.3% yield; m.p. 77°–79° dec. Attempts to purify the compound by recrystallization from ethanol-water resulted in excessive loss due to ease of decomposition.

To 300 ml. of water in a 1-liter flask equipped with a magnetic stirrer and maintained at 50°–55° was added 24.45 g. (0.072 mole) of *N*-nitroso-*N*-acetyl-*o*-aminophenyl benzenethiolsulfonate and 6.04 g. (0.072 mole) of sodium bicarbonate. The mixture was heated at 50° and continually stirred for a period of 12 hr. to ensure complete decomposition. At the end of this period the yellow nitroso compound had decomposed to give a brown oil which was suspended in the water. The aqueous mixture was then extracted with 250 ml. of ether and the ethereal solution was concentrated to 25 ml., at which time a precipitate formed. The white precipitate was removed by filtration and was observed to be 3.33 g. of *N*-acetyl-*o*-aminophenyl benzenethiolsulfonate, m.p. 114°–115°; a mixed melting point with material melting at 114.6°–115.4° melted at 114°–115°. The remaining ether solution was concentrated and distilled under vacuum to give 4.14 g. (42.3%) of 1,2,3-benzothiadiazole, m.p. 36°–37°; 2.62 g. of charred resinous material remained in the distilling flask. A mixed melting point with an authentic sample of 1,2,3-benzothiadiazole, m.p. 36°–37°, melted at 36°–37°. The infrared spectrum was identical with a known sample.

The benzothiadiazole was characterized further by means of the 4-nitro derivative which was prepared by adding 1 g. of the benzothiadiazole to a mixture of 5 ml. of concentrated sulfuric acid and 5 ml. of fuming nitric acid, heating the solution over a steam bath for 10 min., and then adding it to 50 ml. of ice water. The white solid was recrystallized from an ethanol-water solution, m.p. 93.8°–94.6° (m.p. 95° prepared with potassium nitrate and sulfuric acid).[17] A mixed melting point with an authentic sample, m.p. 94°–95° was not depressed, m.p. 94°–95°.

The aqueous phase of the reaction mixture was then evaporated on a rotary evaporator. After the water was completely removed, there remained a brown solid contaminated with a brown oil. The solid was washed with a limited amount of absolute ethanol which dissolved the oil. A total of 5.4 g. (41.5%) of solid crude benzene sulfonate was isolated in this way.

The sodium benzenesulfonate was characterized by means of the aniline salt which was prepared by adding 1 g. of freshly distilled aniline to a saturated 1*N* hydrochloric acid solution of 1 g. of the sodium salt. The white aniline salt which precipitated was recrystallized from water and dried in an oven at 100°, m.p. 237°–239°. A mixed melting point with an authentic sample, m.p. 237°–239° (m.p. 240°),[18] melted at 237°–239°.

1,2,3-Benzothiadiazole. The procedure was that described by Jacobson[9] from the diazotization of *o*-aminobenzenethiol. The crude benzothiadiazole was distilled, b.p. 63°/0.5 mm. (57.7%), m.p. 35.4°–36.5° (m.p. 36°–37°).[9]

Attempted Pschorr reactions and formation of small quantities of 1,2,3-benzothiadiazole. (A) To 45 ml. of 6*N* sulfuric acid cooled to −5° was added 1 g. of *o*-aminophenyl benzenethiolsulfonate. The amine sulfate formed was insoluble in the medium. A solution of 0.5 g. of sodium nitrite in 5 ml. of water was then added dropwise to the yellow suspension. After the addition, the yellow diazonium salt solution was added in 5-ml. portions to a vigorously stirred suspension of 2 g. of copper powder in 45 ml. of 6*N* sulfuric acid which was kept at 45°–50°. Care was taken to keep the diazonium salt solution cold prior to its addition to the copper suspension in order to minimize decomposition. When all the diazonium solution was added the reaction mixture was brought to 70° and maintained at that temperature for 1 hr. There was no noticeable evolution of nitrogen during the course of the reaction. The mixture was then cooled and the brown oil which had formed was extracted with ether and washed with 1% sodium bicarbonate solution. Upon evaporation of the ether, 0.32 g. of a yellow oil which had a characteristic nitrobenzene odor was isolated. After several attempted recrystallizations some light yellow solid was obtained, m.p. 31°–34°. The infrared spectrum of this compound was identical with the spectrum of authentic 1,2,3-benzothiadiazole. The procedure of ref. (4) was followed and similar results were obtained, namely a small amount of impure 1,2,3-benzothiadiazole was isolated.

Acknowledgment. The authors wish to thank the Department of the Army, Office of the Surgeon General, for the generous financial support of the research carried out under Contract DA-49-007-MD-557.

BROOKLYN, N. Y.

(17) A. Bernthsen, *Ann.*, **1**, 251 (1888).

(18) C. M. Keyworth, *J. Soc. Chem. Ind.*, **43**, 341T (1924).

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

Synthesis of Potential Anti-cancer Agents. II. Purine Antagonists from 2-Methylhypoxanthine-8-thiol[1]

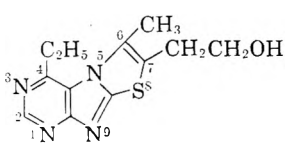
ROBERT C. ELDERFIELD AND RAJ NANDAN PRASAD[2]

Received March 9, 1959

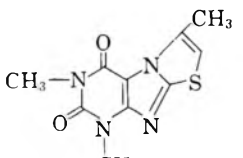
2-Methylhypoxanthine-8-thiol has been condensed with chloroacetic and β-chloropropionic acids to give the corresponding thioacetic and thiopropionic acids which on cyclization gave 4-hydroxy-2-methyl-6,7-dihydrothiazolo-[2.3-*f*]purine-6-one and 4-hydroxy-2-methyl-6,7-dihydro-1,3,6-thiazino[2.3-*f*]purine-6-one. Condensation of the former with *p*-(bis-β,β′-dichloroethyl)aminobenzaldehyde through the reactive methylene group gave the corresponding benzylidene derivative. A similar condensation with the thiazinopurine ketone failed. A series of thio ethers of 2-methylhypoxanthine-8-thiol has been prepared.

One general approach to the synthesis of compounds potentially capable of acting as purine antagonists and hence as inhibitors of tumor growth involves blocking possible sugar incorporation at the 7 or 9 positions of a purine by the introduction of suitable substituents. Alkyl groups are not particularly suited for this purpose since evidence is at hand that, at least in the case of methyl groups, considerable demethylation occurs during metabolism of such substances.[3]

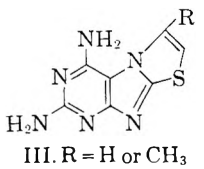
The use of fused ring systems as blocking groups has been reported by a few investigators. Todd and Bergel[4] prepared a homolog of dihydrothiazolo-[2.3-*f*]xanthine(I), Ochiai[5] prepared an analogous derivative of theophylline (II), and Gordon[6] prepared a [2.3-*f*]dihydrothiazolo derivative of 2,6-diaminopurine (III).[7]



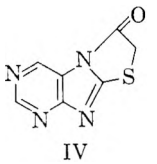
I



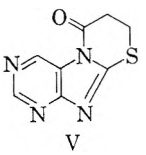
II



III. R = H or CH_3



IV



V

As far as we are aware, no purine derivatives carrying fused rings of the type of IV or V, have been described. It therefore seemed of interest to prepare representative compounds for evaluation as possible tumor inhibitors. Compounds analogous to IV have been reported by Kendall and Duffin,[8] as resulting from cyclization of 2-benzimidazolylmercaptoacetic acid. Inasmuch as a plentiful supply of 4,5-diamino-6-hydroxy-2-methylpyrimidine (VI) was available from other work, VII was selected as the starting purine.

Fusion of VI with thiourea gave 2-methylhypoxanthine-8-thiol (VII) in almost quantitative yield. When VII was refluxed with the appropriate chloro acid, the mercapto acids VIII and IX were obtained. The mercapto acids, in turn, provided 4 - hydroxy - 2 - methyl - 6,7 - dihydrothiazolo-[2.3 - *f*]purine - 6 - one (X) and 4 - hydroxy - 2-methyl - 6,7 - dihydro - 1,3,6 - thiazino - [2.3 - *f*]-purine - 6 - one (XI) respectively, when they were refluxed with acetic anhydride. Ring closure is formulated as occurring at position 7 of the purine system by analogy with the closures reported by Todd and Bergel[4] and by Ochiai.[5] It should be pointed out that no definitive evidence for excluding ring closure at the 9 position of the purine system has been offered by either of the latter workers.

Having thus obtained X and XI it seemed desirable to incorporate the *p*-[*N*,*N*-bis(2-chloroethyl)amino]benzylidene alkylating function into the molecules. Certain other purines carrying this group[9] have given evidence of tumor inhibitory activity in animals.[10] For this purpose, it was hoped to take advantage of the activity of the methylene hydrogens in the 7 positions of X and XI. X condensed readily with *p*-[*N*,*N*-bis(2-chloroethyl)amino]benzaldehyde (XII) in the presence of glacial acetic acid to give XIII. XIV, however, could not be

(1) This investigation was supported by Research Grant CY-2961 from the National Cancer Institute of the National Institutes of Health.

(2) On leave of absence from the Chemistry Department, B. N. College, Patna University, India.

(3) V. C. Meyers and R. F. Hanzal, *J. Biol. Chem.*, **162**, 309 (1946).

(4) A. R. Todd and F. Bergel, *J. Chem. Soc.*, 1559 (1936).

(5) E. Ochiai, *Ber.*, **69B**, 1650 (1936).

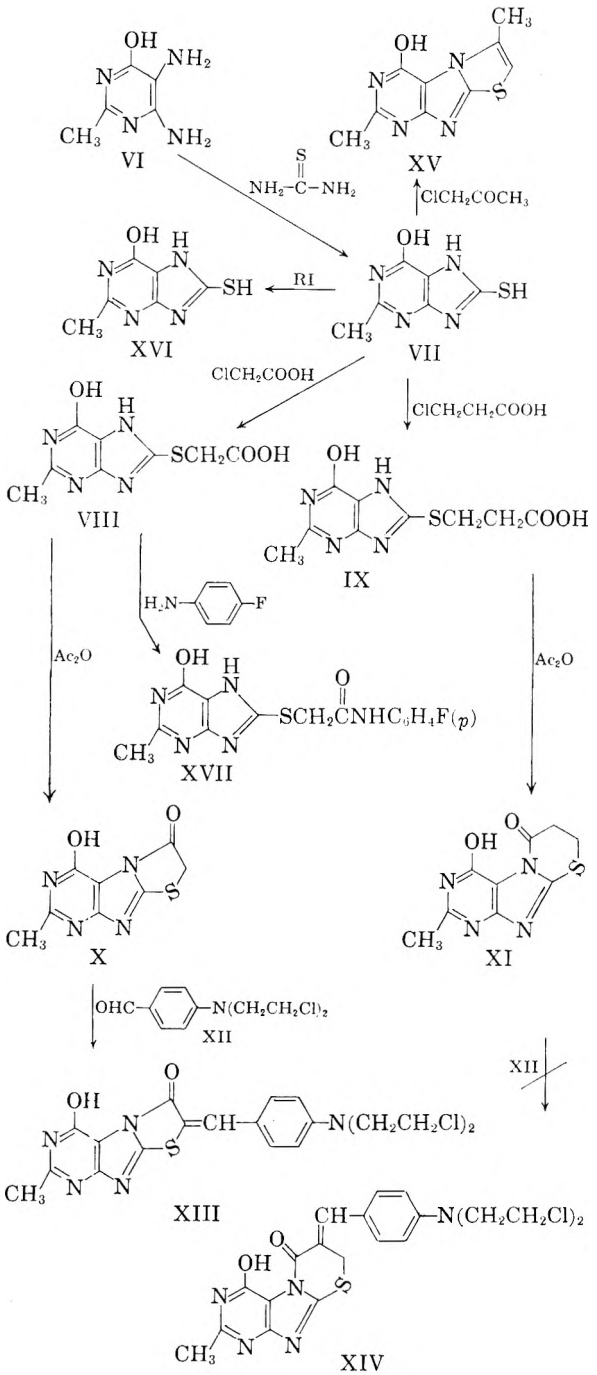
(6) M. Gordon, *J. Am. Chem. Soc.*, **73**, 984 (1951).

(7) Nomenclature and numbering of these fused ring systems is that used by Chemical Abstracts and the Ring Index and differs from that employed in refs. 4–6.

(8) J. D. Kendall and G. F. Duffin, Brit. Patent **634,951**.

(9) Unpublished work from this laboratory.

(10) Private communication from Dr. Ralph Jones, Jr.



obtained under the conditions used for the preparation of XIII, and only the unreacted materials were recovered. Even under more severe conditions (acetic anhydride and sodium acetate, triethylamine or piperidine and acetic anhydride) XI failed to condense with XII. It appears that in X, the electronegative sulfur atom exerts some activating influence on the methylene hydrogens in addition to the usual effect of the carbonyl group which is not possible in XI.

In complete analogy with earlier reports,[4-6] when VII was boiled for several days with chloroacetone in ethanol, 2,6-dimethyl-4-hydroxythiazolo[2.3-*f*]purine (XV) resulted. It was not necessary to isolate the intermediate acetonyl derivative.

Finally, a series of 2-methyl-8-mercaptohypoxanthine derivatives of the general type of XVI were prepared for investigation for tumor-inhibiting action. These included a number of thioethers and a series of esters of 6-hydroxy-2-methyl-8-purinylmercaptoacetic acid. In the preparation of the mercaptoacetates, an observation originally made by Gordon[6] was confirmed and extended. In order to prepare such esters, it is unnecessary to start with the appropriate bromoacetic ester. Rather, merely refluxing a solution of VII with about one to two equivalents of bromoacetic acid in the appropriate alcohol until a clear solution resulted, gave excellent yields of the mercaptoacetates. In general, the time required for complete reaction decreased with the higher boiling alcohols. Obviously, the mercaptoacetic acid must be formed initially, followed by esterification catalyzed by the liberated hydrogen bromide. Also of interest is the ready formation of esters of secondary alcohols by this procedure. Pertinent data concerning the synthesis and properties of these compounds are given in Table I.

An attempt at nucleophilic displacement of the mercaptoacetic acid group of VIII by *p*-fluoroaniline did not succeed, although a similar displacement has been reported[11] with 6-purinylmercaptoacetic acid. Instead the product isolated was found to be an anilide (XVII).

Reaction of the mercaptoacetates (XVI) with hydrazine resulted in the formation of a hydrazide in agreement with Huber's[11] findings.

Results of physiological tests on the compounds described in this paper will be reported elsewhere.

EXPERIMENTAL[12,13]

2-Methylhypoxanthine-8-thiol (VII). An intimate mixture of 9.52 g. (0.04 mole) of the sulfate of 4,5-diamino-6-hydroxy-2-methylpyrimidine (VI)[14] and 12 g. (0.157 mole) of thiourea was heated at 230–250° for 15–20 min. The mixture melted, then frothed with evolution of ammonia and finally became quite viscous. After cooling, the dark brown mass was dissolved in dilute potassium hydroxide solution, treated with decolorizing carbon and the filtered solution was acidified with acetic acid to yield 7.2 g. of light brown material. An analytical sample was obtained by repeating the above process. Ultraviolet absorption data on this and other compounds are given in Table II.

2-Methyl-8-methylmercaptohypoxanthine (XVI, R = CH_3). A solution of 4.5 g. (0.0246 mole) of VII in 100 ml. of aqueous 1.5% potassium hydroxide solution was cooled in ice. After the addition of 5 g. of iodomethane, the solution was stirred vigorously for 3 hr. and allowed to stand overnight in the refrigerator. The white precipitate was collected and thoroughly washed with water to give 4 g. of material which slowly decomposed above 290°. Recrystallization from 1.5 l. of boiling water gave 2.1 g. of cream-colored material which

(11) G. Huber, *Angew. Chem.*, 68, 706 (1956).

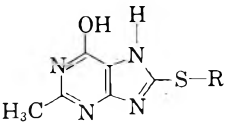
(12) All melting points are uncorrected for stem exposure.

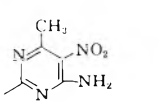
(13) Microanalysis by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(14) W. Traube, *Ann.*, 432, 287 (1923).

TABLE I

DERIVATIVES OF 2-METHYLHYPOXANTHINE-8-THIOL



R	Reaction Time[a]	Recrystallization solvent[b]	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	M.P., °C.
H		A	39.56	3.30	30.77	39.60	3.21	30.85	>300
CH_3		A	42.85	4.08	28.57	42.81	4.07	28.58	>300
$CH_2(C=O)OH$[c]		A	37.21	3.87	21.70	37.62	4.01	21.48	>300
$CH_2CH_2(C=O)OH$		B	42.52	3.93	22.04	42.37	4.08	22.11	>300
$CH_2(C=O)OCH_3$	18	C	42.54	3.93	22.28	42.74	4.09	21.63	250–251.5 dec.
$CH_2(C=O)OCH_2CH_3$	16	D	44.77	4.47	20.88	44.72	4.48	21.05	232.6–233.6 dec.
$CH_2(C=O)OCH_2CH_2CH_3$	8	D	46.80	4.96	19.85	46.76	4.96	19.95	230–231 dec.
$CH_2(C=O)OCH(CH_3)_2$	48[d]	D	46.80	4.96	19.85	46.88	5.17	20.14	223–226 dec.
$CH_2(C=O)O(CH_2)_3CH_3$	2	D	48.64	5.38	18.91	48.69	5.52	19.13	204–205 dec.
$CH_2(C=O)OCH_2CH(CH_3)_2$	18	D	48.64	5.38	18.91	48.82	5.62	19.11	221–222 dec.
$CH_2(C=O)OCH(CH_3)CH_2CH_3$	20	D	48.64	5.38	18.91	48.72	5.61	18.89	234–235 dec.
$CH_2(C=O)O(CH_2)_4CH_3$	1	D	50.32	5.80	18.06	50.25	5.84	18.09	201–203 dec.
$CH_2(C=O)OCH_2CH_2Cl$	20 min.	E	39.66	3.63	18.51	39.72	3.61	18.55	180–184 dec.
$CH_2(C=O)NHNH_2$[e]		A	37.13	4.06	32.49	37.46	3.94	32.44	300
CH_2CH_2OH		A or B	42.47	4.42	24.77	42.37	4.37	24.78	>300
$CH_2(C=O)NH$-p-C_6H_4F[f]		A or B	49.77	3.70	20.74	50.04	3.92	20.94	>300
		A	39.52	2.99	33.53	39.24	3.24	33.26	>300

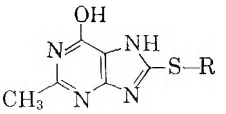
[a] Reflux time (in hours unless otherwise specified) required to obtain a clear solution. [b] A solution in dilute potassium hydroxide and reprecipitation by acetic acid; B, water; C, methanol and benzene; D, dilute methanol; E, acetone and ether. [c] Analysis calculated for $C_8H_8N_4O_3S \cdot H_2O$. [d] The solution was not quite clear after 48 hr of refluxing. [e] Analysis calculated for $C_8H_{10}N_6O_2S \cdot 0.25\ H_2O$. [f] Analysis calculated for $C_{14}H_{12}FN_5O_2S \cdot 0.25\ H_2O$.

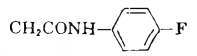
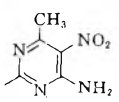
was further purified by solution in cold dilute potassium hydroxide and reprecipitation by acetic acid. The decomposition point was substantially unchanged.

2-Methyl[8-(β-hydroxyethyl)-mercaptohypoxanthine (XVI, R = CH_2CH_2OH). A solution of 1.82 g. (0.01 mole) of VII in a solution of 1.2 g. (0.022 mole) of potassium hydroxide in 30 ml. of water was stirred and cooled in ice. After the addition of 1 g. (0.0125 mole) of 2-chloroethanol, the mixture was vigorously stirred for 24 hr. at room temperature. The yellow solution was then treated with decolorizing carbon, filtered, and acidified with acetic acid. On standing in the refrigerator for 24 hr., 1.9 g. of yellow crystalline solid

TABLE II

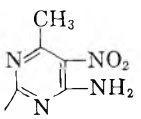
ULTRAVIOLET ABSORPTION SPECTRA OF SOME 8-SUBSTITUTED 2-METHYLPOXANTHINES



R	*p*H 1		*p*H 11	
	λmax., mμ	ε max.	λ max., mμ	ε max.
H	232	10,400	234	21,100
	289	25,200	291	21,500
CH_3	277	19,300	280	18,500
CH_2COOH	276	17,200	280	17,500
CH_2CH_2COOH	277	18,300	280	19,100
CH_2CH_2OH	277	18,700	280	18,400
CH_2COOCH_3	276	17,800	280	18,600
$CH_2COOC_2H_5$	276	17,500	280	18,500
$CH_2COOC_3H_7$-(*n*)	276	17,300	280	18,900
$CH_2COOC_3H_7$-(*i*)	276	17,500	280	18,100
$CH_2COOC_4H_9$-(*n*)	276	17,000	280	18,000
$CH_2COOC_4H_9$-(*i*)	277	18,000	280	18,800
$CH_2COOC_4H_9$-(*sec.*)	276	17,600	281	17,900
$CH_2COOC_5H_{11}$-(*n*)	277	17,700	280	18,300
$CH_2COOCH_2CH_2Cl$	271	19,400 (in methanol)		
$CH_2CONHNH_2$	276	17,500	279	17,100
	275	18,200	279	16,500
	230	17,600	232	31,300
	289	37,400	290	30,400
	297 (shoulder)	34,000	297 (shoulder)	28,300
			345	5,000

was collected. Solution in 150 ml. of boiling water and subsequent concentration to about 100 ml. gave, on cooling, 1.1 g. of yellow solid, which did not melt at 300°.

2-Methyl-8-[2'-(4'-amino-6'-methyl-5'-nitro)-pyrimidyl]-mercaptohypoxanthine (XVI R =



A solution of 0.96 g. (0.0051 mole) of 4-amino-2-chloro-6-methyl-5-nitropyrimidine in 30 ml. of absolute ethanol was added to an ice cold solution of 0.91 g. (0.005 mole) of VII in 50 ml. of aqueous 0.6% potassium hydroxide solution, and the mixture was vigorously stirred for 8 hr., the ice bath being removed after 1 hr. of stirring. The deep brown solution was left overnight at room temperature, then mixed with decolorizing carbon, filtered, and acidified with acetic acid, to give 0.9 g. of brownish yellow solid, which decomposed slowly above 300°. The material was purified by repeating the above process, to give pale yellow crystals (0.5 g.).

6-Hydroxy-2-methyl-8-purinylmercaptoacetic acid. (VIII). A mixture of 5.5 g. (0.03 mole) of VII, 3.0 g. (0.0317 mole) of chloroacetic acid and 5.1 g. (0.091 mole) of potassium hydroxide in 50 ml. water was heated under reflux for 2 hr. The solution was treated with decolorizing carbon and filtered. After acidification with acetic acid, 5.0 g. of light yellow crystalline granules separated on cooling. Reprecipitation from its solution in potassium hydroxide by acetic acid gave analytically pure material as a monohydrate. The acid showed infrared absorption bands at 970, 1210, 1590, and 1700 cm.$^{-1}$.

β-(6-Hydroxy-2-methyl-8-purinylmercapto)propionic acid. (IX). This was prepared by the same procedure as that used for VIII, except that β-chloropropionic acid was substituted for chloroacetic acid. The product (56%) was recrystallized first from dilute methanol and then from water to give cream-colored material. This substance showed infrared absorption bands at 970, 1200, 1600, and 1680 cm.$^{-1}$.

4-Hydroxy-2-methyl-6,7-dihydrothiazolo[2.3-f]purine-6-one. (X). A solution of 1.2 g. (0.005 mole) of the thioacid (VIII) in 30 ml. of acetic anhydride was heated under reflux for 30 min. The solvent was removed from the brown solid under reduced pressure. The residue was purified by reprecipitation from cold dilute aqueous potassium hydroxide by acetic acid. The yield of material, m.p. above 300°, was 1.0 g. The substance showed infrared absorption bands at 940, 1250, 1285, 1600, 1700, and 1870 cm.$^{-1}$ It gave analytical data corresponding to the retention of 1.75 moles of water of crystallization. The ultraviolet spectrum showed λ_{max} 276 mμ (ε 15,400) at pH 1 and λ_{max} 280 mμ (ε 17,100) at *p*H 11.

Anal. Calcd. for $C_8H_6N_4O_2S \cdot 1.75\ H_2O$: C, 37.86; H, 3.75; N, 22.08. Found: C, 37.53, 37.65; H, 3.83, 3.97; N, 22.35, 22.41.

4-Hydroxy-2-methyl-6,7-dihydro-1,3,6-thiazino[2.3-f]-purine-6-one (XI). This was prepared by the procedure used for X, except that refluxing was continued for 1 hr. The yield of white crystalline material, m.p. above 300°, was 78%. The substance showed infrared absorption bands at 960, 1250, 1280, 1580, 1650, 1700, and 1730 cm.$^{-1}$ The ultraviolet spectrum showed λ_{max} 276 mμ (ε 18,800) at *p*H 1 and λ_{max} 281 mμ (ε 19,000) at *p*H 11.

Anal. Calcd. for $C_9H_8N_4O_2S \cdot H_2O$: C, 42.51; H, 3.93; N, 22.04. Found: C, 42.35; H, 3.91; N, 22.34.

7-[p-Bis(β-chloroethyl)amino]benzylidene-4-hydroxy-2-methyl-6,7-dihydrothiazolo[2.3-f]purine-6-one (XIII). A mixture of crude X prepared from 2.4 g. (0.01 mole) of VIII, 2.5 g. (0.0102 mole) of XII and 15 ml. of glacial acetic acid was heated under reflux. The color changed from yellow to

brown within 5 min. After addition of 0.1 g. of fused potassium acetate, heating was continued with good stirring for 2 hr. The mixture was stirred at room temperature for an additional 12 hr. and poured into 250 ml. of anhydrous ether. The orange-yellow material (3.0 g.) which separated, was purified by solution in hot dimethylformamide and filtration of the solution into hot benzene. After cooling, addition of ether gave 1.3 g. of product, m.p. above 300°. The ultraviolet spectrum showed λ_{max} 270 mμ (ε 11,300) in dimethylformamide.

Anal. Calcd. for $C_{10}H_{17}Cl_2N_5O_2S$: C, 50.66; H, 3.77; N, 15.55. Found: C, 50.87; H, 3.97; N, 15.42.

2,6-Dimethyl-4-hydroxythiazolo[2,3-f]purine (XV). A mixture of 1.8 g. (0.01 mole) of VII, 1.2 g. (0.013 mole) of chloroacetone and 200 ml. of absolute ethanol was refluxed for 5 days. After 24 hr. an additional 1.2 g. of chloroacetone was added. The precipitate was filtered from the hot mixture and dissolved in cold dilute potassium hydroxide solution. After filtering from a small amount of insoluble material, acidification of the filtrate with acetic acid gave 1.75 g. of white crystalline material. After recrystallization by concentration of its solution in 500 ml. of ethanol to about half its volume, the substance formed fibrous crystals, m.p. above 300°. The ultraviolet spectrum showed λ_{max} 241 mμ (ε 20,300) and a shoulder at 272 mμ (ε 12,100) at *p*H 1; λ_{max} 242 mμ (ε 27,100) and λ_{max} 271 mμ (ε 12,600) at *p*H 11.

Ethyl 6-hydroxy-2-methyl-8-purinylmercaptoacetate (XVI), R = $CH_2COOC_2H_5$). A. A mixture of 1.8 g. (0.01 mole) of VII, 5.0 g. of ethyl chloroacetate and 200 ml. of 95% ethanol was heated under reflux with stirring for 65 hr. The resulting clear solution was filtered from a small amount of impurities and concentrated to about 50 ml. on the steam bath. Dilution of the hot concentrate with hot water and cooling gave crystalline material. After purification by solution in methanol, dilution and distillation of the methanol, 0.5 g. of fine needles, m.p. 233–235° (dec.), was obtained.

When ethyl bromoacetate was substituted for ethyl chloroacetate, a clear solution (indicating complete reaction) was obtained after refluxing for 3 hr.

B. A mixture of 1.82 g. (0.01 mole) of VII, 2.0 g. (0.014 mole) of bromoacetic acid and 110 ml. of 95% ethanol was heated under reflux with stirring. After 16 hr., a clear brown solution resulted, from which 1.5 g. of XVI (R = $CH_2COOC_2H_5$) was isolated.

The other esters of 6-hydroxy-2-methylpurine-8-thioacetic acid were prepared by method B, using the appropriate alcohol as solvent. Melting points and analytical data are given in Table I. All the acetates showed characteristic infrared absorption peaks at 1160–1190 and 1720–1750 cm.$^{-1}$

6-Hydroxy-2-methyl-8-purinylmercaptoacet-p-fluoroanilide. [XVI, R = $CH_2CONHC_6H_4F$-(*p*)]. A mixture of 2.4 g. (0.01 mole) of VIII, 10 ml. of benzene, and 10 ml. of *p*-fluoroaniline was heated under reflux with stirring, using a water separator, for 24 hr. The deep brown mixture was cooled, diluted with methanol and filtered to give 2.1 g. of nearly white solid, which did not melt at 300°. The solid was dissolved in one l. of boiling water, filtered and concentrated to about 250 ml. On cooling 1.1 g. of white solid, m.p. above 300°, separated.

6-Hydroxy-2-methyl-8-purinylmercaptoacethydrazide. (XVI, R = $CH_2CONHNH_2$). A solution of 1.0 g. of 95% hydrazine hydrate in 10 ml. of ethanol was added to a solution of 0.74 g. (0.0025 mole) of XVI (R = $CH_2COOCH_2CH_2CH_2CH_3$) in 20 ml. ethanol. The mixture was heated under reflux for about 1.5 hr. The mixture was refrigerated for 12 hr. and the white precipitate (0.6 g.) filtered. It was purified by solution in cold dilute potassium hydroxide and reprecipitation by acetic acid. The cream-colored solid did not melt until 300°.

Acknowledgment. We acknowledge the valuable assistance of James Hudson in the preparation of certain of the intermediates used in this work.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, PUREX CORPORATION, LTD.]

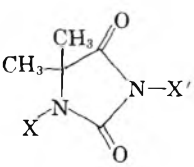
N-Halogen Compounds. I. Decomposition of 1,3-Dichloro-5,5-dimethylhydantoin in Water at *p*H 9[1]

ROBERT C. PETTERSON AND URSZULA GRZESKOWIAK

Received March 9, 1959

When 1,3-dichloro-5,5-dimethylhydantoin(I) dissolved in water at *p*H 9, it decomposed rapidly and completely; 1-chloro-5,5-dimethylhydantoin(IIIa), *N*-chloroisopropylamine(IV), chloride ion, nitrogen, and carbon dioxide were the major products. Nitrogen chloride was a transient intermediate. *N*-chloro-α-aminoisobutyric acid (VIII) was shown to give mainly acetone, and not more than 12% of IV, on decomposition at *p*H 9, which excludes it as an intermediate. All known monochloro-5,5-dimethylhydantoins proved to be identical and are assigned the 1-chloro structure.

1,3-dichloro-5,5-dimethylhydantoin(I) is one of a number of *N*-halogen compounds under study in this laboratory with regard to their utility in powdered bleaching and disinfecting compositions. While several studies[2,3] of the hydrolysis of hydantoins in alkaline solutions have been made, none has dealt with *N*-chloro derivatives except that of Biltz and Behrens[3] who made a few observations on 1,3-dichloro-5,5-diphenylhydantoin(V).



I. X = X′ = Cl
II. X = X′ = H
IIIa. X = Cl, X′ = H
IIIb. X = H, X′ = Cl

It has commonly been assumed that weakly alkaline solutions of I, which are of interest for bleaching fabrics, contain only I and products resulting from hydrolysis of the N—Cl bonds,

(1) Presented in part before the Organic Division at the New York Meeting of the American Chemical Society, September 1957.

(2) C. K. Ingold, S. Sako, and J. F. Thorpe, *J. Chem. Soc.*, **121**, 1177 (1922); L. A. Cohen and E. M. Fry, *J. Am. Chem. Soc.*, **78**, 5863 (1956).

(3) H. Biltz and O. Behrens, *Ber.*, **43**, 1984 (1910).

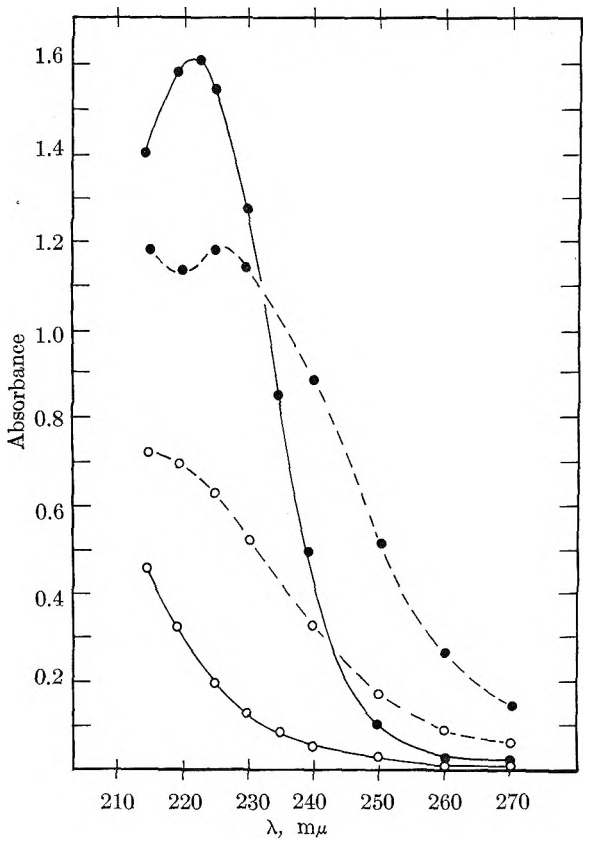


Fig. 1. Ultraviolet spectra of 2.5 × $10^{-4}M$ solutions of 1-chloro-5,5-dimethylhydantoin (- - - -) and 5,5-dimethylhydantoin (———) in water (○) and in 0.01 N sodium hydroxide (●).

particularly hypochlorite ions. The present investigation commenced with the observation that large losses of active chlorine occurred rapidly when I was dissolved in water at pH 9.[4] The disappearance of active chlorine during the first hour at room temperature was found to vary greatly over the pH range of 3.2 to 12.7, being small at the extremes but reaching 50 to 60% in the region of pH 8 to 9 for 5 × $10^{-3}M$ solutions. The initial fast reaction near pH 9 was followed by a much slower decomposition which we have not investigated in detail. We have concentrated on identifying the major products of the initial reaction and estimating the amounts of them present, under one set of conditions. Unless otherwise noted the following discussion refers to the reaction of finely ground I with water at pH 9 (borate buffer) in the ratio of 1.97 g./1.($10^{-2}M$) at room temperature over a 3.5-hr. period.

Depending on the degree of agitation, between 0.25 and 3.5 hr. elapsed before a clear solution was obtained; most of the decomposition seemed to occur during the process of dissolution. About 50% of the iodometrically titratable chlorine disappeared, and 2.5 moles of base was consumed by the time the solution became clear. The lachrymatory odor of nitrogen trichloride was observed while the solid was dissolving, and its identity was confirmed by the ultraviolet spectra of solutions of the vapors. Nitrogen trichloride is unstable at pH 9, decomposing to nitrogen and hypochlorite and chloride ions.[5] By the time a clear solution was obtained nitrogen trichloride was no longer detectable.

A slowly stirred solution evolved 15% of the total nitrogen in the form of nitrogen gas in 3.5 hr., and another 10% in 5 weeks. At least part of this nitrogen presumably arose *via* nitrogen trichloride, little of which could escape under these conditions. The inactive chlorine after 3.5 hr. was all present as chloride ion, within experimental error. Carbon dioxide was present as carbonic acid ions.

The most puzzling phenomena associated with the decomposition of I at pH 9 were a peculiar pyridine-like odor found over the solutions after disappearance of all of the solid and the presence of bands near 2900, 1440, and 1370 cm.$^{-1}$ in the infrared spectrum of carbon tetrachloride solutions of the volatile components of these solutions. The responsible compound was finally isolated in a special experiment by distillation from a highly concentrated solution as a colorless, unstable, lachrymatory oil. This was proved to be the hitherto unknown N-chloroisopropylamine(IV) on the basis of: (i) iodometric chlorine determinations; (ii) elemental analysis; (iii) molecular refraction; (iv) decomposition in both acid and alkali to acetone and ammonia, with reduction of the (weakly) active chlorine atom; and (v) infrared absorption bands (see Experimental). Determination of the amount of volatile active chlorine, which seems to be due entirely to IV in the ordinary 3,5 hr.-old solutions, indicated that about 36% of I was degraded to IV. Limited attempts to prepare IV by conventional methods[6] were not successful.

The major product (63% yield), and the only nonvolatile active chlorine compound found present at 3.5 hr., was an N-monochloro-5,5-dimethylhydantoin(III), m.p. 145°. It was isolated quantitatively in almost pure form by extraction of an acidified solution with chloroform.

We could not determine from the literature whether III was the 1-chloro (IIIa) or 3-chloro (IIIb) derivative, or even if two different monochloro isomers were known. Rogers[7] described one, melting at 144–145° obtained by chlorination of 5,5-dimethylhydantoin(II), while Magill[8] obtained a monochloro compound, for which he reported m.p. 149–150°, by equilibrating an equimolar mixture of I and II. In our hands both procedures afforded good yields of the same

(4) We are indebted to Mr. Charles P. McClain, who first observed this, for pointing it out to us.

(5) R. M. Chapin, *J. Am. Chem. Soc.*, **53**, 912 (1931).

(6) A. Berg, *Ann. chim. et phys.*, [7] 3, 289 (1894).

(7) A. O. Rogers, U. S. Patent **2,392,505**, Jan. 8, 1946.

(8) P. LaF. Magill, U. S. Patent **2,430,233**, Nov. 4, 1947.

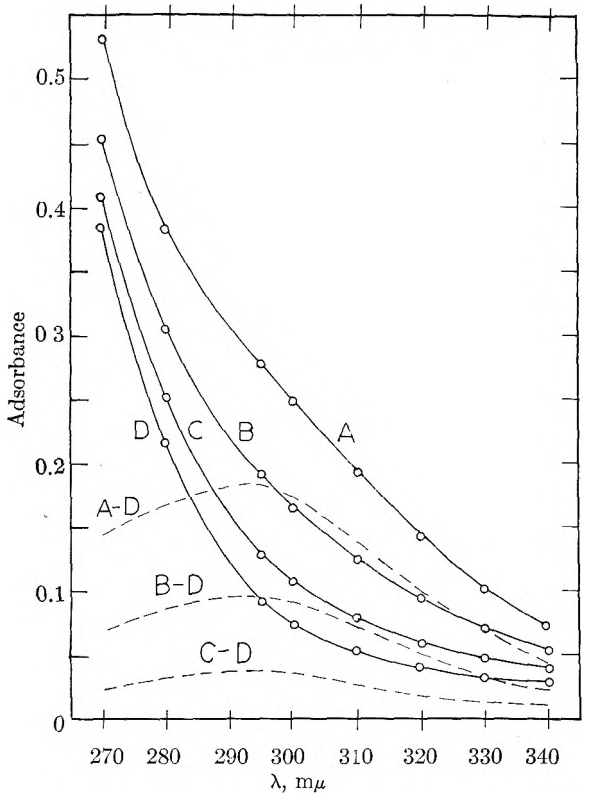


Fig. 2. Ultraviolet spectrum of a $10^{-3}M$ solution of 1,3-dichloro-5,5-dimethylhydantoin after: *A*, 15; *B*, 45; *C*, 75, and, *D*, 165 to 195 min. Dashed lines show result of subtracting curve *D* from curves *A*, *B*, and *C*.

product, m.p. 145°; identity with each other, and with our decomposition product, was established by mixture melting points, and by comparisons of their infrared and ultraviolet spectra.

The available evidence favors structure IIIa. The compound is a very strong acid for a hydantoin, since about one equivalent of sodium hydroxide is required to raise the *p*H of its solutions to 9; imides are generally more acidic than secondary amides. The ultraviolet spectrum of an aqueous solution of III showed a large bathochromic shift with increasing *p*H (see Fig. 1). Stuckey[9] has shown this to be characteristic of hydantoins having an unsubstituted imide group (*e.g.*, II). An aqueous solution of III at *p*H 9 slowly lost active chlorine, and *N*-chloroisopropylamine(IV) was one of the decomposition products; this is most simply explained if the chlorine of III is on the 1-position. We conclude that the monochloro compound is 1-chloro-5,5-dimethylhydantoin(IIIa), and that the 3-chloro isomer IIIb has never been described.[10]

Of particular interest was the seeming absence of hypochlorite ion, which we could not detect in $10^{-2}M$ solutions, although it would be expected to form by hydrolysis of I as well as by decomposition of nitrogen chloride. Certainly there can have been little of it at 3.5 hr. since the active chlorine remaining is fairly well accounted for as either IIIa or IV. Tests for chlorate ion and oxygen gas, products of its spontaneous decomposition,[11] were negative. Because of the importance of hypochlorite in bleaching, a search for it was made under varied conditions. No proof that it was formed in $10^{-2}M$ solutions was found but some evidence for its presence as a transitory intermediate was obtained when the concentration of I was reduced to $10^{-3}M$. Subtraction of the ultraviolet absorption spectrum of a 2.75 hr.-old solution from that of fresher solutions gave difference curves characteristic of the hypochlorite ion (λ_{max} 292 mμ, see Fig. 2) accounting, however, for not more than 25% of the total active chlorine. The 292 mμ peak in the difference curve disappeared rapidly and was entirely absent in 2.75 hr. The spectra of solutions of I made at *p*H 10 and at *p*H 13 both showed a well-defined shoulder in the 290 mμ region which suggests that more hypochlorite is formed at higher *p*H's. Biltz and Behrens[3] believed, probably correctly, that 1,3-dichloro-5,5-diphenylhydantoin(V) hydrolyzed to the 1-chloro derivative and hypochlorite in dilute alkali, because they were able to recover much of the original V on acidification. In a similar experiment we recovered 65% of I on acidification of a 3% solution made from I and 1*N* sodium hydroxide. However, no I separated when a solution made at *p*H 9 was acidified, which correlates with the essential absence of hypochlorite at *p*H 9 in all but very dilute solutions.

Evidently at least two competing reactions, differently affected by *p*H, are involved here. In one, which predominates in highly alkaline solution, the dichloro compound I simply hydrolyzes to the 1-chloro derivative IIIa and hypochlorous acid. Both products will be completely ionized at high *p*H, and the ionized form of IIIa is probably relatively resistant to ring cleavage.[12]

The ring cleavage reaction is important in the neighborhood of *p*H 9. There can be little doubt that some hypochlorite is always formed from I in aqueous solution, but when conditions are such that ring cleavage occurs, the hypochlorite is rapidly reduced to chloride in oxidizing the resulting hydrolysis products to molecular nitrogen and probably other products.

One of the intermediate hydrolysis products may be chloramide, NH_2Cl, which was not detected but is known[13] to be oxidized by hypochlorite to the observed NCl_3.

(9) R. E. Stuckey, *J. Chem. Soc.*, 331 (1947).

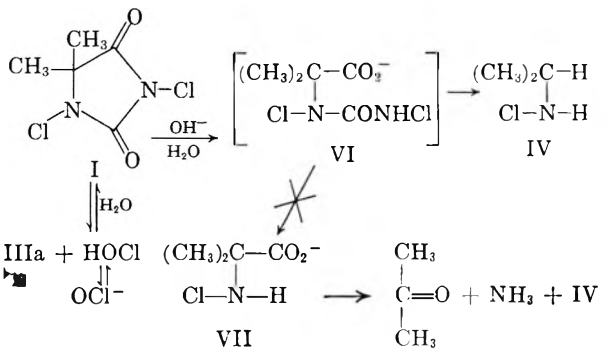
(10) A sample of "3-chloro-5,5-dimethylhydantoin" purchased from Bios Laboratories proved to be identical with our 1-chloro compound IIIa. C. G. Kamin mentioned the 3-chloro isomer IIIb in his U. S. Patent **2,441,360**, May 11, 1948, but gave no properties; IIIa was probably meant.

(11) M. W. Lister, *Can. J. Chem.*, **34**, 465 (1956).

(12) J. T. Edward and K. A. Terry, *J. Chem. Soc.*, 3527 (1957), have shown that succinimide and diacetylamine are probably cleaved by attack of hydroxide ion on the unionized forms of the imides.

(13) W. Marckwald and M. Wille, *Ber.*, **56**, 1319 (1923).

One possible mechanism for the formation of *N*-chloroisopropylamine from I was tested and found wanting. Hydrolytic cleavage of I in the normal[2] manner would give the chlorinated hydantoic acid VI, which might either decarboxylate or lose its —CONHCl group to form *N*-chloro-α-aminoisobutyric acid (VII). The latter possibility could be checked by finding out if VII would decarboxylate cleanly to IV at *p*H 9 and room temperature. VII has never been isolated but is almost certainly formed when equimolar amounts of α-aminoisobutyric acid and sodium hypochlorite react. Under the vigorous conditions used by Langheld[14] the product isolated from this reaction was acetone (75% yield), which is believed to have resulted from loss of chloride ion and carbon dioxide by VII, followed by hydrolysis of the isopropylidenimine thus formed. It was conceivable, however, that VII might be stable or decompose primarily to IV under our milder conditions. To test this possibility, buffered solutions of the amino acid and hypochlorite were mixed at room temperature to form a $10^{-2}M$ solution of VII at *p*H 9. The active chlorine content of the mixture fell to 12% of its original value in 1 hr., then continued to decrease at a much slower



rate. During the first hour the formation and decomposition of VII was apparently complete, and the surviving 12% of the active chlorine was probably all in the form of *N*-chloroisopropylamine, which was qualitatively identified. In any case, not more than 12% of VII can have gone to IV. However, the major product (70–88%) was acetone as in Langheld's work. Since acetone was not found among the decomposition products of I, *N*-chloro-α-aminoisobutyric acid is not an important intermediate in the decomposition of I to IV. Since it has been shown that VII can decarboxylate to IV it is likely that VI, which has an even more electronegative group *alpha* to the carboxyl group, would decarboxylate under these conditions.

A consequence of the rapid decomposition rate of I in alkaline solution is that stained cloth is bleached more effectively if the cloth is immersed in the bath before a formulation containing I is added than if the cloth is added to a solution made from I.

(14) K. Langheld, *Ber.*, **42**, 2360 (1909).

An investigation of the decomposition of di- and trichloroisocyanuric acids under similar conditions is in progress. These *N*-chloroimides have been found to undergo a similar ring cleavage reaction, albeit much more slowly than I, yielding finally cyanuric acid, nitrogen, chloride ion, and carbon dioxide; hypochlorite ion and nitrogen chloride are intermediates.

EXPERIMENTAL[15]

Decomposition of I *at pH 9. General method.* The 1,3-dichloro-5,5-dimethylhydantoin (I) used in this work was recrystallized from ethylene chloride and melted at 132° (lit.[16] 132°).

Anal. Calcd. for $C_5H_6Cl_2N_2O_2$: Active Cl, 35.99. Found: Active Cl, 35.99.

Except where noted, decomposition experiments were conducted by mixing finely ground I with an aqueous *p*H 9 buffer solution (made by adding about 2.14 l. of 0.5*M* sodium hydroxide to 5 l. of 0.5*M* boric acid solution) in the ratio of 1.97 g. of I per liter. The mixture was stirred at room temperature (23 ± 2°) for about 3.5 hr., the solid dissolving in from 15 min. to 3.5 hr. depending on the amount of agitation. An initial rapid reaction involving reduction of some 50% of the active chlorine, and evolution of a gas with a lachrymatory odor, occurred during the dissolution. The nature of this decomposition was apparently little affected by the rate of dissolution (agitation). Most measurements were made at 3.5 hr. for convenience. Where buffer salts would interfere with product determinations, distilled water was used and the *p*H was held near 9 (*p*H meter) by continually adding sodium hydroxide solution, about 2.5 equivalents of base being required for the fast stage of the decomposition.

The decomposition products. Nitrogen trichloride. A solution of nitrogen trichloride in chloroform was obtained by passing nitrogen gas through an aqueous solution of NCl_3 made from sodium hypochlorite by Chapin's method (a),[5] then through concentrated sulfuric acid, and finally into chloroform. Its ultraviolet spectrum closely resembled that of an aqueous solution[17] in general shape with λ_{max} at 342 and λ_{min} at 310 mμ.

Nitrogen was passed through a mixture of I (1.97 g.) and buffer solution (1 l.) and then through chloroform during the time needed for complete dissolution; the resulting chloroform solution of the volatile decomposition products was indistinguishable from that of the afore-described NCl_3 solution in the 260–365 mμ region and had very strong absorption below 260 mμ. The solution contained 8% of the initial active chlorine.

Nitrogen. A flask was filled to the top with a mixture of I (1.97 g.) and borate buffer (1030 ml.), and quickly connected through a water-filled capillary to a gas burette containing water. Under mild agitation the solid dissolved during 3.5 hr. and 33.9 ml. of gas was evolved. Its volume was not detectably changed by contact with alkaline pyrogallol, acidified potassium iodide, or ammoniacal cuprous chloride; thus the gas contained no oxygen, chloroamines, or carbon monoxide, and is presumed to have been nitrogen. The yield

(15) Melting points are uncorrected. Elemental analyses, except for active chlorine, were done by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif. A Beckman Model DU spectrophotometer was used for the ultraviolet spectra; the infrared spectra were run by Mr. Everett Honorof on a Perkin-Elmer Model 21 spectrometer (sodium chloride prism).

(16) H. Biltz and K. Slotta, *J. prakt. Chem.*, **113**, 233 (1926).

(17) W. S. Metcalf, *J. Chem. Soc.*, 148 (1942).

was 15.1% of the total nitrogen of I; in a similar experiment lasting 5 weeks the yield increased only to 25%.

Chloride ion. In another run with 1.97 g. of I/l., in which only weak agitation was employed, a 50 ml. aliquot was removed after 3.5 hr., acidified with nitric acid, and treated with excess silver nitrate. The silver chloride (72.3 mg.) which separated contained 50.4% of the total chlorine. Iodometric titration of another aliquot showed that 49.7% of the chlorine was still active. A $10^{-2}M$ solution of 1-chloro-5,5-dimethylhydantoin (IIIa) in the same buffer gave no precipitate when treated the same way.

Carbon dioxide. Qualitative identification was made on an unbuffered solution which had been held at *p*H 9 for 3.5 hr. by additions of sodium hydroxide. The colorless precipitate which separated when excess barium hydroxide solution was added was crude barium carbonate.

Anal. Calcd. for $BaCO_3$: Neut. equiv., 99. Found: neut. equiv., 101.

A 100 ml. portion of a similar solution, aged 5 weeks, was acidified with dilute sulfuric acid and heated to boiling while a stream of air was passed through it. The air was led into barium hydroxide solution where 0.1538 g. (39%, based on both C=O groups) of barium carbonate was formed.

N-Chloroisopropylamine (IV). Passing nitrogen gas through solutions made from I at any time after the disappearance of the initial nitrogen trichloride odor removed a volatile substance containing active chlorine which could be absorbed in organic solvents; such solutions exhibited absorption bands at $\lambda_{max}^{2,2,4\text{-trimethylpentane}}$ 212 mμ.

The compound responsible was isolated in a special experiment in which a mixture of I (100 g.) and water (2 l.) was maintained near *p*H 9 by additions of sodium hydroxide until the solid disappeared (several hours). After 24 hr. at room temperature the solution (still at *p*H 9) was transferred to a simple distillation apparatus equipped with a cold finger containing a Dry Ice–acetone mixture. When the pot was warmed to 30° and the pressure reduced to 30 mm. a mixture of an oil and ice collected on the cold finger. Crude *N*-chloroisopropylamine separated as a colorless oil (yield, 23%, calcd. from active Cl) when the sludge melted. Nearly all of the dried (sodium sulfate, −5°, overnight) oil distilled through a short column at 33.5° (33.5 mm.) to give pure IV, a colorless oil with a pungent lachrymatory odor, n_D^{25} 1.4468, d_4^{25} 1.019, $\lambda_{max}^{2,2,4\text{-trimethylpentane}}$ 212 mμ (log ε, 3.24). The infrared spectrum of the pure liquid showed bands at 2990, 2960, 2910, and 2860 m (NH, CH), 1630 and 1615 (N—H), 1430 and 1360 (CH_3) and at 2720 vw, 2610 w, 2415 vw, 2300 vw, 2190 vw, 1235, 1144 w, 1115, 1078, 1058, 960 w, 816, 759 w, 695, and 665 cm.$^{-1}$

Anal. Calcd. for C_3H_8ClN: C, 38.51; H, 8.62; N, 14.97; Active Cl, 37.90; MR_D, 24.34. Found: C, 38.52; H, 8.62; N, 14.65; Active Cl, 37.74; MR_D, 24.53. The active chlorine analysis was done iodometrically on a *t*-butyl alcohol solution of IV.

The conversion of I to IV in a $10^{-2}M$ solution of I in 3.5 hr. was at least 25%, on the basis of the absorption at 212 mμ of a 2,2,4-trimethylpentane solution of the IV which could be blown out of the reaction mixture by an air stream. It was probably closer to 36%, estimated from the loss in active chlorine contents of a portion of the reaction mixture during rapid evaporation nearly to dryness *in vacuo* (rotating evaporator at 30°). The higher figure requires the reasonable assumption that IV was the only volatile active chlorine compound present in the solution.

Pure IV, stored over anhydrous sodium sulfate at −5°, lost about 1% of its active Cl in 12 days. A $3 \times 10^{-3}M$ solution buffered at *p*H 9 for 39 days at room temperature in an amber flask, lost 33% of its active chlorine.

Hydrolysis of IV *to acetone and ammonia.* Attempts were made to reduce IV to isopropylamine by (a) treating IV (3 g.) with granular zinc (3 g.) and concentrated hydrochloric acid (25 ml.) for 5 hr., and (b) letting a mixture of IV (5 g.) and an excess of 0.25*N* sodium arsenite solution buffered with sodium bicarbonate stand at 25° for 36 days. In both cases, when the resulting solutions were made strongly alkaline with sodium hydroxide and distilled the products were acetone, identified as its 2,4-dinitrophenylhydrazone, m.p. 124–125°, and ammonia (benzoyl derivative, m.p. 126–127°), which was apparently the only amine present.

When a carbon tetrachloride solution of IV was shaken with 50% hydrochloric acid, and allowed to stand for 24 hr., the organic layer developed a yellow color and very pungent lachrymatory odor, probably of *N,N*-dichloroisopropylamine,[18] while the aqueous layer proved to contain ammonia and acetone.

1-Chloro-5,5-dimethylhydantoin (IIIa). After 3.5 hr. a 200 ml. aliquot of a solution made from I in the usual manner was acidified with dilute sulfuric acid and extracted several times with 25-ml. portions of chloroform. Evaporation of the washed and dried (sodium sulfate) extracts gave 0.202 g. of colorless solid IIIa, m.p. 139–144°, yield, 63%. After a crystallization from ethylene chloride, the 1-chloro compound was pure, m.p. 144.5–145.0°, and showed absorption bands (Nujol) at 3230, 3080 m, 2703 w, 1778, 1740, 1350, 1296 m, 1137 w, 1086 m, 1078 m, 1048 w, 934 m, 795 w, 760 m and 663 m cm.$^{-1}$, and λ_{max} (0.01*N* NaOH) 228 mμ (log ε, 3.67). See Fig. 1.

Anal. Calcd. for $C_5H_7ClN_2O_2$: Active Cl, 21.81. Found: Active Cl, 22.00.

II (12.8 g.) was chlorinated by Rogers method,[7] yielding 12.0 g. (74%) of IIIa, m.p. 143–144°. Using a more convenient method of Magill,[8] II (13.4 g.) and I (19.7 g.) were stirred in 100 ml. of water at room temperature for 4 hr. to yield 30 g. (92%) of IIIa, m.p. 144.5–145.5°. Magill reported an 88% yield, m.p. 149–150°. Both of these products, on crystallization from ethylene chloride, melted sharply at 145°. The ultraviolet and infrared spectra of samples of IIIa obtained by all methods were identical and their melting points were not depressed by admixture with each other. When 0.1626 g. of IIIa (10^{-3} mole) was dissolved in 250 ml. of water, brought to *p*H 9 with 0.1*N* sodium hydroxide, and maintained at that *p*H for 2 hr., 10.3 ml. of the base was required; however, the active chlorine content decreased to 97.5% of its original value in the process.

When 2 g. of IIIa was dissolved in 500 ml. of buffer solution at *p*H 9 and allowed to stand at room temperature for 72 hr., *N*-chloroisopropylamine was formed. It was identified by its odor, and by the ultraviolet spectrum (λ_{max} 212 mμ) of the vapors blown out of the solution and collected in 2,2,4-trimethylpentane. Several aliquots were removed from a solution of IIIa (0.1702 g.) in borate buffer (250 ml.) kept at *p*H 9 and room temperature, and titrated for active chlorine. The cumulative losses of active chlorine at 1, 3, 5, 22, 46, and 92 hr. were respectively 1.8, 4.7, 6.3, 16.2, 18.8, and 46.7% of the original.

Evidence for hypochlorite. The ultraviolet spectrum of a $10^{-3}M$ solution of I in borate buffer (*p*H 9) was determined as soon as possible (about 15 min. after the solid I was added to the buffer), and again at intervals up to 3.25 hr. Subtraction of the absorbance at 2.75 hr. (when changes had ceased) from earlier values gave difference curves resembling the spectrum of hypochlorite ion[19] (see Fig. 2). The magnitude of the difference at 295 mμ corresponds to a hypochlorite ion concentration of not over $5 \times 10^{-4}M$ in the freshest solution measured, decreasing to zero by 2.75 hr. Useful difference curves were not obtained with $10^{-2}M$ solutions of I; these required 30 min. to become clear, after which time only a small decrease in absorption with time could be observed.

When a fresh solution of I (3 g.) in 1*N* sodium hydroxide (100 ml.) was acidified with 10*N* sulfuric acid, 65% of the

(18) L. K. Jackson, G. N. R. Smart, and G. F Wright, *J. Am. Chem. Soc.*, 69, 1539 (1947).

(19) H. L. Friedman, *J. Chem. Phys.*, 21, 319 (1953).

starting material was recovered as a colorless precipitate, m.p. and mixed m.p. 130–131°.

Reaction of α-aminoisobutyric acid with sodium hypochlorite. The ultraviolet spectrum of a mixture made by adding a sodium hypochlorite solution to a suspension of α-aminoisobutyric acid in water at 15° had a strong absorption maximum at 266 mμ, suggesting that acetone had been formed. The mixture was distilled in the manner described in the section on *N*-chloroisopropylamine, and the infrared spectrum of a dried carbon tetrachloride extract of the distillate was examined in a 0.1 mm. cell. The spectrum was exactly that expected of a mixture of *N*-chloroisopropylamine and acetone in this solvent. Bands characteristic of IV only were found at 2900 m, 2830 w, 1635 m, 1618 m, 1236, 1075 m, 1054 m, and 699 vs cm.$^{-1}$, acetone bands were at 1720 vs, 1218 vs, 1089 w, and 897 w cm.$^{-1}$, and bands due to both compounds appeared at 2980 m, 2940 m, 1436, and 1360 vs cm.$^{-1}$

To a stirred solution of α-aminoisobutyric acid (1.08 g., 1.05×10^{-2} mole) in 500 ml. of 0.25*M* borate buffer (*p*H 9) was added dropwise (15 min.) a solution of sodium hypochlorite (0.745 g., 10^{-2} mole) in 500 ml. of 0.25*M* borate buffer at 23°. The clear solution, which had an odor of *N*-chloroisopropylamine, was allowed to stand at room temperature and aliquot portions were titrated iodometrically. After 5, 31, and 55 min., 2.5, 15, and 39 hr. there remained 36, 16, 12.8, 11.5, 11.0, and 8.9% respectively of the original active chlorine. The ultraviolet spectrum of the reaction mixture after 23 hr. exhibited strong absorption below 240 mμ, presumably due to IV and the slight excess of α-aminoisobutyric acid used, and a well-defined shoulder (λ_{max} 260, λ_{min} 247 mμ) ending at 305 mμ, above which the solution was transparent. The shoulder must be caused by acetone (lit.[20] $\lambda_{max}^{0.04M}$ 264 mμ, ϵ = 18.8); its concentration may be estimated very roughly from the absorbance at 260 mμ (0.14) to be in the neighborhood of $7.5 \times 10^{-3}M$ (75% yield). The conversion to IV in the first hour cannot have been more than about 12%, while that to acetone may have been 88% and was probably at least 70%. No indication of hypochlorite was found in the spectrum. During the first hour portions of the reaction mixture oxidized potassium iodide to iodine at *p*H 9, which hypochlorite will do, but after 1 hr., did not give iodine until acidified, which is typical of very weak oxidizing agents, including IV.

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(20) F. O. Rice, *J. Am. Chem. Soc.*, **42**, 731 (1920).

[CONTRIBUTION FROM SOUTHERN REGIONAL RESEARCH LABORATORY,[1] UNITED STATES DEPARTMENT OF AGRICULTURE]

N-Methyl Amides of Phosphorus(V) Acids[2]

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A number of *N*-methyl amides of phosphorus (V) acids, have been prepared and characterized. Reactions involving thermal deamination and salt formation were studied on some of the compounds.

In the research conducted at the Southern Regional Research Laboratory leading to the development of flame-retardant finishes for cotton textiles, one phase of the work was directed toward the practical use of amides of phosphorus(V) acids. This report deals with the preparation and properties of some *N*-methyl amides of the acids which were studied during the course of this investigation. Most of the compounds have not been reported previously.

In general the amides were prepared by the addition of the acid chloride of a phosphoric or phosphonic acid to an excess of methylamine in inert solvent at reduced temperature under anhydrous conditions. The amine served also as an acid acceptor. The properties of the *N*-methyl amides which were prepared are shown in Table I. With the exception of *N,N'*-dimethyl-*P*-trichloromethylphosphonic diamide and *N,N',N''*-trimethylphosphorothionic triamide all of the amides are very soluble in water. Michaelis[4] has reported that the imido derivatives of phosphorothionic triamides have better organic solubility than the corresponding oxygen analogs. The same solubility relationship was found to hold for the sulfur-oxygen analogs examined in this investigation.

Michaelis[4] described the synthesis of *N,N'*-disubstituted phosphoramidic imides, with the structure RHNP(O):NR, by the thermal decomposition of trisubstituted phosphoramides. These compounds were reported as being monomeric when the substituents are alkyl groups and dimeric when the substituents are aryl groups. The thionic analogs were reported to be monomeric also.

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) This is a report on one phase of a program of research on the flame-resistant treatment of cotton textiles, being supported at the Southern Utilization Research and Development Division by funds supplied by the Air Research and Development Command, United States Air Force and conducted under the general supervision of the Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

(3) J. R. Geigy A.-G., Brit. Patent **790,663**, Feb. 12, 1958.

(4) A. Michaelis, *Ann.*, **407**, 290 (1915).

TABLE I

N-METHYL AMIDES OF PHOSPHORUS(V) ACIDS

Formula	Yield, %	B.P. at 3 mm.	M.P.	n_D^{25}	Analysis % N Calcd.	N Found	P Calcd.	P Found	Other Element	Other Calcd.	Other Found
$C_2H_5OP(O)(NHCH_3)_2$	40	132–6[a]	...	1.4489	18.4	18.4	20.4	20.2	....	..	..
$P(O)(NHCH_3)_3$[b]	66	..	102–3	..	30.6	30.0	22.6	23.0	....	..	..
$P(S)(NHCH_3)_3$	87	..	105–7	..	27.4	27.1	20.2	20.2	Sulfur	20.9	20.7
$P(O)[N(CH_3)_2]_2NHCH_3$	47	137–43	...	1.4551	25.4	24.9	..	..	....	..	..
$CCl_3P(O)(NHCH_3)_2$	38	..	133–5	..	12.4	12.3	13.8	13.6	Chlorine	47.2	47.2
$[(CH_3)_2NP(O)NCH_3]_2$[c]	..	..	168–170	..	23.3	22.8	25.8	23.8	....	..	..
$[CH_3HNP(S)NCH_3]_2$	95	..	220–5	..	22.9	22.6	25.4	25.5	Sulfur	26.2	26.5
$(C_2H_5O)_2P(O)NCH_3$-O-(CH_2CHCH_2)	40	118–9	...	1.4365	6.3	6.0	13.9	13.3			

[a] Lit.[3] B.p. 110–111 at 0.005 mm. [b] Previously reported as a liquid.[3] [c] Product formed during distillation of $P(O)[N(CH_3)_2]_2NHCH_3$.

In this investigation, it was found that thermal deamination occurred when no less than two amido groups, at least one of which is not completely substituted, are attached to the phosphorus. In no case, however, was a monomeric product isolated. *N,N',N''*-Trimethylphosphoric triamide yielded a resinous product with higher than dimeric molecular weight, presumably a polymer. Ethyl *N,N'*-dimethylphosphorodiamidate also yielded a resinous product. Diethyl *N*-methylphosphoramidate did not deaminate below 250°.

Pentamethylphosphoric triamide was partially deaminated on distillation. The crystalline "imide" formed was dimeric.

N,N',N''-Trimethyphosphorothionic triamide also gave, on thermal deamination, a crystalline "imide" which had a dimeric molecular weight.

It has been reported by Arbuzov, Alimov, and Zvereva[5] that sodium salts can be formed from the *N*-methyl amides of phosphorus (V) acids by reaction of the amide with metallic sodium. Diethyl *N*-methyl-*N*-(2,3-epoxypropyl) phosphoramidate was prepared by treating the sodium salt of diethyl *N*-methylphosphoramidate with epichlorohydrin. An attempt was made to prepare the *N,N'*-bis(2,3-epoxypropyl) derivative of ethyl *N,N'*-dimethylphosphorodiamidate by a similar procedure. Sodium, however, would react with the diamidate only in equimolar quantities. Epichlorohydrin reacted with the monosodium salt to yield a product containing epoxy groups. The product could not be purified but is believed to be crude ethyl *N,N'*-dimethyl-*N*-(2,3-epoxypropyl) phosphorodiamidate.

The reaction of epichlorohydrin with the sodium salt of the *N*-methyl amides probably proceeds by reaction of the epoxy group, followed by dehalogenation of the sodium alkoxide formed to regenerate an epoxy group. Treatment of the sodium salt of diethyl *N*-methylphosphoramidate with benzyl chloride gave only a small yield of a product that appeared to be diethyl *N*-benzyl-*N*-methylphosphoramidate.

(5) B. A. Arbuzov, P. I. Alimov, and M. A. Zvereva, *Izvest. Akad. Nauk S.S.S.R., Otdel, Khim. Nauk*, 1042 (1954); *Chem. Abstr.*, 50, 215i (1956).

EXPERIMENTAL

Ethyl N,N'-dimethylphosphorodiamidate. Ethyl phosphorodichloridate[6] 210 g. (1.29 moles) was added dropwise with stirring to 180 g. (5.80 moles) of methylamine dissolved in 1 l. of dry benzene at 5 to 10°. After addition was completed, the mixture was allowed to warm to room temperature and stand overnight. The methylamine hydrochloride was removed by filtration, and the benzene was distilled under vacuum. The residue, 123 g., was crude ethyl *N,N'*-dimethylphosphorodiamidate. A 25 g. portion was vacuum distilled and yielded 10 g. of purified material.

N,N',N''-Trimethylphosphoric triamide. Phosphoryl chloride, 153.5 g. (1.0 mole) was added dropwise with stirring to methylamine, 186 g. (6.0 moles) in 1.4 l. of dry chloroform at −40 to −20°. The mixture was allowed to stand overnight at room temperature and the methylamine hydrochloride, 162.1 g. (79.5%), removed by filtration. The filtrate was evaporated under reduced pressure and the residue dissolved in methanol. The remainder of the methylamine hydrochloride was neutralized with an amount of potassium hydroxide in methanol equivalent to the unprecipitated hydrochloride. The potassium chloride formed was filtered and the filtrate evaporated under reduced pressure. The residual oil was taken up in boiling benzene and boiled until the remaining methanol was removed. The solution was filtered hot and *N,N',N''*-trimethylphosphoric triamide crystallized on cooling.

N,N',N''-Trimethylphosphorothionic triamide. Phosphorothionyl chloride, 34 g. (0.2 mole), was added dropwise with stirring to 37 g. (1.2 moles) of methylamine in 250 ml. of dry toluene at −30° to −20°. The methylamine hydrochloride and product separated as a gummy precipitate. After addition was completed, the mixture was allowed to warm to room temperature with stirring and stand overnight. The mixture was heated to boiling and filtered hot to remove the methylamine hydrochloride. *N,N',N''*-Trimethylphosphorothionic traimide crystallized from the filtrate.

Pentamethylphosphoric triamide and trimethylphosphoramidic imide. Tetramethylphosphorodiamidic chloride,[7] 85.25 g. (0.5 mole), was added dropwise with stirring to 36 g.

(6) B. C. Saunders, G. J. Stacey, F. Wild, and I. G. E. Wilding, *J. Chem. Soc.*, 699 (1948).

(7) J. E. Gardiner and B. A. Kilby, *J. Chem. Soc.*, 1769 (1950).

(1.16 mole) of methylamine in 400 ml. of dry benzene between 5° and 10°. After addition was completed, the mixture was allowed to warm to room temperature and stand overnight. The methylamine hydrochloride was removed by filtration and the benzene distilled from the filtrate under reduced pressure. The residue was distilled under reduced pressure. Some deamination occurred during distillation with the release of dimethylamine. Crystals formed in the distillate and were separated by filtration. The filtrate, 39 g. was pentamethylphosphoric triamide.

The crystalline material was washed with ether and could not be further purified. This product is believed to be trimethylphosphoramidic imide.

Mol. wt. 242 determined ebullioscopically[8] in benzene.

N,N'-Dimethyl-P-trichlorcmethylphosphonic diamide. Methylamine, 40 g. (1.28 moles), in 500 ml. of chloroform was cooled to 2° and trichloromethylphosphonic dichloride[9] 75 g. (0.32 mole), in 100 ml. chloroform was added dropwise with stirring below 8°. The mixture was stirred for 1 hr. after addition was complete and then allowed to warm to room temperature. The methylamine hydrochloride was removed by filtration and the chloroform distilled from the filtrate under reduced pressure. The residue was recrystallized from benzene yielding 27 g. of *N,N'*-dimethyl-*P*-trichloromethylphosphonic diamide, m.p. 122–124°. Recrystallization from water raised the m.p. to 133–135°.

Thermal deaminations. A sample, 20 g., of the amides listed below was heated at 200–250° under vacuum until a weight loss equal to one equivalent of methylamine was observed. This required 4 to 8 hr. of heating. *N,N',N''*-Trimethylphosphoric triamide yielded a resinous solid.

Anal: Calcd. for $C_2H_7N_2OP$: N, 26.4.

Found: N, 26.2. Mol. wt. 301, determined ebullioscopically[8] in methanol.

N,N',N''-Trimethylphosphorothionic triamide yielded a crystalline solid which was recrystallized from toluene.

Mol. wt. 244, determined ebullioscopically in benzene. (See Table I.)

Ethyl *N,N'*-dimethylphosphorodiamidate yielded a resinous-like material.

Anal: Calcd. for $C_3H_8NO_2P$: N, 11.6. Found: N, 15.5.

Diethyl *N*-methylphosphoramidate did not diaminate at 250°.

Reactions of sodium salts. Diethyl *N*-methylphosphoramidate,[6,10] 27 g. (0.15 mole), was dissolved in 100 ml. of dry benzene and 3.5 g. (0.15 mole) of sodium sand was added. There was a slight temperature rise and the evolution of hydrogen. Warming the mixture to 50° was necessary to completely dissolve the sodium. The solution was added to epichlorohydrin, 14 g. (0.15 mole), and the mixture stirred for 1 hr. at 50°, then allowed to stand overnight at room temperature. The solution was decanted off leaving a gummy residue. The solvent was removed under vacuum from the decanted solution, and the residue distilled under reduced pressure, yielding 13.0 g. (40%) diethyl *N*-methyl-*N*-(2,3-epoxypropyl)phosphoramidate.

A similar preparation using 30.4 g. (0.2 mole) ethyl *N,N'*-dimethylphosphorodiamidate, 9.2 g. (0.4 mole) sodium sand, and 20 g. (0.2+ mole) epichlorohydrin yielded 4.6 g. unreacted sodium and 34 g. of undistillable oil.

Anal: Calcd. for $C_7H_{17}N_2O_3P$: Oxirane oxygen 7.8. Found: Oxirane oxygen[11] 6.6.

An attempted preparation of diethyl *N*-benzyl-*N*-methylphosphoroamidate by the reaction of equimolar quantities of diethyl-*N*-methyl phosphoramidate, sodium sand, and benzyl chloride by this procedure yielded only 1 g. of product. B.p. 110–119° (1 mm.).

Anal: Calcd. for $C_{12}H_{20}NO_3P$: N, 5.45. Found: N, 5.35.

Acknowledgment. The authors are indebted to Mr. H. P. Pastor, Mr. J. A. Harris, Mr. V. P. Whitley, and Miss M. Curtis for some of the analytical data presented in this article.

NEW ORLEANS, LA.

(8) A. W. C. Menzies and S. L. Wright, Jr., *J. Am. Chem. Soc.*, **43**, 2314 (1921).

(9) K. C. Kennard and C. S. Hamilton, *J. Am. Chem. Soc.*, **77**, 1156 (1955).

(10) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 921 (1945).

(11) A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF TULANE UNIVERSITY]

Pyrolysis of Thiophene[1]

HANS WYNBERG AND A. BANTJES

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Pyrolysis of thiophene at 850° gives a mixture of the three isomeric bithiophenes in 7–8% conversion. Mass spectral analysis of the pyrolyzate furnishes evidence for the occurrence of a variety of additional condensation products.

In 1894 Auwers and Bredt[2] published a brief study on the isolation of two crystalline fractions, m.p. 44–48° and 127–128°, respectively, from the pyrolyzate when thiophene was passed through a tube at "cherry-red" heat. In view of the proximity of these melting points as well as those of the derived bromides to those reported for authentic 2,2'- and 3,3'-bithiophene, the authors concluded that these compounds were present in their crystalline pyrolyzate. Inspection of the data in Table I appears to confirm these conclusions.

We have now reinvestigated the pyrolysis of thiophene, and have found that passage through a Vycor glass tube at 800–850° converts 40% of the thiophene into other products. Table II contains the results of the initial fractionation of this crude pyrolyzate.

Fraction I could be separated into an oily fraction A (38%) and a crystalline fraction B (55%) by repeated sublimation. Mass spectral analysis, as well as the infrared and ultraviolet spectra of frac-

(1) This work was supported by the office of Ordnance Research, Contract Number DA-01-009-ORD-500.

(2) K. Auwers and T. V. Bredt, *Ber.*, 27, 1741 (1894).

TABLE I

IDENTIFICATION OF BITHIOPHENES IN PYROLYZATE

Compound	M.P., °C.	Auwers' work	Our work
2,2′-Bithiophene	33[3]	44–48	Oil
2,3′-Bithiophene	65[4]		62–63
3,3′-Bithiophene	133[2]	127–128	132–133
5,5′-Dibromo-2,2′-bithiophene	143[2]		146.0–146.5
3,3′-,4,4′-5,5′-Hexabromo-2,2′-bithiophene	257[2]	249	

TABLE II

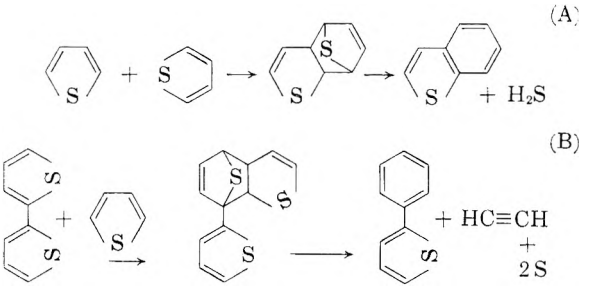
DISTRIBUTION OF CRUDE PRODUCTS IN PYROLYZATE

Product	%
Carbon disulfide	15
Carbon	10
Hydrogen sulfide	4
Oil volatile in steam, fraction I	14
Oil nonvolatile in steam, fraction II	34
Volatile gases, losses	22

tion IA indicated that it was composed of thianaphthene (60%) and bithiophenes (25%). Traces of naphthalene, phenylthiophenes, and thiophthenes may also have been present in this fraction on the basis of its mass spectrogram. Spectral analysis of solid fraction IB indicated the presence of bithiophenes (85%) and phenylthiophenes (8%) as the major constituents. Traces of benzothiophene also appeared to be present. By a combination of chromatography and fractional crystallization it was possible to isolate two fractions, m.p. 61.5–62.8° and 132.5–133.2°. These were identified as 2,3′-bithiophene and 3,3′-bithiophene, respectively, by mixture melting point determinations with authentic specimen. From the mother liquors a small amount of material melting at 42–44° was isolated to which the 2-phenylthiophene structure was tentatively assigned, while an oil remained which could be converted to the known[2] 5,5′-dibromo-2,2′-bithiophene, m.p. 146.0–146.5° undepressed on admixture with an authentic sample. These data are summarized in Table I.

Although it might be assumed that under the conditions of this pyrolysis almost any type of fragmentation and recombination could occur, a rational pathway appears to suggest itself for many of the products of this reaction.

If the assumption is made that self-addition of the Diels-Alder type is possible and that aromatization of the adducts prevents reversal of this reaction, the formation of thianaphthene and the phenylthiophenes could be visualized as follows:



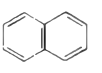
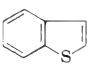
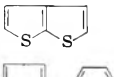
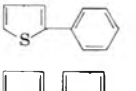
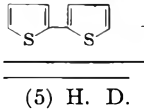
Since it is known[5] that acetylene will react with sulfur and hydrogen sulfide to furnish, among other products, the thiophthenes, the above scheme could form the basis for most of the products found in the pyrolyzate. It is clear that route A provides for the formation of dibenzothiophene while route B would furnish 3-phenylthiophene if 2,3′-bithiophene or, better 3,3′-bithiophene were the diene.

EXPERIMENTAL

Thiophene[6] (150 g.) was heated to 60–65° and passed through a 90 × 1 cm. Vycor tube at a rate of 5 ml. per hr. with the aid of a slow stream of dry nitrogen. A tube oven maintained 50 cm. of the Vycor tube at 800–850°. A series of cold traps (Dry Ice) was used to collect the pyrolyzate. Hydrogen sulfide was collected as lead sulfide. When all of the thiophene had been swept through the system (31 hr.), the contents of the traps, 143.7 g., were distilled. A forerun of 8.7 g. (15%)[7] of carbon bisulfide, b.p. 35–45°, was followed by 89.7 g. (60%) of unreacted thiophene, b.p. 69–85°. Steam distillation of the residue furnished 8.2 g. (13.6%)[7] of steam-volatile material leaving 20 g. (34%) of residue. The steam-volatile fraction was separated into 3.09 g. of an oily fraction, IA, and 4.45 g. of a crystalline fraction, IB, by sublimation at 40–60° (0.3 mm.). The mass spectrum of these fractions is shown in Table III.[8]

TABLE III

MASS SPECTRUM

Structure		Mass	% Fraction IA	% Fraction IB
		128	6	
		134	60	2
	+ isomers	140	4	
	+ isomers	160	2	8
	+ isomers	166	25	85

(3) W. Steinkopf, R. Leitsmann, and K. H. Hoffman, *Ann.*, **546**, 180 (1941); J. W. Sease and L. Zechmeister, *J. Am. Chem. Soc.*, **69**, 270 (1947); C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **72**, 5543 (1950); H. Wynberg and A. Logothetis, *J. Am. Chem. Soc.*, **78**, 1958 (1956).

(4) J. Teste and N. Lozach, *Bull. soc. chim. France*, 492 (1954); H. Wynberg, A. Logothetis, and D. VerPloeg, *J. Am. Chem. Soc.*, **79**, 1972 (1957).

(5) H. D. Hartough *"Thiophene and Its Derivatives,"* Interscience Publ., Inc., N. Y., 1952, p. 49; see also W. E. Parham and P. L. Stright, *J. Am. Chem. Soc.*, **78**, 4683 (1956) for the elimination of acetylene from vinyl sulfides.

(6) Generously donated by The Texas Co.

(7) These percentages are based on the 60. g. of thiophene actually converted.

TABLE IV

INFRARED ABSORPTION BANDS FOR BITHIOPHENES

2,2′-Bithiophene	3,3′-Bithiophene	2,3′-Bithiophene
3.25 mμ	3.25 mμ	3.25 mμ
5.56	6.44	5.56
6.07	6.64	6.07
6.26	6.93	6.44
6.64	7.12	6.64
6.91	7.46	6.95
7.08	8.00	7.11
7.40	8.22	7.24
7.55	8.36	7.50
8.09	8.50	8.01
8.29	9.20	8.13
8.49	9.58	8.36
8.65	9.95	8.52
9.25	10.24	9.22
9.56	11.44	9.55
10.92	11.83	9.94
11.16	13.08	10.06
11.7–12.4	14.36	10.20
13.44	14.64	11.40
14.0–14.8		11.68
		11.90
		12.13
		12.52
		12.95
		14.40
		14.96

TABLE V

ULTRAVIOLET ABSORPTION MAXIMA FOR DITHIOPHENES

Compound	EtOh max mμ	E × 10^{-4}
2,2′-Dithiophene	301	1.30
	263 (min.)	0.38
	246	0.60
2,3′-Dithiophene	283	1.19
	250 (min.)	0.52
	235	0.84
3,3′-Dithiophene	260	1.13
	240 (min.)	0.48
	230	0.9–1.0

The crystalline fraction IB was subjected to fractional crystallization and chromatography as follows: One g. of IB was crystallized from 15 ml. of absolute methanol. The crystalline material thus obtained melted at 82–93°. After six crystallizations there was obtained 15 mg. of pure 3,3′-bithiophene, m.p. 132–133°, undepressed on admixture with an authentic sample.[9] Liquid crystal formation of pure 3,3′-bithiophene appears to occur at 115–122°.

Concentration of the mother liquor from crop I to one half its volume furnished an intermediate fraction, melting at 52–80°. This fraction (100 mg.) was chromatographed over 11.2 g. of basic alumina.[10] Using petroleum ether (distilled, b.p. 34–38°) as the eluant, fractions of 20 ml. each were collected. In this manner fractions 9, 10, and 11 melting at 50–57.5° were combined and recrystallized 3 times from petroleum ether (b.p. 34–38°) furnishing shiny platelets, m.p. 61.5–63.0°. A mixture m.p. with authentic 2,3′-bithiophene (m.p. 60.5–61.0°) was 60.8–62.8°.

All fractions melting below 50° were combined and recrystallized from petroleum ether. In this manner a small amount (less than 2 mg.) of material melting at 42–44° was obtained (2-phenylthiophene is reported to melt at 37° and 43°[11]). Concentration of the mother liquors furnished an oil, which was dissolved in glacial acetic acid. Dropwise addition of a solution of bromine in glacial acetic acid at room temperature resulted in rapid crystallization of 5,5′-dibromo-2,2′-bithiophene as shiny flat plates m.p. 137–140.5°. One recrystallization from methanol furnished the pure dibromide m.p. 146–147.6° as colorless glistening platelets. On admixture with the dibromo compound (m.p. 146.8–148.0° prepared in exactly the same way from authentic 2,2′-bithiophene[12]) the melting point was not depressed.

NEW ORLEANS, LA.

(8) All spectra were determined by Dr. G. D. Hinds, Jr., Chief Research Technologist and his associates of the Houston Research Laboratory of the Shell Oil Co.

(9) Prepared in 10% yield by the method described by Auwers and Bredt.

(10) "Woelm" alumina, activity grade I.

(11) Ref. 5, p. 477; J. L. Melles and H. J. Backer, *Rec. trav. chim.*, **72**, 314, (1953).

(12) Prepared most conveniently by heating a mixture of 2-bromothiophene (66 g.), copper-bronze (66 g.), and 66 ml. of dimethylformamide under reflux for 100 hr. followed by steam distillation. The preparation of 2,2,-dithiophene from 2-bromothiophene has not been reported previously.

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

Synthetic Applications of the Abnormal Reimer-Tiemann Reaction

HANS WYNBERG[1] AND WILLIAM S. JOHNSON

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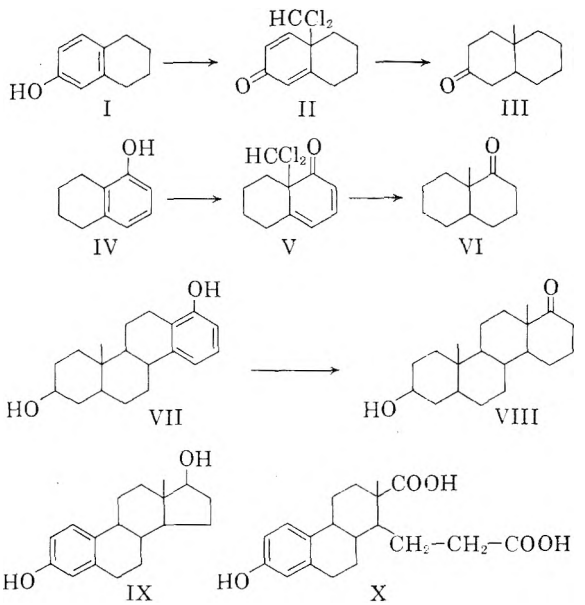
trans-9-Methyl-1-decalone (VI) has been prepared by the Woodward method from *ar.* α-tetralol IV *via* the dienone V. β-(*p*-Hydroxyphenyl)-propionic acid (XI) was similarly converted to the dienone XII and thence to XIII. Mesitol was found to furnish the two isomeric dienones XVIII and XIX. The relationship of these studies to the synthesis of nonaromatic steroids is discussed.

Since aromatic steroid types such as VII[2] and IX or its precursor X[3] are available by total synthesis, their conversion to nonaromatic steroids containing two angular methyl groups becomes a subject of considerable interest.

Woodward's[4] ingenious method for producing *trans*-10-methyl-2-decalone III[5] from *ar.* β-tetralol I *via* the product II of abnormal Reimer-Tiemann reaction promised, *a priori*, to be applicable to the formation of 9-methyl-1-decalone (VI) from *ar.* -α-tetralol (IV) *via* the dienone V. This extension of Woodward's scheme thus serves as a model for conversion of the readily available phenol VII[2] into a D-homo-17-keto steroid VIII. Although this ultimate objective was not realized, the conversion of IV→VI has been successful and an account of this study is the subject of Part I of this paper.



Since attempts by Woodward to apply his scheme to estradiol (IX) failed,[6] we were prompted to examine the applicability of the method to D-homomarrianolic acid (X)[7] in the hope that its greater compatibility, by virtue of the carboxyl groups, with the aqueous-alkaline phase of the reaction mixture would be beneficial. Although this hope was not realized, the model conversion of β-(*p*-hydroxyphenyl)-propionic acid (XI, R=H) to the abnormal Reimer-Tiemann product XII was successful and is reported in Part II.

Part III of this paper deals with a study of the abnormal Reimer-Tiemann reaction with mesitol (XVII) as an interesting example where normal reaction is precluded.

PART I

Treatment of *ar.* α-tetralol with chloroform and 50% aqueous potassium hydroxide afforded a mixture separable into an acidic and neutral fraction by virtue of the insolubility of the sodium salt of the former. The neutral fraction could be separated into two components by chromatography. The first product obtained in 1.5% yield was a crystalline solid which, after purification, melted at 164.5–165°. The analysis was compatible with the formula $C_{31}H_{34}O_3$ which corresponds to the orthoformate structure XVI, an expected product.[8] The second neutral product, obtained in 2.5% yield as a pale yellow crystalline solid melting at 149–150.5° after purification, was identified through compositional analysis and the ultraviolet spectrum, λ_{max} 320 mμ,[9] as the dichloroketone V.

(1) Sterling-Winthrop Research Institute Fellow, Spring 1951; Allied Chemical and Dye Fellow, 1951–52. Present address: Department of Chemistry, Tulane University, New Orleans, La.

(2) W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister, and H. Wynberg, *J. Am. Chem. Soc.*, **78**, 6289 (1956).

(3) J. E. Cole, W. S. Johnson, P. A. Robins and J. Walker, *Proceedings Chem. Soc.*, 114 (1958).

(4) R. B. Woodward, *J. Am. Chem. Soc.*, **62**, 1208 (1940).

(5) For the matter of configuration see M. Yangita, K. Yamakawa, A. Tahara, and H. Dgura, *J. Org. Chem.*, **20**, 1767 (1955).

(6) Private communication from Prof. R. B. Woodward.

(7) For the synthesis of homomarrionolic acid and its conversion to estrone see ref. (3) and articles cited therein.

(8) *Cf.* A. Weddige, *J. prakt. chem.*, (2) **26**, 444 (1882); G. Keil as quoted by K. Auwers and M. Hessenland, *Ann.*, **352**, 273 (1907); H. Baines and J. E. Driver, *J. Chem. Soc.*, **125**, 907 (1924); J. E. Driver, *J. Am. Chem. Soc.*, **46**, 2090 (1924).

Additional proof of this structural assignment was obtained by conversion of V to 9-methyl-1-decalone (VI) and comparison of the latter with an authentic sample.[10] This conversion was achieved by reduction and hydrogenation of the olefinic, carbonyl and dichloromethyl functional groups followed by reoxidation to the ketone. In agreement with the previous observations in the β-tetralol series,[5] mild conditions at the first reduction stage, namely atmospheric pressure hydrogenation in the presence of 5% palladium-on-carbon, effected highly stereoselective reduction of the olefinic bonds of V to give a *trans*- fused ring system. The use of highly active platinum oxide[11] at the first stage of reduction led to a mixture of *cis*- and *trans*-isomers.

Two aldehydes were isolated from the acidic fraction of the reaction mixture. One of these, purified *via* the sparingly soluble sodium salt, was obtained in 9% yield as shiny plates melting at 29.6–30.1° after purification. The other aldehyde, obtained in 2% yield, melted at 141.5–142.5°. This melting point was not depressed on admixture with the aldehyde, m.p. 141–142° obtained from the reaction of *ar.* α-tetralol with zinc cyanide and dry hydrogen chloride. On the basis of the orientation rules in the Reimer-Tiemann and Gattermann reactions, the lower melting aldehyde is assigned the *o*-hydroxy structure XIV, while the 141–142° melting aldehyde is considered to be the *para* isomer XV.

All attempts to obtain a neutral chlorine-containing product from the phenol VII failed.

PART II

Treatment of β-(4-hydroxyphenyl)-propionic acid, (XI R=H) with excess chloroform in the presence of 42% potassium hydroxide furnished a mixture which could be separated into the phenolic and neutral components conveniently after esterification of the carboxylic acid function. The neutral fraction thus obtained in 17% yield as a pale yellow powder melting at 51.4–52.0° after purification, was assigned the dichlorocyclohexadienone structure XII (R=C_2H_5), on the basis of its compositional analysis, ultraviolet absorption maximum at 233 mμ[12] (log ε 4.2) and by analogy to the behavior of other *p*-alkyl substituted phenols. The *o*-hydroxyaldehyde XXI was isolated from the acidic fraction in 13% yield as fine colorless plates melting at 119–121.2° after purification. The dichloroketone XII (R=C_2H_5) was converted by reduction over platimum oxide[11] followed by oxidation with chromic oxide in glacial acetic acid into ethyl (1-methyl-4-ketocyclohexyl)-propionate (XIII) isolated as the yellow-orange 2,4-dinitrophenylhydrazone melting at 189–190°.

Attempts to obtain a chlorine-containing cyclohexadienone from homomarrianolic acid (X) failed. A significant difference between the model phenol, β-(*p*-hydroxyphenyl)-propionic acid (XI, R=H), which could be converted successfully into a cyclohexadienone, and D-homomarrianolic acid (X) consists in the presence of ring C in the letter. The steric interference of the axial hydrogen atoms attached to C_8, C_9 and C_{11} (formula X) evidently precludes reaction at C_{10} with a fragment even as small as dichlorocarbene.[13]

PART III

Although both *ortho*- and *para*-substituted phenols have been converted to the corresponding *ortho*- and *para*-substituted dichloromethyl cyclohexadienones there appears to have been no case recorded where both possible dienones have been isolated[14] from the reaction with one phenol.

Treatment of mesitol (XVII) with chloroform and 50% aqueous potassium hydroxide solution for 12 hours afforded in our hands a mixture from which the starting phenol was separated by extensive extractions with Claisen's alkali. The neutral straw-colored liquid thus obtained in 67.5% yield boiled at 73–74° (0.17 mm.). Its compositional analysis was in agreement with the dichloroketone structure XVIII and XIX. Upon attempted

(9) The ultraviolet spectrum of 2-dichloromethyl-2-methyl-3,5-cyclohexadienone, prepared according to K. Auwers and G. Keil, *Ber.*, **35**, 4207 (1902) showed an absorption maximum at 300 mμ (log ε 3.6). R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956) reported the maximum at 303 mμ (log ε 3.6) while C. LaLane, *J. Chem. Soc.*, 3217 (1953) observed a maximum at 297–299 mμ. D. C. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 6016 (1958) reported λ_{max} 299 mμ for 2,2-dimethyl-3,5-cyclohexadienone. These observations indicate that the λ_{max} at 228 mμ reported by E. N. Marvel and E. Magoon, *J. Am. Chem. Soc.*, **77**, 2542 (1955) for the same substance is incorrect.

(10) (a) W. S. Johnson, *J. Am. Chem. Soc.*, 65, 1317 (1943); (b) W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).

(11) V. L. Frampton, J. D. Edwards, Jr., *J. Am. Chem. Soc.*, and R. R. Henze, **73**, 4432 (1957).

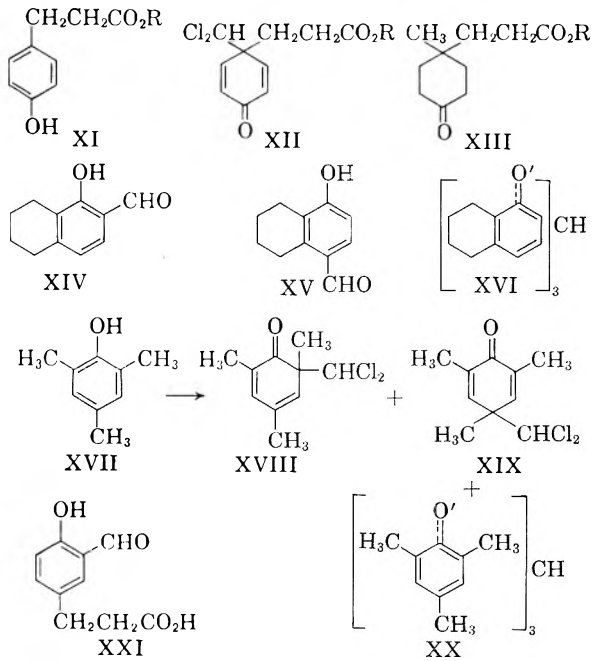
(12) *Cf.* the λ_{max} at 235 mμ (log ε 4.1) for compound II (ref. 4). M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954) report λ_{max} 237 mμ (log ε 4.0) for 2,4,4-trimethyl-2,5-cyclohexadienone. 4-Dichloromethyl-4-methyl-2,5-cyclohexadienone has been found in the present work to absorb at 232 mμ (log ε 4.2).

(13) *Cf.* H. Wynberg, *J. Am. Chem. Soc.*, **76**, 4998 (1954). Note, however, that dichlorocarbene may well be associated with solvent molecules.

(14) K. Auwers and F. Winternitz, *Ber.*, **35**, 465 (1902) isolated a neutral chlorine-containing oil from 2,4-dimethylphenol, which may have contained both isomers. The separation and isolation of these isomers was reported to be unsuccessful. Auwers further reported the Reimer-Tiemann reaction with mesitol as furnishing a neutral chlorine containing oil (elemental analysis 10% low in chlorine) without experimental details. No characterization of this neutral substance has been reported. W. J. Hickinbottom and B. H. M. Thompson are quoted in E. H. Rodd, *Chemistry of Carbon Compounds*, Elsevier Publishing Co., Amsterdam, Holland, Vol. III B, p. 738 as having obtained a 70% yield of dichloromethyl cyclohexadienone from mesitol. Added in proof: after our paper was in press we learned from Prof. D. H. R. Barton that he and P. T. Gilham had obtained results with mesitol essentially the same as our own described here.

crystallization from methanol a 1% yield of a chlorine-free product was isolated as small colorless prisms, melting at 188.0–188.5° after purification, which as shown by compositional analysis, corresponded to the expected mesityl orthoformate (XX). The remaining oil furnished, upon chromatography, an oily fraction in 63% yield which exhibited a sharp maximum at 317 mμ (log ε 3.75) in the ultraviolet spectrum.

This absorption maximum and extinction coefficient is that expected for a 2,2-dialkylcyclohexadienone.[9,15] The second fraction, eluted in 6% yield from the column, was obtained as a white crystalline solid melting at 37.5–38.5° after crystallization from methanol. The ultraviolet spectrum, λ_{max} 240 mμ (log ε 4.0), and compositional analysis were compatable with the *para* dichloroketone structure XIX. From the absorption coefficients of XVIII and XIX at 240 and 317 mμ respectively it was possible to calculate the ratios of isomers as 7 to 3 (*ortho* to *para*) in the original neutral oil. Reduction of the reaction time from twelve hours to one hour caused a decrease in the yield of neutral material from 67.5 to 47.5%. It is noteworthy that the ratio of *ortho* to *para* isomers in this product was changed to 40 to 1 under these conditions.



EXPERIMENTAL[16]

Reimer-Tiemann reaction with ar. α-tetralol (IV). To a solution of 20.0 g. *ar.* α-tetralol IV, m.p. 69–70°[17] in 875 ml. of 50% aqueous potassium hydroxide solution was added in an atmosphere of nitrogen, with vigorous stirring, 450 ml. of chloroform (Eastman Kodak, Pract.) over a period of 1.5 hr. Some external cooling was necessary to moderate the vigorous reaction. The mixture was allowed to reflux for an additional 1 hr., whereupon it was cooled and acidified with dilute sulfuric acid. The aqueous layer was extracted once with chloroform and the combined organic layers were stirred with a 20% sodium hydroxide solution. The insoluble sodium salts of the phenolic aldehydes which precipitated were removed by filtration and washed with chloroform. The chloroform solution was washed free of alkali with water, dried over magnesium sulfate and concentrated. The residue was dissolved in 100–200 ml. of 1:1 ether–petroleum ether (b.p. 60–68°) and passed through 75 g. of activated alumina (Alcoa, F-20 grade). The first 200 ml. of eluate afforded 930 mg. (1.5%) of *ar. α-tetralol orthoformate* (XVI), m.p. 160–162° as well formed white crystals. Three recrystallizations from benzene-methanol furnished the analytical sample as colorless prisms, m.p. 164.5–165.0°.

Anal. Calcd. for $C_{31}H_{34}O_3$: C, 81.90; H, 7.54. Found: C, 82.0; H, 7.56.

The next 600 ml. eluted 938 mg. (3.0%) of yellow crystals melting at 145–151°. An analytical sample of *9-dichloromethyl-1-keto-$\Delta^{2,4}$-hexahydronaphthalene* m.p. 149.0–150.5° was obtained by crystallization from dilute ethanol followed by two sublimations at 145° and (0.01 mm.), λ_{max} 320 mμ (log ε 3.6).

Anal. Calcd. for $C_{11}H_{12}OCl_2$: C, 57.16; H, 5.24. Found: C, 57.2; H, 5.33.

Each of the two isomeric aldehydes was isolated from separate runs. When 14.8 g. of the phenol IV, 350 g. of potassium hydroxide, 300 ml. of water, and 200 ml. of chloroform were employed, 1.5 g. (9%) of an oil, b.p. 140–150° (8–10 mm.) was obtained upon acidification of the sodium salts. The oil was reconverted to the sodium salts, washed with ether, and the hydroxy aldehyde liberated with dilute acetic acid. Upon cooling and scratching the aldehyde crystallized as colorless shiny plates, turning yellow on exposure to air. One crystallization from dilute alcohol followed by another crystallization from petroleum ether (b.p. 35–40°) yielded pure *6-formyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene* (XIV) as nearly colorless shiny plates, m.p. 29.6–30.1°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.7; H, 6.94.

In another experiment in which 5.0 g. of the phenol IV in 5 ml. of chloroform and 15 ml. of ethanol were added to 10 g. of sodium hydroxide in 16 ml. of water at 60° over a period of 2 hr., a fraction b.p. 125–175° (0.1 mm.) was collected. This fraction crystallized to a white solid which furnished 135 mg. (2%) of the *p*-hydroxyaldehyde m.p. 141.5–142.5° undepressed on admixture with the aldehyde, m.p. 141–142° obtained from a Gattermann reaction described below. Although analysis of this aldehyde was not entirely satisfactory. (Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87: Found: C, 74.2; H, 7.21.) *The semicarbazone of 8-formyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene* (XV), melting at 214–215° after one crystallization from dioxane gave satisfactory analytical results.

Anal. Calcd. for $C_{12}H_{15}O_2N_3$: C, 61.78; H, 6.45. Found: C, 62.1; H, 6.42.

Treatment of 5 g. of α-tetralol (IV) in 50 ml. of ether with 6.0 g. of anhydrous zinc cyanide and dry hydrogen chloride for 2 hr. furnished a red oil which was decomposed by heating for 35 min. on the steam bath with 50 ml. of water and 10 ml. of 95% alcohol. Extraction with ether followed by washing with water, drying and removal of the ether left 1.75 g. (29.4%) of tan solid. Two recrystallizations from

(15) It is noteworthy that the abnormal product from *o*-cresol (ref. 8) can be obtained pure with relative ease. Its dimerization was observed by us after a period of two years (see Experimental). Curtin (ref. 9) also reported the isolation of 2,2-dialkylcyclohexadienones as their dimers.

(16) All melting points are corrected for stem exposure. Ultraviolet spectra were determined on a Beckmann DU Spectrophotometer, and 95% ethanol was used as a solvent.

(17) Prepared by S. Kraychy and O. R. Rodig according to the procedure of Musser and H. Adkins, *J. Am. Chem. Soc.*, **60**, 664 (1938).

benzene furnished 8-formyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene (XV) m.p. 140.5–142.0° undepressed on admixture with the aldehyde obtained from the Reimer-Tiemann reaction.

cis- and trans-4-Methyldecalone-1 (VI). A 230 mg. sample of 9-dichloromethyl-1-keto-$\Delta^{2,4}$-hexahydronaphthalene (V), m.p. 149–151°, in 25 ml. of 95% alcohol (purified by distillation from Raney nickel) was added to a suspension of 100 mg. of prereduced platinum oxide[11] in 15 ml. of alcohol. The mixture was stirred in an atmosphere of hydrogen at 25° and 731 mm. until 3 mole-equivalents of hydrogen were absorbed. The catalyst was removed by filtration and hydrogenation was continued over 2.00 g. of 30% palladium-on-strontium carbonate.[18] When no further uptake of hydrogen occurred (total absorption 1.8 mole-equivalents) the mixture was filtered, and the filtrate diluted with water and extracted with ether. The ether solution was washed with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the ether was dissolved in 8.35 ml. of glacial acetic acid, then a solution of 0.336 g. of potassium chromate in 0.62 ml. of water was added and the mixture allowed to stand for 21 hr. at room temperature. The mixture was diluted with water and extracted with benzene and with ether. The combined organic layers were washed free of acetic acid with water and with saturated sodium bicarbonate solution, then dried over anhydrous potassium carbonate. The residue obtained on removal of the solvent was evaporatively distilled at 100–130° (8–10 mm.) to give an oily product with a camphor-like odor which was dissolved in 10 ml. of methanol. A 3-ml. aliquot was used to prepare the semicarbazone and the yield was 22 mg. (corresponding to a 33% over-all yield from the dienone), m.p. 227.5–228° (introduced at 215°). This derivative evidently consisted mainly of the *cis*-isomer since on admixture with an authentic specimen m.p. (222–224°[19]) the m.p. of the latter was not depressed. The m.p. of an authentic specimen of the *trans* semicarbazone, in contrast, was markedly depressed on admixture with the specimen of the present study. When the oxime and 2,4- dinitrophenylhydrazone were prepared from the crude ketone solution, mixtures were obtained which on exhaustive recrystallization afforded, in low yield, pure derivatives of *trans*-9-methyl-1-decalone, m.p. 138–139° and 170.5–171.5°, respectively, undepressed on admixture with the appropriate derivatives of the *trans* series,[10a] but depressed by those of the *cis*.

In another experiment 100 mg. of 5% palladium-on-carbon catalyst[20] was used for the first reduction stage during which 1.8 mole equivalents of hydrogen were absorbed. After removal of the catalyst, the reduction (of the carbonyl group) was then continued, over 200 mg. of platinum oxide,[11] then finally over 0.25 teaspoonful of W-1 Raney nickel catalyst in the presence of added solid potassium hydroxide (3 pellets). This last reduction stage required 23 hr. at atmospheric pressure and room temperature, 2.06 mole equivalents of hydrogen being absorbed. After oxidation as described above, part of the crude product was converted into the semicarbazone which, after a single recrystallization, melted at 217–218°, undepressed on admixture with authentic *trans* derivative, but depressed by the *cis*. The 2,4-dinitrophenylhydrazone was obtained in 26% over-all yield from the dienone, and after a single recrystallization melted at 171–171.5°, undepressed on admixture with authentic *trans* derivative but depressed by the *cis*.

Attempted Reimer-Tiemann reaction with the phenol VII. One g. of the phenol VII,[2] m.p. 195–197.5° (vac.) and 25 g. of potassium hydroxide in 20 ml. of water was treated with 30 ml. of chloroform just as described above for the reaction with α-tetralol (IV). Chromatography of the neutral fraction furnished 2 mg. of oily material, λ_{max} 318 mμ (ϵ 1000). This absorption corresponds to a maximum of 0.5 mg. of possible abnormal ketone in the reaction product. All attempts to increase the yield were unsuccessful.

Reimer-Tiemann reaction with β-(p-hydroxyphenyl)-propionic acid (XI, R = H). Five g. of β-(*p*-hydroxyphenyl)-propionic acid (XI)[21] m.p. 127–128.5° in 35 ml. of chloroform was treated with a solution of 35 g. of potassium hydroxide in 35 ml. of water in an atmosphere of nitrogen. The mixture was vigorously stirred under reflux for 1 hr., cooled, diluted with 40 ml. of water and stirred rapidly into an excess of cold dilute hydrochloric acid. The aqueous layer was extracted with ether and the combined organic layers washed with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was esterified by heating under reflux for 4 hr. with 65 ml. of absolute ethanol containing 4 drops of concentrated sulfuric acid. One half of the alcohol was then removed under reduced pressure, 65 ml. of water added, and the mixture extracted with ether. Unesterified material (4.5%) was separated by washing the ethereal layer with 5% sodium bicarbonate solution. The phenolic material was extracted with 10% sodium hydroxide solution. The ether solution was washed with water and dried over anhydrous magnesium sulfate. The neutral material left after removal of the ether was obtained as an oily solid weighing 1.42 g. (17% yield) and was purified by two successive evaporative distillations at 50° (0.1 mm.) to furnish *ethyl β-(1-dichloromethyl-(4-ketocyclohexa-2,5-dienyl)-propionate* (XII, R = C_2H_5) as a pale yellow powder, m.p. 51.5–52°.

Anal. Calcd. for $C_{12}H_{14}O_3Cl_2$: C, 52.00; H, 5.09. Found: C, 52.3; H, 5.03.

The normal product could be isolated from the reaction mixture by fractional crystallization before the esterification step. Thus from an experiment like that described above (2-g. scale) there was obtained 0.3 g. (13%) of aldehydic material m.p. 117–121.5° after crystallization from benzene–petroleum ether (60–68°). A pure sample of *β-(3-formyl-4-hydroxyphenyl)-propionic acid* (XXI) was obtained, after 2 recrystallizations from ether–petroleum ether (60–68°) as fine, colorless plates, m.p. 119–121.2°, λ_{max} 257.5 m (log ϵ 4.03), 335 (3.53).

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 61.87; H, 5.19. Found: C, 62.0; H, 5.34.

An 830-mg. sample of the keto-ester XII (R = C_2H_5) was reduced as described for V (initial reduction stage with platinum oxide) and oxidized with 400 mg. of chromic oxide in 15 ml. of glacial acetic acid containing 12 ml. of water. The crude oily product, isolated by continuous extraction with ether, was evaporatively distilled at 80° (0.3 mm). The distillate upon treatment with 500 mg. of 2,4-dinitrophenylhydrazine in 15 ml. of 95% ethanol furnished after 3 crystallizations from 95% ethanol, 53.5 mg. of the *2,4-dinitrophenylhydrazone of β-(1-methyl-4-ketocyclohexanyl)-propionic acid* (XIII, R = H) as very fine yellow-orange needles m.p. 189–190°.

Anal. Calcd. for $C_{16}H_{20}O_6N_4$: C, 52.80; H, 5.50. Found: C, 52.9; H, 5.70.

Attempted Reimer-Tiemann reaction with homomarrionolic acid (X). A 500 mg. sample of D-homomarrionolic acid[6] m.p. 233–238° was treated with 5 ml. of chloroform and 4 ml. of 50% potassium hydroxide solution (nitrogen atmosphere) in exactly the manner as described above for the phenolic acid XI. Acidification of the cooled reaction mixture furnished 541 mg. of crude organic material which had been washed completely free of ionic chloride. Three 50-mg. samples were submitted to sodium fusion and chlorine deter-

(18) *Cf.* ref. 2 and footnote 39 cited therein.

(19) See footnote 15 of reference 10(b).

(20) R. Mozingo, *Org. Syntheses*, **Coll. Vol. III**, 685, (1955).

(21) E. Bowden and H. Adkins, *J. Am. Chem. Soc.*, **62**, 2422 (1940), reported m.p. 128–129°. This substance was prepared in the present work by hydrogenation over platinum oxide of *p*-hydroxycinnamic acid [G. C. Overberger, E. J. Luhrs, and P. K. Chien, *J. Am. Chem. Soc.*, **72**, 1201 (1950)].

mined by the Volhard method. The results in each case were negative within the experimental error.

Reimer-Tiemann reaction with mesitol (XVII). Ten g. of mesitol, m.p. 71–72° was heated under reflux for 12 hr. with 200 ml. chloroform, 200 g. of potassium hydroxide, and 170 ml. of water. Upon cooling, the organic layer was extracted with five 50-ml. portions of Claisen's alkali,[22] then dried over magnesium sulfate and the solvent removed under reduced pressure leaving 10.86 g. (67.5%) of neutral oil. Upon standing in the refrigerator overnight in absolute methanol, 0.90 g. (1%) of white crystals m.p. 185–186° had separated. Colorless prisms of *mesityl orthoformate* (XX), m.p. 188.0–188.5° were obtained after three recrystallizations from benzene-methanol.

Anal. Calcd. for $C_{28}H_{34}O_3$: C, 80.35; H, 8.19. Found: C, 80.3; H, 8.19.

Distillation of the remaining oil furnished a mixture of the two cyclohexadienones as a faintly straw colored liquid, b.p. 73.8–74.0° (0.17 mm.), λ_{max} 239 mμ (log ε 3.66) 317 (3.51).

Anal. Calcd. for $C_{10}H_{13}OCl_2$: C, 54.84; H, 5.52. Found: C, 54.7; H, 5.67.

Assuming λ_{max} 239 mμ (ε 12,100) 317 (ε 1000) for the *para* isomer[12] and λ_{max} 317 (4500) 239 (200) for the *ortho* isomer[9] the following calculations can be made:[23]

$$\textit{para}\text{ isomer }\frac{4600 - 1000}{12{,}100 - 1000} \times 100 = 32\%\text{ and}$$

$$\textit{ortho}\text{ isomer }\frac{3240 - 200}{4500 - 200} \times 100 - 70\%$$

(22) L. F. Fieser, *Experiments in Organic Chemistry*, C. D. Heath and Co., Boston, Mass. 3rd Ed. p. 310.

(23) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957) describe a general method for the analysis of mixtures using ultraviolet spectroscopy.

One g. of this distillate was chromatographed over 70 g. of alumina using 1:10 ether–petroleum ether (b.p. 34°) as the eluant. The first nine 50-ml. fractions furnished 650 mg. of oil. Fractions 3,6, and 8 exhibited sharp maxima at 317 mμ with log ε 3.7, 3.7, and 3.75 respectively. Crystallization of this oil was unsuccessful, while attempted purification by evaporative distillation at 120–150° (8–10 mm.) resulted in some decomposition as indicated by a shift of the absorption maximum in the ultraviolet to 305 mμ. The next four 50-ml. fractions eluted from the column furnished 60 mg. of solid which, after recrystallization from dilute methanol, yielded 20 mg. of colorless crystals of *4-dichloromethyl-2,4,6-trimethyl-3,5-cyclohexadienone* (XIX), m.p. 37.5–38.5° with softening at 36°, λ_{max} 240–242 mμ (log ε 4.0).

Anal. Calcd. for $C_{10}H_{13}OCl_2$: C, 54.84; H, 5.52. Found: C, 54.7; H, 5.45.

In another experiment in which 5.0 g. of mesitol was refluxed for 1 hr. with 25 ml. of chloroform, .25 g. of potassium hydroxide, and 20 ml. of water, 3.85 g. (47.5%) of neutral oil was obtained. Its λ_{max} 317 mμ (log ε 3.58) 240 (3.15) allowed the percentage of isomers to be determined in the manner described above: *para*-isomer 4%, *ortho*-isomer 84%.

Dimer of 2-dichloromethyl-2-methyl-3,5-cyclohexadienone. When 6.0 g. of the abnormal Reimer-Tiemann product[14] of *o*-cresol, m.p. 30.5–32.0°, was allowed to stand in a stoppered flask at room temperature for 2 years, 250 mg. of a white crystalline solid m.p. 188.5–189.5° could be obtained with petroleum ether (b.p. 60–68°). Two crystallizations from methanol-acetone furnished colorless prisms, m.p. 190–190.5°.

Anal. Calcd. for $C_8H_8OCl_2$: C, 50.29; H, 4.22. Found: C, 50.2; H, 4.29.

MADISON, WIS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Bicyclic Sulfonium Salts with Sulfur at a Bridgehead[1]

RICHARD H. EASTMAN AND GENE KRITCHEVSKY

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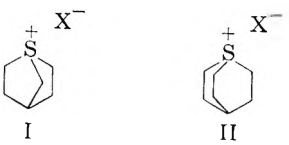
By treatment of the appropriate mercaptans or tetrahydrothiophene derivatives with hydrogen halides, bicyclic sulfonium salts of the bicyclo[3.3.0]octane-1-thianium, bicyclo[4.3.0]nonane-1-thianium, and bicyclo[4.4.0]decane-1-thianium types have been prepared.

A few bicyclic sulfonium compounds in which the sulfonium function is located at a bridgehead have been prepared. In addition to the interest inherent in such structures, the compounds of this type are frequently pharmacologically active. The most active are the bicyclo[2.2.1]heptane-1-thianium (I) and bicyclo[2.2.2]octane-1-thianium (II) halides reported by Prelog,[2] the former having a minimum lethal dose of 30γ in white mice. A few other compounds have been prepared.[3] The compounds which were tested exhibited a lower order of activity, the activity apparently being related to the ability of the bicyclic sulfonium function to act as an alkylating agent.



I II

In connection with the question of valence-shell expansion to 10 electrons in the sulfur atom,[4] we have prepared the bicyclo[3.3.0]octane-1-

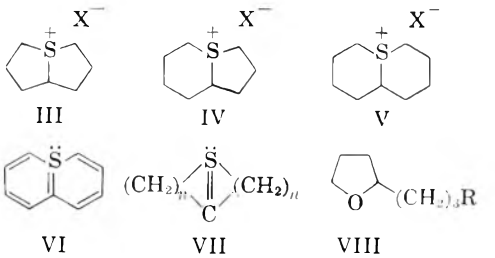
(1) Taken from the Ph.D. dissertation of Gene Kritchevsky in the Department of Chemistry at Stanford University.

(2) V. Prelog and E. Cerkovnikov, *Ann.*, **537**, 214 (1939); V. Prelog and D. Kohlbach, *Ber.*, **72**, 672 (1939).

(3) B. R. Baker, M. Query, S. Safir, and S. Berstein, *J. Org. Chem.*, **12**, 138 (1947); M. W. Goldberg and L. H. Sternbach, U.S. Patent 2,489,232, U.S. Patent 2,489,235; W. F. Cockburn and A. F. McKay, *J. Am. Chem. Soc.*, **76**, 5703 (1954); **77**, 397 (1955).

(4) For recent work and a bibliography see W. E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **77**, 521 (1955).

thianium (III), bicyclo[4.3.0]nonane-1-thianium (IV), and bicyclo[4.4.0]decane-1-thianium (V) salts as possible precursors for the hypothetical systems VI and VII in which the sulfur atom bears a decet of electrons. We were not successful in producing VI or VII, but wish to report here the syntheses and pharmacological activities of III, IV, and V. Compound III has recently become of special interest in regard to transannular effects in macrocyclic thiaketones,[5] and it seems likely that IV and V will similarly become of interest as reference systems.

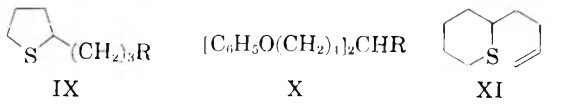


III IV V

VI VII VIII

Bicyclo[3.3.0]octane-1-thianium compounds (III). Treatment of 3-(2-tetrahydrofuryl) propanol (VIII, R = OH) with thionyl chloride in benzene solution, followed by heating the crude chloride (VIII, R = Cl) with thiourea in ethanol gave the corresponding isothiuronium salt [VIII, $R=SC(NH_2)_2^+Cl^-$] which was then hydrolyzed to 3-(2-tetrahydrofuryl) propyl mercaptan (VIII, R = SH) by warm aqueous ammonia. Bicyclo[3.3.0]octane-1-thianium bromide (III, X = Br) resulted from heating the mercaptan in a mixture of equal volumes of acetic anhydride and 48% hydrobromic acid for 18 hours.

Bicyclo[4.3.0]nonane-1-thianium compounds (IV). The method of Fieser and Kennelly[6] was used to prepare 4-(2-thienyl) butyric acid which was converted to methyl 4-(2-tetrahydrothienyl) butyrate (IX, $R=COOCH_3$) by palladium-on-charcoal catalyzed hydrogenation[7] in methanolic sulfuric acid. The ester was isolated as its mercuric chloride addition product, from which it could be recovered by treatment with hydrogen sulfide. Reduction of methyl 4-(2-tetrahydrothienyl) butyrate with lithium aluminum hydride gave 4-(2-tetrahydrothienyl) butanol (IX, $R=CH_2OH$). Bicyclo[4.3.0]-nonane-1-thianium chloride (IV, X = Cl) and bromide (IV, X = Br) were prepared by heating 4-(2-tetrahydrothienyl) butanol (IX, $R=CH_2OH$) with solutions of equal volumes of acetic anhydride with concentrated hydrochloric and hydrobromic acids, respectively. These sulfonium salts were markedly hygroscopic.



IX X XI

Bicyclo[4.4.0]decane-I-thianium compounds (V). The key substance in the synthesis of compounds of type V was 1,9-diphenoxy-5-mercaptononane (X, R = SH) which, on being refluxed with a solution of equal volumes of acetic anhydride and 48% hydrobromic acid, underwent cleavage of the phenoxy groups and cyclization to give bicyclo (4.4.0) decane-1-thianium bromide (V, X = Br). The corresponding picrate (m.p. 178–179°), iodide, chloride, and hydroxide were prepared (Experimental).

Two routes were developed for the preparation of the mercaptan (X, R = SH) from 1,9-diphenoxy-5-bromononane (X, R = Br), in turn prepared by treatment of the corresponding alcohol (X, R = OH) with phosphorus tribromide in carbon disulfide solution. In one, the bromide was converted in essentially quantitative yield to the corresponding thiocyanate (X, R = SCN) which was reduced with lithium aluminum hydride to the desired mercaptan (X, R = SH). Alternatively, the bromide was converted to the isothiuronium salt [X, $R=SC(NH_2)_2^+Br^-$], and the latter hydrolyzed with ammonia to the mercaptan.

The preparation of 1,9-diphenoxy-5-nonane 1 (X, R = OH) is described in the Experimental section.

Discussion. Attempts to dehydrohalogenate and aromatize the bicyclo[4.4.0]decane-1-thianium system to VI using sulfur and palladium gave only tars. When the sulfonium hydroxide V (X = OH) was thermally decomposed, Hoffmann elimination occurred to yield 2-(3-butenyl) tetrahydrothiopyran (XI) as evidenced by intense bands at 990 and 910 $cm.^{-1}$ in the infrared spectrum of the product that are characteristic[8] of the terminal vinyl group.

Although the possibility of *cis-trans* isomerism of the decalin type exists in compounds III, IV, and V, no evidence for the existence of such isomers was obtained.

The most toxic of the compounds tested was bicyclo[4.4.0]decane-1-thianium bromide (V, X = Br) which showed a minimum lethal dose of 43 mg./kg. on intraperitoneal injection in Webster white mice. The drug-induced convulsions and death could be prevented by prior administration of central nervous system depressants (Nembutal) but not by atropine.[9]

(5) N. J. Leonard, T. L. Brown, and T. W. Milligan, *J. Am. Chem. Soc.*, **81**, 504–5 (1959); C. G. Overberger and A. Lusi, *J. Am. Chem. Soc.* **81**, 506–7 (1959).

(6) L. F. Fieser and R. G. Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

(7) R. Mozingo, *J. Am. Chem. Soc.*, **67**, 2092 (1945).

(8) N. Sheppard and G. B. B. M. Sutherland, *Proc. Roy. Soc.*, **A196**, 195 (1949).

(9) We wish to express our appreciation of Professor R. H. Dreisbach and J. V. Levy of the Department of Pharmacology and Therapeutics of the Stanford University School of Medicine for testing the compounds.

EXPERIMENTAL[10]

3-(2-Tetrahydrofuryl)propyl isothiuronium picrate [VIII, $R = SC(NH_2)_2^+$ *picrate*]. To a solution of 40 g. of 3-(2-tetrahydrofuryl)propanol in 125 ml. of dry benzene was added 39 g. of thionyl chloride during 15 min. The reaction mixture was boiled for 20 min. and then freed of solvent at room temperature using the aspirator. To the residue was added 120 ml. of ethanol containing 21 g. of thiourea and the resulting solution was heated at 90° for 16 hr. Removal of solvent at the aspirator left a thick glass which could not be induced to crystallize. A small portion was taken up in alcohol and treated with picric acid. Addition of water yielded a bright yellow solid, 3-(2-tetrahydrofuryl)propyl isothiuronium picrate, which was crystallized from ethanol giving yellow crystals of m.p. 177.5–178.7°.

Anal. Calcd. for $C_{14}H_{19}N_5O_8S$: C, 40.28; H, 4.59. Found: C, 40.58; H, 4.75.

Bicyclo[3.3.0]octane-1-thianium picrate (III, X = *picrate*). A mixture of 45 g. of the crude 3-(2-tetrahydrofuryl)propyl isothiuronium chloride (see above) and 100 g. of concentrated ammonia was heated for 3 hr. on the steam bath. The cooled mixture was extracted with benzene and the benzene was removed by distillation leaving 18 g. of crude 3-(2-tetrahydrofuryl)propyl mercaptan (VIII, R = SH). A mixture of 17 g. of the crude mercaptan and 300 ml. of concentrated hydrochloric acid was heated for 16 hr. on the steam bath, cooled, diluted with 200 ml. of water, and filtered to remove a small amount of solid. The filtrate was extracted with 75 ml. of benzene and then evaporated to dryness at 50° and reduced pressure. The residue was taken up in 75 ml. of water, the solution was filtered, and the filtrate combined with a solution of 30 g. of picric acid and 4.6 g. of sodium hydroxide. The yellow precipitate which appeared was separated by filtration and crystallized twice from water to give 31 g. of bicyclo[3.3.0]octane-1-thianium picrate in the form of bright yellow crystals of m.p. 257–258°.

Anal. Calcd. for $C_{13}H_{15}N_3O_7S$: C, 43.69; H, 4.23; N, 11.76. Found: C, 43.83; H, 4.25; N, 11.55.

Bicyclo[3.3.0]octane-1-thianium bromide (III, X = *Br*). The crude 3-(2-tetrahydrofuryl)propyl mercaptan obtained from 3.5 g. of 3-(2-tetrahydrofuryl)propyl isothiuronium picrate by hydrolysis with 50 ml. of concentrated ammonia and hexane extraction of the hydrolysis mixture followed by removal of solvent, was heated at 80° for 18 hr. with a mixture of 15 ml. of 48% hydrobromic acid and 15 ml. of acetic anhydride. The cooled reaction mixture was diluted with an equal volume of water and filtered. The filtrate was extracted with 75 ml. of benzene, and then evaporated to dryness at 70–80° (20 mm.). The residue was taken up in 30 ml. of absolute ethanol, the solution was decolorized with Darco, then evaporated to dryness. The residue was taken up in 20 ml. of absolute ethanol, the solution was decolorized, concentrated to a volume of 4 ml., and then diluted with dry ether to the point of cloudiness. After 10 hr. at 0°, filtration followed by an ether wash of the solid, gave 1.3 g. of white crystals which sublimed above 240°. Recrystallization from absolute ethanol gave material which sublimed sharply at 249.5–250.5°. Treatment with a solution of picric acid in water converted this material to bicyclo[3.3.0]octane-1-thianium picrate, identical in melting point and mixed melting point with that described above.

Methyl 4-(2-tetrahydrothienyl)butyrate (IX, $R = COOCH_3$). A suspension of 6.3 g. of Darco in 130 ml. of methanol containing 0.3 g. of palladium chloride was shaken with hydrogen at 40 p.s.i. during 30 min.[7] Then, 0.20 ml. of concentrated sulfuric acid and 1.2 g. of 4-(2-thienyl) butyric acid[6] were added, and the hydrogenation was effected by shaking the mixture for 6 hr. at 40 p.s.i. hydrogen pressure. After filtering off the catalyst, 3.55 g. of powdered mercuric chloride was added to the filtrate. The mercuric chloride was dissolved by gentle warming, and when a solution was obtained an equal volume of water was added. After 12 hr. at 0°, the white crystals which had formed were separated by filtration, washed with water, dried in air, and crystallized twice from methanol to give a 50% yield of the mercuric chloride adduct of methyl 4-(2-tetrahydrothienyl)-butyrate of m.p. 106.4°–106.9°.

Anal. Calcd. for $C_9H_{16}O_2S.HgCl_2$: C, 23.58; H, 3.51; S, 6.97. Found: C, 23.46; H, 3.48; S, 6.90.

4-(2-Tetrahydrothienyl) butanol (IX, $R = CH_2OH$). A suspension of 27 g. of the mercuric chloride adduct of methyl 4-(2-tetrahydrothienyl)butyrate in 100 ml. of methanol was saturated with hydrogen sulfide. After filtering off the precipitate of mercuric sulfide, the methanol was removed by distillation at reduced pressure. The oil so obtained was taken up in dry ether, the solution was dried with Drierite, and the solvent was removed to leave 9.9 g. of methyl 4-(2-tetrahydrothienyl)butyrate, a pale yellow oil. This ester was reduced by adding it in solution in 200 ml. of absolute ether, during 30 min. to a solution of 8.0 g. of lithium aluminum hydride in 300 ml. of absolute ether. The reaction mixture was refluxed for 30 min., and the excess hydride was decomposed by the addition of 70 ml. of methanol followed by 6*N* hydrochloric acid in such amount as to dissolve the solids present. The ether layer was separated, the aqueous layer was extracted with five 100-ml. portions of ether, and the combined extracts were dried over potassium carbonate, and freed of solvent by distillation. The residue, crude 4-(2-tetrahydrothienyl)butanol, weighed 8.0 g. (85% yield).

For characterization, the α-naphthylurethane (m.p. 78.6–79.3°) was prepared in the usual manner by heating the reactants at 90° for 4 hr., followed by extraction and crystallization of the product using hexane.

Anal. Calcd. for $C_{19}H_{23}O_2NS$: C, 69.26; H, 7.04; N, 4.25; S, 9.73. Found: C, 69.17; H, 6.90; N, 4.31; S, 9.73.

Bicyclo[4.3.0]nonane-1-thianium chloride (IV, X = *Cl*). A mixture of 100 mg. of crude 4-(2-tetrahydrothienyl)butanol and 5 ml. of concentrated hydrochloric acid was heated at 120° for 3 hr. The clear solution was evaporated to dryness at 50° (25 mm.) and the residue was 4 times taken up in 3-ml. portions of absolute ethanol with intervening evaporations to dryness at 50° (25 mm.). The final residue was dissolved in 5 ml. of hot water and the solution was combined with a solution of 0.16 g. of picric acid in 5 ml. of hot water. After 12 hr. at 0°, the yellow crystals which had separated were collected and crystallized from 5 ml. of water to yield 0.15 g. of bicyclo[4.3.0]nonane-1-thianium picrate of m.p. 234.5–235°.

Anal. Calcd. for $C_{14}H_{17}O_7N_3S$: C, 45.28; H, 4.61; N, 11.31; S, 8.63. Found: C, 45.48; H, 4.56; N, 11.39; S, 8.52.

The picrate (0.10 g.), dissolved in 15 ml. of warm water, was passed through a 1 × 20 cm. column of Dowex 2 anion exchange resin which had previously been washed with 4*N* hydrochloric acid and water. The solution of the picrate was followed by 20 ml. of water, and the eluate was evaporated to dryness to yield bicyclo[4.3.0]nonane-1-thianium chloride in the form of highly hygroscopic white crystals. Treatment of an aqueous solution of the chloride with picric acid regenerated the picrate.

Bicyclo[4.3.0]nonane-1-thianium bromide (IV R = *Br*). The bromide was prepared in 87% yield from 4-(2-tetrahydrothienyl)butanol (4.0 g.) by treatment with 80 ml. of a 1:1 mixture by volume of 48% hydrobromic acid and acetic anhydride for 17 hr. at 85°. The reaction mixture was diluted with an equal volume of water and extracted with 75 ml. of benzene. The aqueous layer was filtered and taken to dryness at 80° (25 mm.). The residue was taken up in absolute ethanol and ether was added to incipient crystallization. After refrigeration, the crystalline mass was collected and crystallized from absolute ethanol to yield 4.9 g. of the bromide, m.p. 216.5–217° (sublimes).

Anal. Calcd. for $C_8H_{15}BrS$: C, 43.05; H, 6.77; Br, 35.81. Found: C, 43.14; H, 6.79; Br, 35.91.

(10) Melting points are not corrected. Analyses by Microchemical Specialties, Berkeley, Calif.

1,9-Diphenoxy-5-nonanol (X, *R* = *OH*). The preparation of this compound was effected by two procedures.

Procedure A. A solution of 56 g. of 1,9-diphenoxy-5-nonanone (prepared by the method of Walther,[11] and having m.p. 77.8–78.1°) in 600 ml. of methanol was maintained at 55–60° during the addition of a solution of 5 g. of sodium borohydride in 50 ml. of methanol. The solution was allowed to stand at room temperature for 2 hr., then acidified to *p*H 5 by the addition of concentrated hydrochloric acid. The solvent was removed at reduced pressure and the residue was extracted with the minimum amount of carbon tetrachloride. The extract was cooled to 3° and the crystals which separated were filtered off to yield 50.4 g. of 1,9-diphenoxy-5-nonanol of m.p. 58.3–59.0°. This material did not depress the melting point of that prepared by procedure B in a mixture.

Procedure B. A mixture of 59.1 g. of magnesium turnings and 400 ml. of dry ether was combined with a solution of 450 g. of ε-phenoxybutyl chloride (prepared in 63% yield by the action of sodium phenolate on 1,4-dichlorobutane in aqueous solution and having b.p. 92–93° (0.5 mm.) m.p. *ca.* 20°) in 1 l. of anhydrous ether, at such a rate as to maintain gentle reflux. To the solution of the Grignard reagent, cooled in an ice bath, was added a solution of 87.5 g. of ethyl formate in 250 ml. of dry ether during 4 hr. The reaction mixture was decomposed with 160 ml. of water followed by a solution of 136 g. of concentrated sulfuric acid in 640 ml. of water. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ether solutions were dried over potassium carbonate, and distilled to dryness. The oily residue was crystallized from carbon tetrachloride to yield 315 g. of 1,9-diphenoxy-5-nonanol of m.p. 59–60°. Several crystallizations from carbon tetrachloride gave material of m.p. 60.0–60.5°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.84; H, 8.67.

1,9-Diphenoxy-5-bromononane. A mixture of 125 g. of 1,9-diphenoxy-5-nonanol and 125 g. of phosphorus tribromide was dissolved in 100 ml. of carbon disulfide and the solution was allowed to stand for 1 week. The carbon disulfide was removed in a current of air, the residue was decomposed by the addition of ice and the product was taken up in ether. Evaporation of the dried ether solution followed by crystallization of the residue from 300 ml. of methanol (0°) gave 128 g. of 1,9-diphenoxy-5-bromononane, m.p. 44–46°. Recrystallization from methanol raised the m.p. to 45.4–46.8°.

Anal. Calcd. for $C_{21}H_{27}BrO_2$: C, 64.43; H, 6.95. Found: C, 64.35; H, 7.02.

1,9-Diphenoxy-5-mercaptononane-S-mercuribromide (X, *R* = *SHgBr*). This derivative of the mercaptan X (R = SH), was prepared in two ways.

Procedure A. A solution of 10 g. of 1,9-diphenoxy-5-bromononane and 5.0 g. of potassium thiocyanate in 120 ml. of ethanol was boiled for 15 min., then cooled to yield 9.5 g. of 1,9-diphenoxy-5-thiocyanononane (X, R = SCN) in the form of white crystals of m.p. 62.8–64°.

Anal. Calcd. for: $C_{22}H_{27}NO_2S$: C, 71.50: H, 7.37; N, 3.79. Found: C, 71.55; H, 7.36; N, 4.00.

A mixture of 0.2 g. of thiocyanate and 3.5 g. of granulated zinc in 7 ml. of acetic acid was heated for 90 min. on the steam bath. The supernatant liquid was decanted, diluted with several volumes of water, and extracted with hexane. The hexane was boiled off and the residue was treated with a solution of mercuric bromide in ethanol to give a white precipitate of 1,9-diphenoxy-5-mercaptononane-*S*-mercuribromide of m.p. 117–118°. The yield was 50% of the theory and recrystallization from ethanol raised the m.p. to 118.5–120.1°.

Anal. Calcd. for $C_{21}H_{27}BrHgO_2S$: C, 40.42; H, 4.36. Found: C, 40.72; H, 4.61.

Reduction of the thiocyanate (14.4 g.) with lithium aluminum hydride (8 g.) in ether, followed by addition of mercuric bromide to an alcoholic solution of the product gave a 58% yield of the mercaptan-mercuribromide, identical with that described herewith.

Procedure B. A solution of 8.0 g. of 1,9-diphenoxy-5-bromononane and 1.6 g. of thiourea in 75 ml. of ethanol was refluxed for 48 hr. Five g. of picric acid was added to the reaction mixture and the product was precipitated as an oil which, after being cooled to 0°, crystallized. Crystallization of the solid from ethanol gave 7.5 g. of yellow crystals of m.p. 117.5–119.5°. Recrystallization gave pure 1,9-diphenoxynonane-5-isothiuronium picrate [X, R = $SC(NH_2)_2^+$ picrate$^-$] of m.p. 119.5–121°.

Anal. Calcd. for $C_{28}H_{33}N_5O_9S$: C, 54.62; H, 5.40; N, 11.38. Found: C, 54.81; H, 5.64; N, 11.12.

An 8.6-g. sample of the isothiuronium picrate was combined with 50 ml. of concentrated ammonia and 10 ml. of hexane, and the mixture was heated on the steam bath for 1-hr. The cooled reaction mixture was extracted with hexane, the extract was dried over sodium sulfate, and freed of solvent using the aspirator. The product, crude 1,9-diphenoxy-5-mercaptononane, was a pale yellow oil which crystallized when cooled to −10°. The oil was combined with a solution of 5.0 g. of mercuric bromide in 230 ml. of ethanol. The solution was brought to a boil, then allowed to cool. Filtration yielded 7.7 g. of 1,9-diphenoxy-5-mercaptononane-*S*-mercuribromide which melted at 117.5–119.2°. Digestion of the mercuribromide with hexane raised the melting point to 118.5–120.1°. This material showed no melting point depression when combined with the mercuribromide prepared by procedure A.

Bicyclo[4.4.0]decane-1-thianium picrate (V, *X* = *picrate*). A mixture of 4 g. of 1,9-diphenoxy-5-mercaptononane (prepared by treatment of the equivalent amount of the mercuribromide with H_2S in ethanol, followed by filtration and solvent removal), 20 ml. of 48% hydrobromic acid, and 20 ml. of acetic anhydride was refluxed for 18 hr. The cooled reaction mixture was diluted with water to a volume of 80 ml. and then extracted with 100 ml. of benzene. The aqueous layer was evaporated to dryness at 70° (20 mm.), and the residue was combined with a hot solution of 2.5 g. of picric acid in 200 ml. of water to give a yellow precipitate which after 2 crystallizations from water melted at 178.6–179.7° and constituted 2.9 g. of bicyclo[4.4.0]decane-1-thianium picrate.

Anal. Calcd. for $C_{15}H_{19}N_3O_7S$: C, 46.74; H, 4.97; N, 10.90. Found: C, 47.04; H, 5.06; N, 10.84.

In a similar experiment, the residue left after the removal of the aqueous layer (see above) was repeatedly crystallized from absolute alcohol to give a 66% yield of *bicyclo[4.4.0]-decane-1-thianium bromide* (V, *X* = *Br*), a white nonhygroscopic solid which sublimed at 266–267°.

Anal. Calcd. for $C_9H_{17}BrS$: C, 45.57; H, 7.25. Found: C, 45.82; H, 7.35.

Treatment of the bromide with picric acid in aqueous solution gave a picrate of m.p. 179–179.6°, identical with that described above.

When 1,9-diphenoxy-5-mercaptononane-*S*-mercuribromide was subjected to the hydrobromic acid–acetic anhydride treatment described above, a small amount of a green solid was obtained, which, after crystallization from ethanol, had m.p. 59.2–62.2°. Analysis indicated that this green solid was a double salt of mercuric bromide with bicyclo-[4.4.0]decane-1-thianium bromide.

Anal. Calcd. for $(C_9H_{17}S)_2HgBr_4$: C, 25.89; H, 4.10. Found: C, 25.89; H, 4.21.

Saturation of a suspension of the green solid in water with hydrogen sulfide, followed by filtration and addition of picric acid to the filtrate gave bicyclo[4.4.0]decane-1-thianium picrate of m.p. 177.5–179.0° which did not depress the melting point of the picrate described above.

Bicyclo[4.4.0]decane-1-thianium hydroxide (V, *R* = *OH*). The hydroxide was obtained as colorless, viscous, strongly basic sirup on evaporation of the filtrate from the combina-

(11) G. Walther, *Ber.*, 84, 306 (1951).

tion of 50 ml. of water, 9.0 g. of silver oxide, and 4.5 g. of bieyclo[4.4.0]decane-1-thianium bromide.

A 3.5-g. sample of the hydroxide was heated for 6 hr. at 150°. The product was taken up in hexane, the solution was dried and freed of solvent. Distillation of the residual oil gave a mobile, colorless liquid, b.p. 100° (15 mm.), believed to be *2-(3-butenyl)tetrahydrothiopyran.*

Anal. Calcd. for $C_9H_{16}S$: C, 69.16; H, 10.32. Found: C, 68.94; H, 10.44.

Bicyclo[4.4.0]decane-1-thianium iodide (V, $X = I$). The iodide was prepared by titrating a sample of the sulfonium hydroxide with 47% hydriodic acid, followed by removal of water at 80° (20 mm.), and crystallization of the residue from absolute alcohol. The iodide was a white crystalline, relatively nonhygroscopic solid which sublimed at 264–265° with decomposition. Treatment with a solution of the iodide with picric acid gave the picrate, identical with that described herewith in a mixed melting point determination.

STANFORD, CALIF.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Structures Related to Morphine. XI.[1] Analogs and a Diastereoisomer of 2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan

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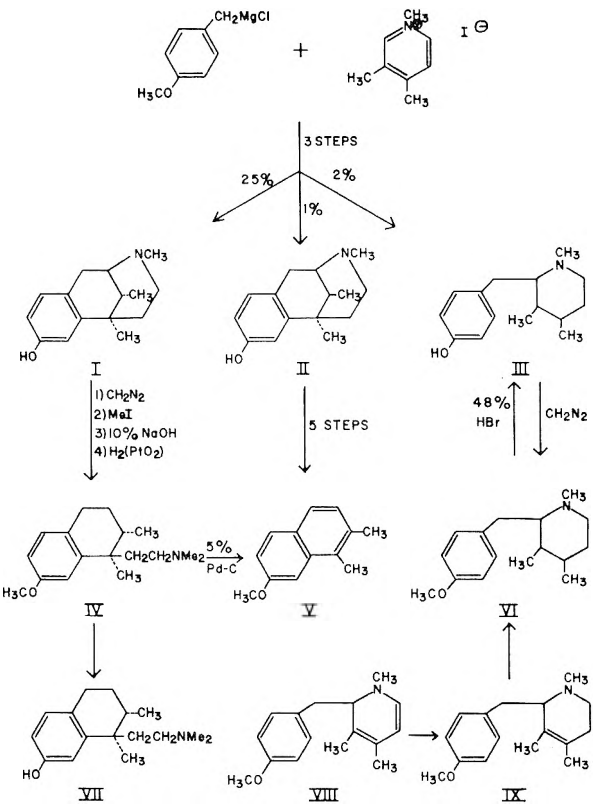
2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) has been degraded to 7-methoxy-1,2-dimethylnaphthalene (V) *via* 7-methoxy-1,2-dimethyl-1-(2-di-methylaminoethyl)-1,2,3,4-tetrahydronaphthalene (IV). Similar degradation of an isomeric by-product (II) obtained in 1% yield in the synthesis of I also gave V proving diastereoisomerism for I and II at carbon 9. Another by-product isolated in 2% yield appears to be the piperidine derivative (III). Hydrobromic acid treatment of IV yielded the phenolic base (VII) which is practically devoid of analgesic activity, paralleling results obtained in another series (*cf.* reference 3).

It has been amply demonstrated[2–4] that the introduction of a phenolic hydroxyl *meta* to the quaternary carbon in a number of synthetic compounds containing a phenyl- or benzo-azabicyclo structure characteristic of morphine, markedly improves analgesic behavior. On the other hand in the one published instance of similar substitution in an open nitrogen counterpart[3] there was an increase in acute toxicity and a fourfold decrease of analgesic potency unless the phenolic hydroxyl was protected by methyl. To determine whether this would be true in another series, 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) has been converted to 7 - hydroxy - 1,2 - dimethyl - 1 - (2 - dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VII) for comparison with the corresponding methoxy (IV) and deoxy[4] compounds. The transformation of I to VII was effected by exhaustive methylation of the methyl ether of I, hydrogenation of the resulting methine to the methyl ether (IV), and *O*-demethylation of IV with aqueous hydrobromic acid. Either the methine or the corresponding hydrogenated base (IV) could be aromatized to 7-methoxy-1,2-dimethylnaphthalene (V) which was used as a reference compound as described here.



In synthesizing larger amounts of I[4a] not only was an improved procedure developed but, in

(1) Communication X, E. L. May, *J. Org. Chem.*, **23**, 947 (1958).

(2) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949); O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949); O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(3) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955).

(4) (a) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); (b) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

addition, two phenolic by-products[5] were isolated from the residues of several combined preparations. One of these proved to be a diastereoisomer (II, 1% yield from 3,4-lutidine methiodide) of I as shown by its degradation to V in a manner identical to that described for I. Since the 5,8-iminoethano system is constrained to a *cis*-fusion, I and II can differ only at carbon 9. For this reason and for reasons stated previously,[4a] the methyl of carbon 9 is tentatively placed *trans* (equatorial) to the *quasi*-equatorial methyl of carbon 5 for the hydroaromatic ring.[6]

The other by-product from the synthesis of I appears to be 2-(*p*-hydroxybenzyl)-1,3,4-trimethylpiperidine (III). This compound would be produced by complete hydrogen saturation of the *N*-containing ring of the dihydro base (VIII)[7] and *O*-demethylation of the resultant VI under the conditions used to cyclize and *O*-methylate the major product (IX) to I and II.

By deliberate over-reduction of VIII in two stages, the second involving the use of palladium-charcoal and the *base* (IX) a 40% yield of VI could be obtained along with 25–30% of an isomeric product. The two are presumed to be diastereoisomers corresponding to VI. The predominant isomer VI and the III isolated as a by-product were interconvertible; diazomethane methylation of III gave VI and 48% hydrobromic acid treatment of VI (15 min. reflux) yielded III.

As for analgesic activity, the diastereoisomer II has a subcutaneously effective dose in mice of 0.4 mg./kg.[8] compared to 3.0 mg./kg. for I and 2.1 for morphine. Therefore, one can predict reasonably that the *levo*-isomer of II is 9–10 times as potent as (*levo*-) morphine. The piperidine derivative (III), without a quaternary carbon, and the methyl ether of I produced analgesia in mice at *ca.* 15 and 10 mg./kg. respectively. The phenolic open nitrogen analog (VII) of I was ineffective at doses up to 100 mg./kg. while the corresponding methyl ether (IV) and the deoxy analog[4b] were active at 25–30 mg./kg. This is at least the second example[3] of the detrimental effect of a free phenolic hydroxyl situated *meta* to the quaternary carbon in an analgesic possessing an aliphatic tertiary nitrogen. As stated before there is a favorable effect when the nitrogen is heterocyclic. Perhaps there is intramolecular interference of the free-swinging aliphatic nitrogen with the phenolic hydroxyl which prevents each from exercising its function *in vivo*. Molecular models and hydrogen ion titration curves for I and VII are consistent with this postulate. Further studies and publication of data along these lines are planned.

EXPERIMENTAL

Microanalyses were performed by Paula M. Parisius, Elizabeth Fath, and Byron Baer of the Institutes service analytical laboratory, Dr. William C. Alford, director. Melting points (Hershberg apparatus) are corrected.

2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I).[4a] A stirred suspension of 50 g. of 3,4-lutidine methiodide and 75 ml. of dry ether was treated during 15–20 min. with 700 ml. of 0.3–0.35*M* ethereal *p*-methoxybenzylmagnesium chloride. The mixture was stirred for an additional 60–90 min. and poured with vigorous stirring into 250 ml. of ice water containing 50 g. of ammonium chloride. The ethereal layer was extracted 3–4 times with a total of 250 ml. of 2*N* hydrochloric acid. The combined extracts were made alkaline with ice–ammonium hydroxide and the liberated base was extracted with 250 ml. of ether in three portions. The combined, dried (Na_2SO_4) extracts were evaporated at the water pump leaving 42–45 g. of oil (VIII) which was dissolved quickly in 200 ml. of ice cold *N* hydrochloric acid (nitrogen atmosphere) and the solution shaken under hydrogen with 8 g. of 5% palladium–barium sulfate. After 10–15 hr. 0.8–0.9 molar equivalent of hydrogen had been absorbed and reaction had almost ceased. The mixture was filtered through Super-Cel and made alkaline with ice cold ammonium hydroxide. The liberated material was shaken into ether. The dried extracts were distilled, the residue at a bath temperature of 125–140°/0.1 mm., to give 20–24 g. of tetrahydro base (IX) which, with 175 ml. of 48% hydrobromic acid, was kept at 135–140° for 20–25 hr. The resultant solution was poured into ice water and made alkaline with concentrated ammonium hydroxide. Extraction with 250–300 ml. of chloroform followed by drying and evaporation of the chloroform gave a residue which crystallized on trituration with 25 ml. of cold methanol. After 10–20 hr. at −5° the yield of I was 10–12.5 g.; m.p. 228–233°.

Distillation of the methanol from the filtrates of 2 of the above preparations gave a residue which was evaporatively distilled at 180°/0.5 mm. The viscous distillate[9] was dissolved in about 25 ml. of methanol. On cooling for 2 hr. at 5°, 2.1 g. of solid, m.p. 195–220°, separated. It was dissolved in 20 ml. of methanol and acidified with gaseous hydrogen chloride. After an hour at −10° 0.5 g.[10] of the hydrochloride of II, m.p. 268–271°, was obtained. It crystallized from 95% ethanol-ether in needles of m.p. 269–272° (dec.).

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28. Found: C, 67.02; H, 8.41.

The *base* II crystallized from alcohol in prisms, m.p. 215–217.5°.

(5) These same by-products have been independently isolated and characterized by the Smith Kline and French Laboratories (personal communication).

(6) These assignments appear consistent with data obtained from infrared spectral comparisons of I and II with 3-hydroxy-*N*-methylmorphinan[2] and 3-hydroxy-*N*-methylisomorphinan.[8]

(7) The hydrogenation of VIII, formed in the first step in the preparation of I, never proceeded beyond the absorption of 0.9 molar equivalent even on prolonged shaking, in the presence of dilute hydrochloric acid and palladium–barium sulfate. Reaction was essentially complete after 4–5 hr.

(8) Compare this also with (±)-3-hydroxy-*N*-methylisomorphinan of M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, 80, 1186 (1958). The pharmacological data for our compounds are from Dr. N. B. Eddy, Chief, Section on Analgesics, and staff.

(9) Attempts at chromatographic separation were not particularly promising.

(10) An additional 0.3–0.4 g. of II could be obtained through the difficultly soluble (in methanol) hydrochloride salt by combining all mother liquors and adding gaseous hydrogen chloride. Furthermore the 12 g. of I, m.p. 228–232°, above usually contained about 0.3 g. of II which was separated in the same fashion (hydrochloride salt from methanol).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.13; H, 9.15.

2-(*p-Hydroxybenzyl*)-*1,3,5-trimethylpiperidine* (III). The filtrate from the 2.1 g. of solid of m.p. 195–220° (above) was concentrated to 10–15 ml. and kept at −5°. After 15–20 hr. 2.1 g. of crystals, m.p. 160–174° were obtained. A recrystallization from 10 ml. of methanol gave 1.5 g. of m.p. 176–179°. The analytical sample melted at 178–179.5°; rectangular plates.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.23; H, 9.94. Found: C, 77.53; H, 9.83.

The *hydrochloride* crystallized from alcohol-ether in square plates, m.p. 220–222°.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97. Found: C, 66.75; 66.63; H, 8.86, 8.98.

2-(*p-Methoxybenzyl*)-*1,3,4-trimethylpiperidine* (VI) *picrate.* (a) *From* III. Ethereal diazomethane methylation of III in methanol-ether as described for I below gave a 90% yield of VI isolated as the picrate. It crystallized from alcohol-acetone in yellow rods of m.p. 175–176°.

Anal. Calcd. for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92. Found: C, 55.57; H, 5.90.

(b) *From* IX. Two g. of distilled IX, 1.0 g. of 5% palladium-charcoal and 15 ml. of alcohol absorbed 0.9 molar equivalent of hydrogen during 3.5 hr. The mixture was filtered through Super-Cel and the combined filtrate and washings (*ca.* 25 ml.) were treated with 2.3 g. of picric acid. On warming to solution and keeping at 25° for 1.5–2 hr., 1.9 g. (45%) of picrate, m.p. 157–165°, separated. After two careful recrystallizations from acetone or acetone-alcohol it melted at 170–173° and was undepressed by picrate prepared in the diazomethane methylation of III.

The filtrate from the 1.9 g. of picrate, m.p. 157–165° deposited rapidly 1.2 g. (35%) of another (isomeric)[11] picrate, m.p. 158–162°. Two recrystallizations from acetone made the melting point constant at 166.5–168.5°; yellow prisms.

Anal. Calcd. for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92. Found: C, 55.51; H, 5.72.

Conversion of VI *to* III. The base VI (0.5 g. from 1.0 g. of picrate, m.p. 171–173.5°, prepared from IX) and 4 ml. of 48% hydrobromic acid were refluxed for 30 min., cooled, diluted with water, and made alkaline with ammonium hydroxide. On addition of a few ml. of ether, the base gradually crystallized. It was kept at 5° overnight and filtered; yield 0.4 g. (80%), m.p. 173–177°. Upon recrystallization from 2–3 ml. of methanol the m.p. was 178–179.5° alone or in mixture with III isolated from the residues of the preparation of I. The infrared spectra of the two were also identical.

2'-Methoxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromide. Three g. of I, 30 ml. of methanol, and 45 ml. of 3% ethereal diazomethane were stirred to solution (30–45 min.). After 4 hr., 45 ml. additional diazomethane solution was added and the mixture kept for 2–3 days at *ca.* 25°. Solvents were distilled *in vacuo* and the methyl ether evaporatively distilled at 130° (bath temperature) and 0.1–0.5 mm. to give 3.0 g. (94%). The hydrobromide salt (from ether–33% HBr–acetic acid) crystallized from acetone in flakes, m.p. 234–236.5°.

Anal. Calcd. for $C_{16}H_{24}BrNO$: C, 58.90; H, 7.41. Found: C, 58.74; H, 7.63.

The *methiodide* (from acetone) melted at 177–180°.[12]

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.71; H, 6.76. Found: C, 52.47; H, 6.64.

7-Methoxy-1,2-dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (IV) *hydrobromide.* The methiodide above (2.4 g.) and 30 ml. of 10% sodium hydroxide were refluxed for 3 hr. The oily base was dried (sodium sulfate) in ether and evaporatively distilled (150°/0.5 mm.). The 1.3 g. of distillate, 20 mg. of platinum oxide, and 10 ml. of methanol absorbed one molar equivalent of hydrogen in 20 min. The filtered solution was evaporated to dryness *in vacuo*, the oil was dissolved in ether and acidified with 33% hydrogen bromide in acetic acid; yield of IV hydrobromide 1.3 g. (62%), m.p. 187–190°; flakes from acetone, m.p. 192–193.5°.

Anal. Calcd. for $C_{17}H_{28}BrNO$: C, 59.64; H, 8.24. Found: 59.49; H, 8.22.

7-Hydroxy-1,2-dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VII). One g. of IV and 10 ml. of 48% hydrobromic acid were refluxed for 30 min., cooled, made alkaline with ammonium hydroxide, and extracted with ether. Evaporation of the dried ethereal solution left 0.6 g. (84%) of VII; plates from ether, m.p. 132–136°.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.70; H, 10.19. Found: C, 77.87; H, 10.36.

The *picrate* (containing 2 molar equivalents of picric acid)[13] crystallized from alcohol (containing a little picric acid) in prisms, m.p. 142–142.5°.

Anal. Calcd. for $C_{16}H_{25}NO \cdot 2[C_6H_2(NO_2)_3OH]$: C, 47.66; H, 4.43; N, 13.90; mol. wt., 705.6. Found: C, 47.69; H, 4.31; N, 13.76; mol. wt.,[13] 710, 724.

The *hydrochloride* (from acetone) was hygroscopic but became a stable powder melting at 187–189°.

Anal. Calcd. for $C_{16}H_{26}ClNO \cdot 1/2\ H_2O$: Cl, 12.10. Found: Cl, 12.16.

There was no weight loss on drying the hydrochloride at 100° without vacuum. The base VII could be regenerated from either the hydrochloride or dipicrate.

7-Methoxy-1,2-dimethylnaphthalene (V) *picrate.* (a) *From* I. The methiodide of 2'-methoxy-2,5,9-trimethyl-6,7-benzomorphan (methyl ether of I), 0.5 g., and 5 ml. of 10% sodium hydroxide were refluxed for 2 hr. and the resultant methine[14] isolated and hydrogenated as described above. The resultant 0.3 g. of base IV and 0.3 g. of 5% palladium-charcoal were intimately mixed in a test tube fitted with an air vent. The tube was then immersed in a 250° bath. The temperature of the bath was raised to 315° during 10 min. and kept at 305–320° for 20 min. The cooled mixture was extracted thrice with ether. The ether extracts were washed with dilute hydrochloric acid, dried and evaporated leaving a residue which was evaporatively distilled at an air-bath temperature of 100–110° (0.1 mm.). The distillate (0.1 g.), 0.1 g. of picric acid, and 4 ml. of 95% ethanol were warmed to solution, then cooled gradually to −15° to give 80–130 mg. (15–25% based on starting methiodide) of the picrate of V, m.p. 132–134°; orange needles from methanol.

Anal. Calcd. for $C_{19}H_{17}N_3O_8$: C, 54.93; H, 4.13. Found: C, 55.16; H, 4.01.

(b) *From* II. Methylation of 0.4 g. of II as described for I gave 0.65 g. of the *methiodide* of the methyl ether of II; needles from absolute alcohol–ether, m.p. 217–218°, plates from acetone, m.p. 232–234°. The needles were analyzed.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.72; H, 6.77. Found: C, 52.60, 52.83, H, 6.83, 6.64.

This *methiodide* (0.6 g.), 0.6 g. of potassium hydroxide and 6 ml. of water were kept on the steam bath for 2 hr. and the oily base dissolved in ether. The dried ethereal extracts were evaporated. The resulting base was aromatized with 0.4 g. of 5% palladium-charcoal as described above. The picrate (90 mg., 14% based on methiodide) melted at 131–133° and was undepressed when mixed with that prepared from I. The infrared spectra of the two were also identical.

(11) We believe this picrate is a diastereoisomer corresponding to VI. Its melting point was depressed by the isomeric picrate and the IR spectra of the two showed some differences.

(12) E. M. Fry and E. L. May, *J. Org. Chem.*, 24, 116 (1959).

(13) Determined by absolute alcoholic sodium methoxide titration (Thymol Blue) by Dr. A. Patchornik, Visiting Scientist from the Weizmann Institute of Science, Rehovoth, Israel.

(14) Palladium-charcoal treatment of this base also gave a 15% yield of the picrate of V as described in the aromatization of IV.

7-Methoxy-1,2-dimethylnaphthalene. The picrate (0.3 g.) from several combined aromatization experiments was converted to the hydrocarbon (alkali-ether) which was distilled evaporatively (115°/0.5 mm.). It crystallized from methanol in somewhat hygroscopic needles, m.p. 48–49.5°; λ_{max}^{EtOH} 234, 273, 283, 291, 316, (ε 70, 400, 4,070, 4,710, 3,930, 1,430, 2,000).[15] For analysis a sample was dried at 117°.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.33; H, 7.78.

Acknowledgment. We wish to thank Dr. Harry Saroff of this Institute for titration curves and helpful discussions.

BETHESDA 14, MD.

(15) Ultraviolet and infrared data are due respectively to Mrs. Ann Wright and Mr. William Jones, both of this Institute.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Structures Related to Morphine. XII.[1] (±)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (NIH 7519) and Its Optical Forms

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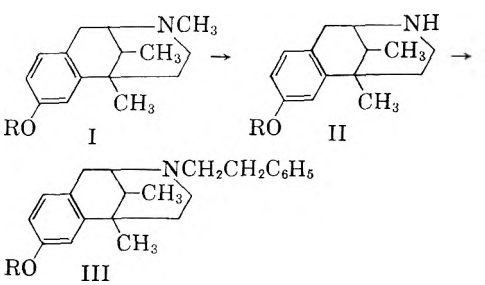
(±)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Ia) and its optical isomers have been converted to analogous *N*-phenethyl compounds (IIIa) in 40% overall yield. The (±)-IIIa (NIH 7519) appears to be a promising agent for the relief of both acute and chronic pain.

In a recent communication[2] we reported the conversion of (±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Ia) and the optical isomers thereof to the corresponding 2-phenethyl analogs (III). In the present report details of these conversions and of the optical resolution of Ia are presented along with additional pharmacological data.

Cyanogen bromide treatment of Ib or Ic in chloroform yielded, after acid hydrolysis, the secondary amines IIb and IIa respectively. Treatment of the crude IIa and IIb with phenylacetyl chloride (aqueous methanol–potassium carbonate medium) afforded the phenylacetamides which, without purification, were reduced to IIIa and IIIb with ethereal lithium aluminum hydride. Refluxing hydrobromic acid was used to convert IIIb to IIIa.



a, R = H; b, R = CH_3; c, R = $COCH_3$

(+)-3-Bromo-8-camphorsulfonic acid [(+)-α-bromo-camphor-π-sulfonic acid] formed crystalline salts of the optical isomers of Ia which could be readily separated on recrystallization from water. The salt of the (−)-isomer of Ia was the less soluble of the two.

Analgesic and toxicity data are given in Table I as specified. It is of interest that the *levo*-isomer of (±)-Ia (NIH 7410) not only contains all of the analgesic activity of the latter but is also much less toxic than the racemate. The *levo*-isomer of (±)-IIIa (20 times more potent than morphine) is about seventy times as potent as the *dextro*-isomer, which nevertheless shows fairly good activity. The methoxy derivatives Ib and IIIb are between morphine and codeine in analgesic effectiveness. Finally, (±)-IIIa has only one sixth the physical dependence potency of morphine in monkeys[3] and appears to be a promising agent for the relief of both acute and chronic pain in man at about one seventh the optimal dose of morphine; its use appears to be attended with fewer and less objectionable side-effects.[4]

EXPERIMENTAL

Melting points are corrected. Microanalyses were performed by Paula M. Parisius and Byron Baer of the Institute's service analytical laboratory, Dr. William C. Alford, Director.

Optical resolution of (±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Ia).[1] The ammonium salt of (+)-3-bromo-

(1) Paper XI of this series. E. L. May and J. Harrison Ager, *J. Org. Chem.*, **24**, 1432 (1959). Ia is the predominant isomer obtained in the synthesis from 3,4-lutidine methiodide.

(2) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(3) G. Deneau, University of Michigan, personal communication.

(4) J. E. Eckenhoff, *Anesthesiology*, **30**, 355 (1959).

(5) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

TABLE I

PHARMACOLOGICAL RESULTS

NIH No.		LD_{50} Mice Subcutaneously	Analgesic Effect[a] ED_{50} Mice Orally	Analgesic Effect[a] ED_{50} Mice Subcutaneously
	Morphine sulfate	576	3.7	2.1
7410	(±)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan.HCl.H_2O (Ia)[1,7]	175	23.9	3.0
7569	(−)-Ia.HBr	>400	14.1	1.7
7571	(+)-Ia.HBr	Convulsant at 20	—	Inactive
7519	(±)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan.HBr (IIIa)	332	6.4	0.25
7613	(−)-IIIa.HBr	147	3.9	0.11
7614	(+)-IIIa.HBr	201	12.9	7.6
7550	(±)-2′-Methoxy-2,5,9-trimethyl-6,7-benzomorphan.HBr (Ib)[1]		21.7	9.8
7625	(±)-2′-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan.HBr (IIIb)		10.6	6.5

[a] For the method of determining analgesic effect see reference (5). All doses are in mg./kg. of substance as administered and are the result of statistical (probit) analysis of the data.

camphor-8-sulfonic acid[6] (5.0 g.), 4.4 g. of Ia hydrochloride[1,7] and 35 ml. of water were kept warm until crystallization began, cooled very gradually to room temperature, then kept at 5° for 3 hr. and filtered. The 6.3 g. of precipitate was dissolved in 200 ml. of boiling water; the solution was concentrated to 150 ml. and kept at −5° overnight to give 3.8 g. of the pure sulfonate salt of (−)-Ia, m.p. 285–288° (dec.). The filtrate, combined with that from the 6.3 g. above was made alkaline with a large excess of concentrated NH_4OH to give 1.7 g. of base of m.p. 178–180° (turbid melt, clear at 212°). This was dissolved in 10 ml. of boiling absolute alcohol and 2–3 ml. of water was added. The solution was seeded with (±)-Ia and kept at −5° for 20 hr. Filtering and washing the crystals with 2:1 alcohol-water gave 0.36 g. of (−)-Ia, m.p. 231–235°. The combined filtrate and washings were warmed and diluted to about 30 ml. with water to give, after cooling gradually to 5°, then at −5° for 24 hr. or more, 1.1 g. (60%) of (+)-Ia, m.p. 181–183°. It crystallized from 1:1 acetone-water in rods of m.p. 183–184.5°, $[\alpha]_D^{20}$ +84.3° (*c* 0.83, abs. ethanol).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.75; H, 9.25.

The *hydrobromide* of (+)-Ia, recrystallized from absolute ethanol–ether, melted at 238–242° (dec.) and had $[\alpha]_D^{20}$ +52.1° (c 1.46, water).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.93; H, 7.15.

The 3.8 g. of pure sulfonate of Ia above was dissolved in 150 ml. of boiling water and treated with excess concd. NH_4OH to give, after 15 hr. at −5°, 1.5 g. (80%) of (−)-Ia, m.p. 183–184.5°, $[\alpha]_D^{20}$ −84.8° (*c* 0.09, absolute ethanol); rods from aqueous acetone.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.91; H, 8.97.

The hydrobromide of (−)-Ia had m.p. 238–241° and $[\alpha]_D^{20}$ −52.0° (*c* 2.00, water).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.66; H, 7.34.

(±)-*2′-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan* (IIIb) *hydrobromide*. A solution of 1.4 g. of Ib[1] in 10 ml. of chloroform was added during 1 hr. to a stirred solution of 0.7 g. of cyanogen bromide in 5 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo*. The residue and 30 ml. of 6% HCl were refluxed for 5–8 hr., the solution was made alkaline and the liberated oil was shaken into ether. Drying and evaporation of the ether left 1.3 g. of crude IIb to which was added 20 ml. of methanol, 6 ml. of water, and 1 g. of K_2CO_3. The mixture was stirred while adding during 10 ml. 1.0 min. of phenylacetyl chloride. After 2 hr. of stirring water was added, and the oil was shaken into ether. The ethereal extracts were washed with dilute HCl then bicarbonate solution, dried, and evaporated to give 1.8 g. of crude phenylacetamide derivative. This in 15 ml. of dry ether was treated gradually (stirring) with 15–20 ml. of 1.6*M* ethereal $LiAlH_4$. The mixture was refluxed 6–8 hr. and treated dropwise with 5–8 ml. of water. The ethereal layer was dried and evaporated to dryness giving 1.7 g. of residue. This in 1:1 acetone-ether was acidified to Congo Red with 33% HBr–AcOH giving 1.2 g. (50%) of IIIb hydrobromide, m.p. 244–245.5°; square plates from acetone.

Anal. Calcd. for $C_{23}H_{30}BrNO$: C, 66.34; H, 7.26. Found C, 66.12; H, 7.19.

(±)-*2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan* (IIIa) *hydrobromide* (NIH 7519). (a) From (±)-Ia. Acetic anhydride (10 ml.) and 10 g. of (±)-Ia were kept on the steam bath for 30–45 min., cooled and poured into ice water. After 5 min. the mixture was made alkaline (while keeping ice cold) with 50% aqueous KOH. The freed base was shaken quickly into ether and dried over Na_2SO. Evaporation of the ether left 11.5 g. of Ic which, in 35 ml. of chloroform, was added during 30–45 min. to a stirred solution of 5 g. of cyanogen bromide in 25 ml. of chloroform. The solution was then refluxed for 3 hr. and evaporated to dryness. The residue and 150 ml. of 6% HCl were refluxed 6–8 hr. The cooled solution was made alkaline with concentrated NH_4OH. The base was shaken into 2:1 1-butanol–benzene to give, after drying, 8.8 g. of crude IIa.[8] This IIa, 100 ml. of methanol, 15–20 ml. of water, and 10 g. of K_2CO_3 were stirred and treated during 15 min. with 10 ml. of phenylacetyl chloride. After an additional 3 hr. of stirring 300 ml. of water was added and the mixture extracted thrice with 2:1 1-butanol–benzene. The combined extracts were washed with dilute HCl, then water, dried and solvents were evaporated *in vacuo*. The residue (12 g.) and 100 ml. of dry ether were stirred while adding dropwise 60 ml. of 1.5*M* ethereal $LiAlH_4$. The mixture was refluxed overnight, cooled in ice, and treated carefully with 60 ml. of 48% HBr Addition of an equal volume of water, filtration, washing with cold water then ether, and drying the precipitate gave 10.5–12 g. of crude IIIa hydrobromide which crystallized from 11 ml. of acetone and 10 ml. of ethyl acetate in a yield of 7 g. (40% based on Ia) m.p. 166–170°; rods from acetone or absolute ethanol–ether.

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.40; H, 7.00.

The *base*, prepared from the hydrobromide with aqueous

(6) Aldrich Chemical Company, Inc., Milwaukee. Wis.

(7) E. L. May and E. M. Fry, *J. Org. Chem.*, 22, 1366 (1957).

(8) E. M. Fry and E. L. May, *J. Org. Chem.*, 24, 116 (1959).

methanol–NH_4OH crystallized from methanol in rods, m.p. 181–182°.

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.27; H, 8.48.

(b) *From* IIIb. A mixture of 10 ml. of 48% HBr and 1.3 g. of IIIb hydrobromide was refluxed vigorously for 20 min. The solid gradually changed to a fluid, dark oil. The mixture was ice cooled, and the aqueous layer was decanted. The residue was dried *in vacuo* then dissolved in 4 ml. of acetone. The solution was again evaporated to dryness *in vacuo*. The residue crystallized from 4 ml. of acetone in a yield of 1.0 g. (after cooling at −5°). It melted at 165–168° and was identical with the (±)-IIIa hydrobromide described above.

(−)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. This levorotatory IIIa was prepared from (−)-Ia as described above for the conversion of (±)-Ia to (±)-IIIa. It melted at 284–287° and had $[\alpha]_D^{20}$ −84.1° (c, 1.12, 95% ethanol).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.82; H, 7.02.

The *base* (prepared from the hydrobromide with aqueous methanolic NH_4OH) crystallized from aqueous methanol or absolute methanol in needles, m.p. 159–159.5°, $[\alpha]_D^{20}$ −122° (*c* 0.74, 95% ethanol).

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 81.94; H, 8.44.

(+)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. As described in the conversion of (±)-Ia to (±)-IIIa above, (+)-Ia yielded (+)-IIIa hydrobromide, m.p. 284–287°, $[\alpha]_D^{20}$ +84.4° (*c* 1.47, 95% ethanol).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.65; H, 7.15.

The *base* crystallized from methanol in needles, m.p. 159–160°, $[\alpha]_D^{20}$ +120° (c, 0.60, 95% ethanol).

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.35; H, 8.41.

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BETHESDA 14, MD.

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2,2′,2″-Tripyrrylmethenes[1,2]

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The potassium permanganate oxidation of 2,2′,2″-tripyrrylmethanes yields the corresponding methenes in varying yields. Di-2-(3,5-dimethyl-4-carbethoxy)pyrryl ketone was isolated as a by-product from the oxidation of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane. 2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethene forms an inclusion compound with isooctane. Spectral properties of the methenes and prodigiosin are compared and differences noted.

2,2′,2″-Tripyrrylmethenes constitute a relatively unexplored class of organic compounds. Further interest in such compounds stems from Wrede and Rothhaas[4] suggestion that prodigiosin is 2,2′,2″-(4-*n*-amyl-4′-methoxy-5-methyl)tripyrrylmethene. Fischer and Gangl[5] reported the synthesis of two 2,2′,2″-tripyrrylmethenes by oxidation of the corresponding tripyrrylmethanes with lead dioxide in acetic acid. The tripyrrylmethanes can be synthesized by several procedures.[6–8] More recently, Treibs and Hintermeier[9] described the preparation of five other 2,2′,2″-tripyrrylmethenes through the condensation of an α,α′-dipyrryl ketone, or an α-carbo-t-butoxypyrrole, and an α-free pyrrole promoted with phosphorous oxychloride in chloroform. An attempt on our part to oxidize 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy) tripyrrylmethane to the methene by the procedure of Fischer and Gangl gave only a low yield of the methene, as attested by a microscopic examination of the reaction product. Hydrogen peroxide in aqueous acetic acid and oxygen in benzene gave a slight color change to the reaction mixture, indicative of only a small degree of oxidation. Since Corwin and Brunings[10] found that 2,2′-(3,3′,5,5′-tetramethyl-4,4′-dicarbethoxy)-dipyrrylmethane can be oxidized to the corresponding dipyrrylmethene in a good yield with potassium permanganate, we were led to try the conversion of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane to the tripyrrylmethene by this method. We have tried the oxidation at

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(3) Department of Chemistry, San Jose State College, San Jose 14, California.

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

(5) H. Fischer and K. Gangl, *Z. physiol. Chem.*, **267**, 201 (1941).

(6) F. Feist, *Ber.*, **35**, 1647 (1902).

(7) A. H. Corwin and J. S. Andrews, *J. Am. Chem. Soc.*, 59, 1973 (1937).

(8) J. H. Paden, A. H. Corwin and W. A. Bailey, Jr., *J. Am. Chem. Soc.*, **62**, 418 (1940).

(9) A. Treibs and K. Hintermeir, *Ann.*, **605**, 35 (1957).

(10) A. H. Corwin and K. J. Brunings, *J. Am. Chem. Soc.*, **64**, 2106 (1942).

different conditions (Table I, Experimental) and have found that the tripyrrylmethene is easily obtained by this procedure in a yield up to 68%. The nature of the oxidation product was established through analysis and platinum catalyzed hydrogenation to the starting methane.[11] When the oxidation of the tripyrrylmethane was conducted with an excess of potassium permanganate and an extended reaction time was employed, the yield of the tripyrrylmethene was lowered noticeably and di-2-(3,4-dimethyl-4-carbethoxy)pyrryl ketone was isolated from the reaction mixture. This is as would be expected if the initially formed tripyrrylmethene were subsequently oxidized. By means of the permanganate oxidation of the appropriate tripyrrylmethanes we have also succeeded in synthesizing 2,2′,2″ - (4,4′,4″ - tricarbethoxy - 5,5′,5″-trimethyl)tripyrrylmethene (46%), 2,2′,2″-(3,4′,-4″,5 - tetracarbethoxy - 3′,3″,4,5′,5″ - pentamethyl)-tripyrrylmethene (36%) and 2,2′,2″-(3,4′,4″,5-tetracarbethoxy - 4,5′,5″ - trimethyl)tripyrrylmethene(11%).

2,2′,2″ - (3,3′,3″,5,5′,5″ - Hexamethyl - 4,4′,4″-tricarbethoxy)tripyrrylmethene was found to form an inclusion compound with isooctane containing 2.358 moles of the methene per mole of isooctane when an attempt was made to crystallize the methene from the latter. Crystallization of the inclusion compound from ethyl alcohol yielded the methene.

The ultraviolet-visible absorption characteristics for isopropyl alcohol solutions of the tripyrrylmethenes and the absorption maxima in the visible portion of the spectrum for acidified isopropyl alcohol solutions are recorded in Table II (Experimental). The band occurring in the visible region of the spectrum of 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene is remarkable in comparison with the same band of the other tripyrrylmethenes, in that it is broader and the contour suggests three bands close together. The closest approach to this is in the spectrum of 2,2′,2″-(3,3′,3″,-5,5′,5″ - hexamethyl - 4,4′,4″ - tricarbethoxy)tripyrrylmethene, which bears a faint resemblance. The change in the spectrum of 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene upon acidification in contrast with the change in the spectra of the other compounds under the same circumstances is equally noteworthy. Hubbard and Rimington[12] considered that the spectrum of 2,2′,2″(3-bromo - 3′,3″,4,5′,5″ - pentamethyl - 4′,4″ - 5 - tricarbethoxy)tripyrrylmethene[5] lends support to the Wrede and Rothhaas formula for prodigiosin. On the other hand, Treibs and Hintermeir[9] have stated that the absorption curves, not included in their report, and properties of the tripyrrylmethenes prepared by them do not give any support to the Wrede and Rothhaas proposal for prodigiosin. We have compared the spectrum of prodigiosin (ϵ_{max} 4.3 × 10^4 at 466 mμ)[13] and prodigiosin perchlorate (ϵ_{max} 11.5 × 10^4 at 540 mμ)[13] in isopropyl alcohol with those of the tripyrrylmethenes described in the present paper and similarly have not found evidence favoring the Wrede formula. Two weak bands shown by prodigiosin at 280 and 336 mμ are missing in the spectra of the tripyrrylmethenes. Models show that in the tripyrrylmethenes methyl or carbethoxy substituents in the 3 positions of the rings should offer greater hindrance to the three rings approaching coplarity than in a molecule free of these substituents. From this standpoint 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″ - trimethyl)tripyrrylmethene should be more like prodigiosin than any of the others. However, this is not exactly the case. Furthermore, the shift in the visible band upon acidification of this methene is less like that for prodigiosin than any of the others, although the intensity of the bands are comparable. A comparison of the infrared spectra (KBr) of the tripyrrylmethenes with that of prodigiosin reveals that a strong band in the spectrum of the latter occuring at 6.16 μ, which is appropriate to a C=N stretching[13] is not found in the spectra of the tripyrrylmethenes. Instead, these compounds show only a weak band at around 6.13 μ, or the band is not apparent.

EXPERIMENTAL[14]

2,2′,2″-Tripyrrylmethanes. The tripyrrylmethanes were synthesized by the method of Feist[6] and purified by crystallization from 95% ethyl alcohol, or a mixture of 95% ethyl alcohol and water. In this fashion 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethane, m.p. 239.5–240.0° (dec.) (lit.[15] 246°), was obtained from 2-formyl-4-carbethoxy-5-methylpyrrole and 2-methyl-3-carbethoxypyrrole; 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane, m.p. 199° (dec.) (lit.[16] 194°), from 2-formyl-3,5-dimethyl-4-carbethoxypyrrole and 2,4-dimethyl-3-carbethoxypyrrole; 2,2′,2″-(3,4′,4″,5-tetracarbethoxy-3′,3″,4,5′,5″-pentamethyl)tripyrrylmethane, m.p. 190–192° (dec.) (lit.[7] 194°), from 2-formyl-3,5-dicarbethoxy-4-methylpyrrole and 2,4-dimethyl-3-carbethoxypyrrole. A new tripyrrylmethane, described here, was synthesized by the same procedure.

The reaction of 0.54 g. of 2-formyl-3,5-dicarbethoxy-4-methylpyrrole with 0.685 g. of 2-methyl-3-carbethoxypyrrole yielded 0.495 g. (20%) of 2,2′,2″-(3,4′,4″,5-tetracarbethoxy-4,5′,5″-trimethyl)tripyrrylmethane, a lightt an, almost white, solid, m.p. 197.5–198.0° (dec.).

(11) Treibs and Hintermeir[9] describe the reduction of 2,-2′,3″-(2″,4″,5,5′-tetramethyl-4,4′5″-tricarbethoxy)tripyrrylmethene to the methane with zinc dust and acetic acid. Using this same procedure they report that 2,2′,2″-(3,3′,3″,-5,5′,5″-hexamethyl-4,4′,4″- tricarbethoxy)tripyrrylmethene yields a product (analysis not given), m.p. 265–267°.

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

(13) A. J. Castro, A. H. Corwin, F. J. Waxham and A. L. Beilby, *J. Org. Chem.*, **24**, 455 (1959).

(14) Melting points were determined with a Fisher-Johns, or a Kofler, apparatus and are uncorrected. Analyses are by Mr. J. Walter and the Berkeley Analytical Laboratory, P.O. Box 150, Berkeley, California.

(15) H. Fischer and F. Schubert, *Z. physiol. Chem.*, **155**, 72 (1926).

(16) H. Fischer and M. Heyse, *Ann.*, **439**, 252 (1924).

Anal. Calcd. for $C_{28}H_{35}O_8N_3$: C, 62.09; H, 6.51; N, 7.76. Found: C, 61.95; H, 6.65; N, 7.83.

2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy)-tripyrrylmethene. The following procedure for one experiment is illustrative of that used in the different experiments for the synthesis of this compound, as well as for the syntheses of the other tripyrrylmethenes described later. Detailed variations are given at the appropriate points.

A 0.775 g. sample of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane was dissolved in 30 ml. of acetone with heating. The acetone was previously purified by refluxing with potassium permanganate and then distilling. The solution of the tripyrrylmethane was cooled to room temperature and stirred, while 5.65 ml. of a solution of potassium permanganate containing 0.1611 g. of the salt was added within a short time. Stirring was continued until a total of 10 min. had elapsed from the initial addition of the permanganate. The manganese dioxide that had precipitated was filtered off on a sintered glass filter and washed with a little acetone. The red filtrate and washing were combined and evaporated leaving a mixture of a red solid, showing some green sheen, and water. The water was removed by filtration and the residue was crystallized from 95% ethyl alcohol. The resulting tripyrrylmethene, an orange solid melting at 202.0–210.2° (dec.) weighed 0.3189 g. Most of this product melted with decomposition at 207.1–210.2°. An additional 0.1149 g. (combined yield 56%) of the tripyrrylmethene, m.p. 209.0–214.0° (dec.) was obtained from the mother liquor. A recrystallized sample of the methene placed on the heating block at 195–196°, melted with decomposition at 210.7–211.6°.

Anal. Calcd. for $C_{28}H_{35}O_6N_3$: C, 65.99; H, 6.92; N, 8.25. Found: C, 65.93; H, 7.00; N, 8.23.

A mixture of 0.517 g. of the methene in 40 ml. of 95% ethyl alcohol and 0.2732 g. of platinum oxide was shaken under hydrogen at 25.5° and 759 mm. until the uptake of hydrogen appeared to have ceased. During this period the solution changed from an initial red color to a light yellow. The hydrogenated product, a white solid, was recrystallized from alcohol and melted with decomposition at 193–194°. The infrared absorption spectra of the reduction product and authentic tripyrrylmethane were identical.

Anal. Calcd. for $C_{28}H_{37}O_6N_3$: C, 65.73; H, 7.29; N, 8.21. Found: C, 66.14; H, 6.96; N, 8.12.

TABLE I

PERMANGANATE OXIDATION OF 2,2′,2″-(3,3′,3″,5,5′,5″-HEXAMETHYL-4,4′,4″-TRICARBETHOXY)-TRIPYRRYLMETHANE[a]

Expt. No.	Methane (g.)	Eqs. $KMnO_4$[b] / Eq. Methane	Reaction[c] Time (Min.)	Methene %	Methene M.p. (dec.)
1	0.47	0.83	10	31	—[d]
2	0.775	1.009	10	56	—[e]
3	6.16	1.047	—	68	214.0–215.0°
4	0.94	1.65	45	18	206.9–208.0°

[a] Acetone was used as a solvent for all experiments except No. 4 where dioxane was employed. [b] Calculated for: 3Tripyrrylmethane + $2MnO_4^-$ = 3Tripyrrylmethene + $2MnO_2$ + $2OH^-$ + $2H_2O$. [c] Disappearance of the permanganate color was completed before the time shown, but stirring of the mixture was continued until the stated period had elapsed. [d] Collected in two fractions: 0.1115 g., m.p. 202.0–208.1°, and 0.0354 g., m.p. 202.0–205.0° (bulk). [e] Collected in two fractions, see preceding detailed experimental description.

Several oxidations were performed at different conditions and these are summarized in the following table. The previously described oxidation is included for the purpose of comparison.

Di-2-(3,5-dimethyl-4-carbethoxy)pyrryl ketone, weighing 0.140 g., was isolated as a dull orange colored solid from the alcohol mother liquors of the tripyrrylmethene from Experiment 4. After one recrystallization from ethyl alcohol the melting point was 223.1–228.4°. The recrystallized product was still orange in color, but when crushed it gave a white solid The color was apparently due to adsorbed methene. A mixture melting point with authentic di-(2,4-dimethyl-3-carbethoxy)pyrryl ketone,[17] m.p. 225.4–228.4°, gave no depression and the infrared spectra of the two were found to be the same.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.19; H, 6.74; N, 7.38.

2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy)-tripyrrylmethene—isooctane inclusion product. A sample of the methene, m.p. 210.1–211.0° (dec.) was recrystallized from isooctane. The orange crystals that formed melted and resolidified in the range 101.0–122.3° and as the temperature was raised remelted at 200.0–203.0° (dec.). In another experiment the first transition was completed for the most part at 108.6–110.1° with droplets remaining at 119.0°. The final melting occurred at 200.0–203.7° (dec.). In a third experiment, the first change occurred at 109.0–121.0°. The ultraviolet-visible absorption spectrum of the inclusion product in isopropyl alcohol is the same as that of the methene when one calculates the molecular extinction coefficients for the different wave lengths for the inclusion product on the basis of the methene content determined by analysis.

Anal. Calcd. for $(C_{28}H_{35}O_6N_3)_{2.358}(C_8H_{18})$: C, 67.57; H, 7.70; N, 7.53. Found: C, 67.57; H, 7.59; N, 7.30.

Upon recrystallization from 95% ethyl alcohol the methene, m.p. 206.5–208.0° (dec.) was recovered. A mixture melting point with authentic 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethene showed no depression.

2,2′,2″-(4,4′,4″-Tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene. A solution of 1.3953 g. of 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethane in 100 ml. of acetone was treated with 9.77 ml. of an aqueous solution containing 0.3134 g. of potassium permanganate in a manner similar to that used in the preceding tripyrrylmethene synthesis. After recrystallization from 95% ethyl alcohol, 0.6351 g. (46%) of red crystalline 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene, m.p. 227.5–229.0° (dec.) was obtained. Using a slower heating rate a recrystallized sample was found to melt with decomposition at 221.9–223.3°.

Anal. Calcd. for $C_{25}H_{29}O_6N_3$: C, 64.22; H, 6.25; N, 8.99. Found: C, 64.24; H, 6.24; N, 8.76.

2,2′,2″-(3,4′,4″,5-Tetracarbethoxy-3′,3″,4,5′,5″-pentamethyl)tripyrrylmethene. A 0.9 g. sample of 2,2′,2″-(3,4′,4″,5-tetracarbethoxy-3,3″,4,5′,5″-pentamethyl)tripyrrylmethane in 2.5 ml. of acetone was oxidized with 0.1668 g. of potassium permanganate in 5.85 ml. of aqueous solution as in the foregoing examples. 2,2′,2″-(3′,4′,4″,5-Tetracarbethoxy-3′,3″,4,5′,5″-pentamethyl)tripyrrylmethene, 0.3198 g. (36%), was obtained as red-orange crystals from a mixture of alcohol and water. When heated, the crystals reddened and appeared to soften, especially around 173–174°, and melted with decomposition at 176.0–177.9°.

(17) Kindly synthesized by P. E. Berteau by the method of H. Fischer and H. Orth, *Ann.*, **489**, 78 (1931).

Anal. Calcd. for $C_{30}H_{37}O_8N_3$: C, 63.47; H, 6.57; N, 7.40. Found: C, 63.47; H, 6.69; N, 7.27.

2,2',2"-(3,4',4",5-Tetracarbethoxy-4,5',5"-trimethyl)tripyrrylmethene. A 0.3216 g. sample of 2,2',2"-(4,5',5"-trimethyl-3,4',4",5-tetracarbethoxy)tripyrrylmethane in 20 ml. of acetone was oxidized with 0.06255 g. of potassium permanganate in 1.95 ml. of water. Crystallization of the reaction product from 95% ethyl alcohol yielded a mixture of red and yellow colored solids. After stirring the mixture twice with acetone and three times with 95% ethyl alcohol most of the yellow solid was dissolved. The red solid that remained and that obtained upon concentration of the combined extracts were combined and crystallized from 95% ethyl alcohol yielding 0.0210 g. of the red crystalline methene, m.p. 221.9–223.0° (dec.). Considering the recovered tripyrrylmethane (below) the yield of methene is 11%.

Anal. Calcd. for $C_{28}H_{33}O_8N_3$: C, 62.32; H, 6.16; N, 7.79. Found: C, 62.45; H, 6.37; N, 8.37.

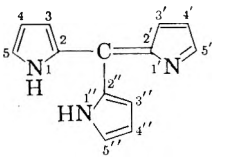
The residue from the tripyrrylmethene mother liquors in 95% ethyl alcohol was applied to a column of Woelm's Alumina (non-alkaline, activity grade I) and the chromatogram was developed with ethyl ether. The lower, broad, tan colored zone was eluted with ether, the solution was evaporated, and the residue was crystallized from 95% ethyl alcohol yielding 0.1305 g. of orange-tan crystals of the methane, m.p. 197.0–198.3° (dec.). The product when crushed appeared as a white powder. The infrared spectrum of this compound is identical with that of the starting methane.

Anal. Calcd. for $C_{25}H_{35}O_8N_3$: C, 62.09; H, 6.51; N, 7.76. Found: C, 62.31; H, 6.55; N, 7.68.

Ultraviolet-Visible Absorption Spectra. Solutions of the tripyrrylmethenes in isopropyl alcohol were examined. Measurements were made with a Beckman Model DU or a Cary Model 11M Spectrophotometer. The results are presented in the following table.

TABLE II

ULTRAVIOLET-VISIBLE ABSORPTION SPECTRA FOR 2,2',2"-TRIPYRRYLMETHENES



Substituents	Isopropyl Alcohol λ_{max}	Isopropyl Alcohol $\epsilon \times 10^{-3}$	Isopropyl alcohol plus $HClO_4$[a] λ_{max}	Isopropyl alcohol plus $HClO_4$[a] $\epsilon \times 10^{-3}$
4,4',4"-Tricarbethoxy-5,5',5"-trimethyl	490	43.1	487	115.7
	465–470	42.0		
	435–440[b]	33.1		
	245–250[c]	14.7		
	220[d]	38.3		
3,3',3",5,5',5"-Hexamethyl-4,4',4"-tricarbethoxy	486	38.3	497	82.1
	255[e]	13.3		
	224	39.3		
3,4',4",5-Tetracarbethoxy-3',3",4,5',5"-pentamethyl	475	40.0	524	51.2
	264	23.1	486[f]	26.1
	220	48.4		
3,4',4",5-Tetracarbethoxy-4,5',5"-trimethyl	460–466	36.1	512	71.9
	262	20.2		
	220[d]	39.8		

[a] One milliliter of 10% aqueous perchloric acid per 100 ml. of solution. [b] Only long wave length maximum recorded. [c] Shoulder on ascending limb. [d] End absorption, not necessarily a maximum. [e] Inflection on ascending limb. [f] Inflection on descending limb.

SANTA CLARA, CALIF.

[FROM THE CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

O-(Substituted)-α-amino-β-hydroxybutyric Acids

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The *O*-carbamyl derivatives of DL-threonine and DL-allothreonine, and *O*-carbazyl-DL-threonine were prepared from the corresponding carbobenzoxy-amino acid benzyl esters by condensation with phosgene followed by ammonia or *N*-carbobenzoxyhydrazine, and then hydrogenolysis, to produce the carbamyl- and carbazyl- derivatives, respectively. In contrast to the comparable serine derivatives, these compounds were not effective metabolic antagonists in several microbiological assays.

Both *O*-carbamyl- and *O*-carbazyl- derivatives of DL-serine have been prepared and found to be competitive antagonists of glutamine in several microörganisms.[1,2] The sulfur analogue of the former compound, *S*-carbamylcysteine,[3] is also an inhibitory amino acid derivative; however, glutamine does not competitively reverse its toxicity, and in this respect it is similar to azaserine[4] an antitumor agent.[5] The antitumor activity of several of these analogs[6] prompted the synthesis and biological testing of a number of additional *O*-(substituted carbamyl)serine derivatives.[7]

In the present investigation, the *O*-carbamyl-derivatives of both threonine and allothreonine,

(1) C. G. Skinner, T. J. McCord, J. M. Ravel, and W. Shive, *J. Am. Chem. Soc.*, **78**, 2412 (1956).

(2) T. J. McCord, J. M. Ravel, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, 80, 3762 (1958).

(3) J. M. Ravel, T. J. McCord, C. G. Skinner, and W. Shive, *J. Biol. Chem.*, **232**, 159 (1958).

(4) J. A. Moore, J. R. Dice, E. D. Nicolaides, R. D. Westland, and E. L. Wittle, *J. Am. Chem. Soc.*, **76**, 2884 (1954).

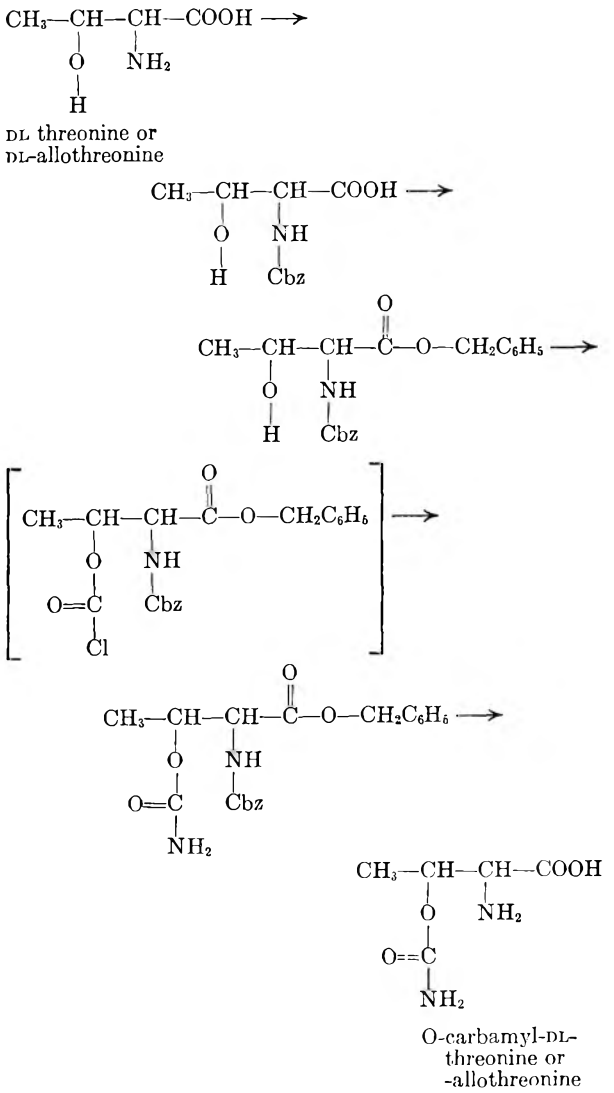
(5) C. C. Stock, H. C. Reilly, S. M. Buckley, D. A. Clarke, and C. P. Rhoads, *Nature*, **173**, 71 (1954).

(6) C. G. Skinner, G. F. McKenna, T. J. McCord, and W. Shive, *Texas Repts. Biol. Med.*, 16, 493 (1958).

(7) T. J. McCord, C. G. Skinner, and W. Shive, *J. Org. Chem.*, **32**, 1963 (1958).

and the *O*-carbazyl- derivative of threonine were prepared and their biological properties were examined. The two diastereoisomeric analogs, *O*-carbamyl-DL-threonine and *O*-carbamyl-DL-allothreonine, were prepared to determine whether either of the two derivatives exhibited a stereochemical specificity for the antagonism of glutamine.

The *O*-carbamyl- derivatives of threonine and allothreonine were synthesized using the same general procedure. The *N*-carbobenzoxy amino acids were esterified with benzyl alcohol, and the isolated intermediates were then treated with phosgene, followed by treatment with ammonium hydroxide, to yield the corresponding *O*-carbamyl-*N*-carbobenzoxy amino acid benzyl ester. The latter products on hydrogenolysis gave the desired amino acid analogue as indicated in the accompanying equations. *O*-Carbazyl-DL-threonine was prepared



by a comparable procedure except that the chloroformyl intermediate was condensed with *N*-carbobenzoxyhydrazine instead of ammonia. The resulting intermediate was then hydrogenolyzed to yield the desired *O*-carbazylthreonine. In contrast to the corresponding *O*-carbazylserine derivatives,[2] the threonine intermediates gave relatively poor yields, and the reaction mixtures crystallized with difficulty.

Neither *O*-carbamyl-threonine or -allothreonine were significantly inhibitory toward *Escherichia coli* 9723, *Lactobacillus arabinosus* 17-5, or *Streptococcus lactis* 8039 even at a level of 2 mg./ml. This is in contrast to *O*-carbamyl-DL-serine which is an effective competitive antagonist of glutamine.[1] The introduction of the additional methyl group in the derivatives apparently sterically hinders the analogs from interacting at appropriate enzyme sites. Similarly, the 3-methyl derivative of glutamic acid is not inhibitory to the growth of *E. coli*. It appears that, in a number of microörganisms, the substitution of methyl groups on the 3-carbon of glutamic acid (as well as on the 3-carbon of oxa analogs of glutamine) sterically prevents enzyme binding of the analogs at the place of attachment of the corresponding natural metabolite. The lack of biological activity of these *O*-carbamyl-threonine and allothreonine derivatives is apparently not due to the introduction of an oxygen for the 4-methylene group of glutamine, since the analog resulting from this single alteration is *O*-carbamylserine, an effective glutamine antagonist.

O-Carbazylthreonine is slightly inhibitory in these microbial systems, but it is still considerably less inhibitory on a weight basis than *O*-carbazylserine.[2] *O*-Carbazylthreonine inhibits the growth of either *E. coli*, *L. arabinosus*, or *S. lactis* at a level of concentration of about 200 γ/ml.; however, these toxicities are not reversed by glutamine. In view of the data observed above with the carbamyl derivative, this latter inhibition is probably due to the hydrazine portion of the molecule combining with active centers in the host, perhaps in a nonspecific manner.

EXPERIMENTAL[8,9]

Biological testing. The microbiological assays were carried out using previously reported procedures.[1] In all assays the inhibitors were dissolved in sterile water and added to sterile assay tubes without being heated.

N-Carbobenzoxy-DL-threonine. Using the general procedure of Baer and Maurukas,[10] 23.8 g. of DL-threonine was dissolved in 350 ml. of water in the presence of 150 ml. of ether and 25 g. of finely powdered magnesium oxide. The mixture was cooled in an ice bath, and 53 g. of carbobenzoxy chloride was added dropwise over a 45 min. period with stirring. After stirring an additional 2 hr. at room temperature, the precipitate was filtered, the ether phase was recovered, and the aqueous phase was extracted with an additional 200

(8) We are indebted to Dr. J. M. Ravel and her staff at the Clayton Foundation Biochemical Institute for the microbiological assays.

(9) The chemical analyses were carried out by Mr. W. H. Orme-Johnson and Miss Judith Morehead. The melting points are uncorrected.

(10) E. Baer and J. Maurukas, *J. Biol. Chem.*, **212**, 31 (1955).

ml. of ether. The aqueous phase was then acidified to *p*H 3 with concentrated hydrochloric acid and extracted twice with ethyl acetate. After removal of the organic solvent *in vacuo*, the residue was crystallized from toluene–Skellysolve B to yield 32.0 g. of product, m.p. 75–78°.

Anal. Calcd. for $C_{12}H_{15}NO_6$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.29; H, 5.79; N, 5.51.

*N-Carbobenzoxy-*DL*-threonine benzyl ester.* Using the general procedure of Ben-Ishai and Berger,[11] 15.0 g. of *N*-carbobenzoxythreonine, 10.0 g. of benzyl alcohol, and 1 g. of *p*-toluenesulfonic acid was dissolved in 125 ml. of benzene and heated to reflux for about 12 hr. The water formed in the reaction was removed by azeotropic distillation, and the benzene solution was washed twice with 5% potassium bicarbonate, and then dried over sodium sulfate. After removal of the solvent *in vacuo*, the residue was crystallized from toluene-*n*-hexane to yield 18 g. of product, m.p. 67–68°.

Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.28; H, 6.08; N, 4.19.

*O-Carbamyl-N-carbobenzoxy-*DL*-threonine benzyl ester.* Phosgene was bubbled through a cold solution of 6.0 g. of *N*-carbobenzoxythreonine benzyl ester in 75 ml. of toluene for about 2 hr., and then the reaction mixture was allowed to stand at room temperature overnight. The solvent was removed *in vacuo*, and the residue was freed of excess phosgene by repeated addition and evaporation *in vacuo* of small volumes of dioxane. The residual oil was finally dissolved in 50 ml. of dioxane, and added dropwise to a cold concentrated ammonium hydroxide solution with stirring. After reduction in volume *in vacuo*, the precipitate was separated and recrystallized from dioxane-water to yield 5 g. of product, m.p. 124–126°.

Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.16; H, 5.40; N, 7.38.

*O-Carbamyl-*DL*-threonine.* A solution of 2.0 g. of *O*-carbamyl-*N*-carbobenzoxy-DL-threonine benzyl ester in 100 ml. of 50% dioxane-water was hydrogenolyzed in the presence of 500 mg. of palladium black at room temperature and atmospheric pressure for about 5 hr. After removal of the catalyst, the filtrate was reduced to dryness *in vacuo*, and the residue was crystallized from ethanol-water to yield 1.0 g. of product, m.p. 189–191° (dec.).

Anal. Calcd. for $C_5H_{10}N_2O_4$: C, 37.03; H, 6.22; N, 17.28. Found: C, 37.32; H, 5.97; N, 17.16.

*O-(N²-Carbobenzoxycarbazyl)-N-carbobenzoxy-*DL*-threonine benzyl ester.* Following a general procedure previously reported for the serine analogue,[2] 10 g. of the chloroformyl intermediate dissolved in 80 ml. of dioxane was added dropwise over a 1 hr. period to a well stirred ice-cold mixture of 6.5 g. of carbobenzoxyhydrazine and 1.1 g. of sodium carbonate in 100 ml. of 80% ethyl alcohol. The reaction mixture was allowed to remain at room temperature for 4 days, and it was then reduced to dryness, taken up in warm alcohol, and the insoluble salt was filtered. Addition of water to the alcohol solution yielded a precipitate, m.p. 80–83°.

Anal. Calcd. for $C_{28}H_{29}N_3O_8$: C, 62.80; H, 5.46; N, 7.85. Found: C, 62.71; H, 5.38; N, 7.67.

The major portion of the reaction mixture crystallized so slowly that the oil residue was normally used directly for the following step without crystallizing.

*O-(Carbazyl)-*DL*-threonine.* A solution of 10 g. of *O*-(*N*²-carbobenzoxycarbazyl) - *N* - carbobenzoxy - DL - threonine benzyl ester in 100 ml. of 50% dioxane-ethanol was hydrogenolyzed in the presence of 700 mg. of palladium black at room temperature and atmospheric pressure for about 3 hr. Throughout the period of hydrogenolysis, water was carefully added as needed to induce a slight turbidity in the reaction mixture. The catalyst was filtered, the filtrate was reduced to dryness *in vacuo*, and the residue was recrystallized from ethanol-water to yield 200 mg. of product, m.p. 172–173°.

Anal. Calcd. for $C_5H_{11}N_3O_4$: C, 33.90; H, 6.26; N, 23.72. Found: C, 34.19; H, 6.49; N, 23.64.

The residue contained additional product, as indicated by paper chromatography; however, it could not be readily separated from other ninhydrin positive contaminants.

*N-Carbobenzoxy-*DL*-allothreonine.* Using the procedure described above for the threonine analog, 12.5 g. of allothreonine and 13.0 g. of magnesium oxide, was suspended in 175 ml. of water and 100 ml. of ether. To this cold well-stirred mixture was added 28 g. of carbobenzoxy chloride. After the work-up procedure there was obtained 18 g. of product which was crystallized from toluene–Skellysolve G, m.p. 114–115°.

Anal. Calcd. for $C_{12}H_{15}NO_6$: N, 5.53. Found: N, 5.83.

*N-Carbobenzoxy-*DL*-allothreonine benzyl ester.* Using the procedure described above for the corresponding threonine derivative, a mixture of 8 g. of *N*-carbobenzoxyallothreonine, 5 g. of benzyl alcohol, and 0.5 g. of *p*-toluenesulfonic acid suspended in 100 ml. of benzene produced 7.9 g. of product, m.p. 74–75°.

Anal. Calcd. for $C_{19}H_{21}NO_5$: N, 4.08. Found: N, 4.25

*O-Carbamyl-N-carbobenzoxy-*DL*-allothreonine benzyl ester.* Using the technique as previously described for the threonine analog, 5.1 g. of *N*-carbobenzoxyallothreonine benzyl ester yielded, after treatment with phosgene followed by ammonium hydroxide, 3.6 g. of product, m.p. 81–82°.

Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.25; H, 5.59; N, 7.25.

*O-Carbamyl-*DL*-allothreonine.* An alcohol-water solution containing 1.1 g. of *O*-carbamyl-*N*-carbobenzoxyallothreonine benzyl ester in the presence of 200 mg. of palladium black was hydrogenolyzed for about 4 hr. at room temperature and atmospheric pressure. After removal of the catalyst, the filtrate was reduced to dryness *in vacuo*, and the residue was recrystallized from alcohol-water to yield 118 mg. of product, m.p. 205–210° (dec.).

Anal. Calcd. for $C_5H_{10}N_2O_4$: C, 37.03; H, 6.22; N, 17.28. Found: C, 37.10; H, 6.33; N, 17.55.

AUSTIN, TEX.

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[CONTRIBUTION NO. 10 FROM THE EXPLORATORY RESEARCH LABORATORY OF DOW CHEMICAL OF CANADA, LIMITED]

Organophosphorus Compounds. VI. *N*-Arylphosphoramidic and *N*-Arylphosphoramidothioic Difluorides

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N-Arylphosphoramidic and *N*-arylphosphoramidothioic difluorides were prepared from phosphorus oxy- and thio-halides and aromatic amines.

The preparation of the *N*-arylphosphoramidic dichlorides has been investigated by many authors,[2-6] most systematically by Michaelis.[7,8] The syntheses were based on the reaction of one mole phosphorus oxychloride with two moles of an aromatic amine in the cold.

$$POCl_3 + 2ArNH_2 \longrightarrow ArNHPOCl_2 + ARNH_2 \cdot HCl$$

or with one mole of an amine hydrochloride on warming.

$$POCl_3 + ArNH_2 \cdot CHl \longrightarrow ArNHPOCl_2 + 2HCl$$

This paper describes the synthesis of the previously unknown *N*-arylphosphoramidic difluorides from phosphorus oxyfluoride and aromatic amines:

$$POF_3 + 2ArNH_2 \longrightarrow ArNHPOF_2 + ArNH_2 \cdot HF$$

The syntheses of *N*-phenyl, *N-m-* and *N-p*-tolyl-phosphoramidic difluorides were performed at temperatures between −80– + 30°. *o*-Toluidine and *o*-anisidine required more drastic conditions to effect reaction. Due to the high volatility of phosphorus oxyfluoride, the reactions were carried out in sealed glass tubes.

The *N*-phenyl-, *N-o-* and *N-p*-tolyl-, and *N*-anisyl-phosphoramidic difluorides were colorless crystalline substances. All of these substances were distillable *in vacuo* without decomposition. But on overheating they easily lose hydrogen fluoride. Table I shows some of the characteristics of the compounds prepared and reaction yields.

N,N-Ethylphenylphosphoramidic difluoride was prepared by a similar method from phosphorus oxyfluoride and *N*-ethylaniline in a sealed glass tube at room temperature.

Phosphorus oxychlorodifluoride and phosphorus oxybromodifluoride were used similarly as starting materials.

$$POClF_2 + 2ArNH_2 \longrightarrow ArNHPOF_2 + ArNH_2 \cdot HCl$$

$$POBrF_2 + 2ArNH_2 \longrightarrow ArNHPOF_2 + ArNH_2 \cdot HBr$$

The present authors have previously described the preparation of *N*-arylphosphoramidic dichlorides and *N*-arylphosphoramidothioic chlorofluorides from phosphorus thiochlorodifluoride.[9] Now we have prepared the previously unknown *N*-arylphosphoramidothioic difluorides, as shown below.

$$PSClF_3 + 2ArNH_2 \longrightarrow ArNHPSF_2 + ArNH_2 \cdot HCl$$

$$PSBrF_2 + 2ArNH_2 \longrightarrow ArNHPSF_2 + ArNH_2 \cdot HBr$$

Of the compounds obtained, the *N*-phenyl-, *N-o-*, *N-m-* and *N-p*-tolylphosphoramidothioic difluorides were colorless, musky-smelling liquids. The *N*-anisylphosphoramidothioic difluoride was colorless, crystalline substance. The liquids were not miscible with water, but on standing under water they hydrolyzed at room temperature. *N*-Arylphosphoramidothioic difluorides were more stable in respect to loss of hydrogen halide than the corresponding dichlorides. No decomposition was observed nor was there any substantial imidophosphorothioate residue left in the distillation flask. Table II shows some of the characteristics of the compounds prepared and reaction yields. The *N*-arylphosphoramidothioic difluorides were also prepared from phosphorus thiofluoride.

$$PSF_3 + 2ArNH_2 \longrightarrow ArNHPSF_2 + ArNH_2 \cdot HF$$

If an excess of the aromatic amine was used *N,N*-diarylphosphoramidothioic difluorides were formed.

$$PSF_3 + 4ArNH_2 \longrightarrow (ArNH)_2PSF + 2ArNH_2 \cdot HF$$

EXPERIMENTAL

Strictly anhydrous conditions were maintained throughout all operations to avoid hydrolysis of reagents and products.

I. *Preparation of N-arylphosphoramidic difluorides from phosphorus oxyfluoride.* A. *N-Phenyl-, N-m- and N-p-tolylphosphoramidic difluorides.* An aromatic amine (0.2 mole) dissolved in 80 ml. anhydrous toluene was added to a suspension of 0.11 mole, 11.5 g. of phosphorus oxyfluoride in 100 ml. of anhydrous toluene with stirring at a temperature between −40 and −50°. The reaction mixture was stirred for 0.5 hr. and then allowed to stand for 3 hr. at −20° and finally allowed to reach room temperature. The amine hydrofluoride was removed by filtration and then washed

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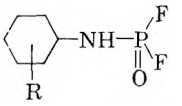
TABLE I

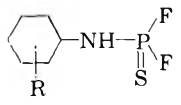
N-ARYLPHOSPHORAMIDIC DIFLUORIDES



R	Yield, %	B.P. (°C./mm.)	M.P. (°C.)	Calcd. N	Calcd. F	Found N	Found F
H	62	103–104/5	48–49	7.90	21.45	8.03	21.4
o-CH_3	59	98–100/6	40	7.32	19.87	7.54	19.7
m-CH_3	60	124–125/6	—	7.32	19.87	7.60	19.6
p-CH_3	58	118/6	79–80	7.32	19.87	7.25	20.1
o-OCH_3	65	105–106/6	61	6.76	18.34	6.54	18.1

TABLE II

N-ARYLPHOSPHORAMIDOTHIOIC DIFLUORIDES



R	Yield, % Method A	Yield, % Method B	B.P. (°C./mm.)	n_D^{20}	Calcd. N	Calcd. F	Found N	Found F
H	91	93	86/1	1.5414	7.25	19.66	7.52	19.9
o-CH_3	95	—	76/0.9	1.5223	6.76	18.33	6.80	18.6
m-CH_3	90	93	85.5/0.9	1.5361	6.76	18.33	6.86	18.3
p-CH_3	88	86	98/1	1.5358	6.76	18.33	6.89	18.5
o-OCH_3	90	—	93/1	M.P. 46–47°	6.27	17.02	6.31	17.1

with toluene. The filtrate and washings were distilled and after removal of toluene the remaining liquid was fractionated *in vacuo*. The *N*-phenyl-, *N*-*m*- and *N*-*p*-tolyl-phosphoramidic difluorides were obtained which solidified to colorless crystalline states. Some physical and analytical data and yields are shown in Table I.

B. *N-o-Tolyl- and N-anisyl-phosphoramidic difluorides.* Phosphorus oxyfluoride, 10.4 g. (0.1 mole) was bubbled into 200 ml. of toluene cooled in a dry ice acetone bath and 0.2 mole of an aromatic amine was added to the mixture. The mixture was transferred to a glass tube and the tube was then sealed. The tube was refrigerated at −20° for 12 hr. It was agitated occasionally at −20° and then allowed to reach room temperature and to stand for an additional 12 hr. The phosphorus oxyfluoride was consumed as noted by lack of excess pressure when the tube was opened. The amine hydrofluorides were removed by filtration. Colorless crystalline *N*-tolyl- and *N*-amisyl-phosphoramidic difluorides were obtained by distillation *in vacuo* as described above. Table I shows the pertinent data.

N,N-Ethylphenylphosphoramidic difluoride. 10.7 g. (52%) of *N,N*-ethylphenylphosphoramidic difluoride was obtained by reacting 10.4 g. (0.1 mole) of phosphorus oxyfluoride and 24.2 g. (0.2 mole) of *N*-ethylaniline as described above. The compound was colorless liquid with an acrid odor boil- at 119–120°C./9 mm. with decomposition.

Anal. Calcd. for $C_8H_8F_2OP$: F, 18.51; N, 5.82. Found: F, 18.1; N, 7.18.

II. *Preparation of N-arylphosphoramidic difluorides from phosphorus oxychlorodifluoride and phosphorus oxybromodifluoride.* Phosphorus oxychlorodifluoride 12 g. (0.1 mole) or 16.5 g. (0.1 mole) of phosphorus oxybromodifluoride was dissolved in 15 ml. of ice cold toluene. A solution of 0.2 mole of an aromatic amine in 50 ml. of toluene was added to the mixture with cooling. The reaction mixture was allowed to stand 24 hr. at −20°, then at room temperature for an additional 12 hr. The precipitated amine hydrohalide was removed by filtration and washed with toluene. The filtrate and washings were fractionated as above.

III. *Preparation of N-arylphosphoramidothioic difluorides from phosphorus thiochlorodifluoride and phosphorus thiobromodifluoride. N-Phenyl-, N-m- and N-p-tolyl-phosphoramidothioic difluoride.* Phosphorus thiochlorodifluoride 14.3 g. (0.105 mole) or 19 g., (0.105 mole) of phosphorus thiobromodifluoride was dissolved in 150 ml. of cold toluene. A solution of 0.2 mole of an aromatic amine in 50 ml. of toluene was added to the mixture with cooling. The mixture was placed in a refrigerator at 0° for 24 hr. after which time it was allowed to reach room temperature and left unopened for an additional 12 hr. The amine hydrofluoride was removed by filtration and washed with toluene. The filtrate and washing were fractionated as above, yielding the *N*-phenyl-, *N*-*m*- and *N*-*p*-tolyl-phosphoramidothioic difluorides as colorless, musky-smelling liquids, more dense than and not miscible with water. Physical and analytical data and yield of the products are given in Table II. Decomposition during distillation did not occur. The compounds did not hydrolyze at room temperature on standing under water and only minute quantities of residue remained.

N-o-Tolyl- and N-o-anisyl-phosphoramidothioic difluorides. In a 600 ml. thick-walled glass tube was placed a solution of 13.6 g. (0.1 mole) of phosphorus thiochlorodifluoride in anhydrous benzene. *o*-Toluidine, 2.14 g. (0.2 mole) or 24.6 g. (0.2 mole) of *o*-anisidine was added to the solution. The tube was then sealed, the reaction mixture allowed to stand for 4 days at room temperature. As above vacuum distillation yielded musky-smelling, colorless *N*-*o*-tolyl- and *N*-*o*-anisyl-phosphoramidothioic fluorides. The *N*-*o*-anisyl-phosphoramidothioic difluoride solidified to a white crystalline substance. Physical and analytical data of the compounds and their yields are shown in Table II.

Similar products are obtained by substituting phosphorus

thiobromodifluoride, b.p. 35°, for the thiochloro compound but room temperature and atmospheric pressure would be used in the reactions.

IV. *Preparation of N-arylphosphoramidothioic difluorides from phosphorus thiofluoride.* Phosphorus thiofluoride 13.6 g. (0.1 mole), b.p. −53° was dissolved at −70° in 100 ml. of toluene. A cold solution of 0.2 mole of the aromatic amine in toluene (50 ml.) was added and the stirred mixture kept at this temperature for 3 hr. After allowing to warm up slowly to room temperature, the partly separated amine hydrofluoride was removed by filtration and the filtrate fractionated. On removing a part of the solvent, a substantial amount of amine hydrofluoride separated again and was removed by filtration.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CENTRAL STATE COLLEGE]

p-Phenylazobenzenesulfonyl Chloride—a New Reagent for Identification and Separation of Amines

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p-Phenylazobenzenesulfonyl chloride has been found to form solid derivatives with a large number of amines. The derivatives are easily prepared and purified and are therefore suitable for use in identification. Anhydrous and aqueous amines were both used to give good yields of the amides. The amide derivatives can be hydrolyzed to the amine hydrochloride. The Tswett adsorption method has been applied to the separation of mixtures of these colored amides. A new method for the separation of mixtures of the three classes of amines is proposed.

Benzoyl chloride has wide applicability for the identification of active hydrogen compounds such as alcohols, amines and phenols. In previous papers it has been shown that the substituted benzoyl chloride, *p*-Phenylazobenzoyl chloride, is an excellent reagent for the identification of alcohols,[2] amines[3] and phenols.[4] In addition, the *p*-phenylazobenzoyl derivatives of these classes of compounds were highly colored (orange to red) and were found to be suitable derivatives for separation of mixtures of them by chromatographic adsorption.

The general use of benzenesulfonyl chloride for the identification and separation of amines has suggested the use of *p*-phenylazobenzenesulfonyl chloride as a derivatizing reagent for amines. It was hoped that the *p*-phenylazobenzenesulfonyl derivatives would be useful for identification of amines and also for the separation, by chromatography, of mixtures of amines. We wish to report the preparation of a large number of derivatives of aliphatic and aromatic amines with this reagent and consider its advantages over presently used reagents.

We have found *p*-phenylazobenzenesulfonyl chloride to have general usefulness in the identification of amines. The reagent has been used to characterize nineteen aliphatic, eighteen aromatic, six mixed aliphatic aromatic, and two heterocyclic amines. It is superior, in general, to the common reagents for amines—even the most widely used reagent, benzenesulfonyl chloride. The derivatives are easily prepared in good yields upon refluxing a mixture of the amine and the sulfonyl chloride in pyridine. This reagent is particularly useful in identifying aliphatic amines which give either oils or low melting solids with other reagents. The sulfonamides are highly crystalline, orange to red solids and may be easily purified by crystallizing from Skellysolve B or ethanol, or by chromatographing on a silicic acid–celite mixture. All of the derivatives prepared melt without decomposition and in a convenient melting point range. A distinct advantage of this reagent over the commonly used reagents is its high molecular weight, which allows for easy identification of small amounts of amines. It has the added advantage of being a stable solid (m.p. 124–125°) which does not deteriorate on standing for long periods of time and is not easily hydrolyzed by water. Therefore, the reagent can be used successfully in preparing derivatives of amines from their dilute aqueous solutions. The derivatives of methyl amine and dimethyl amine were prepared from their 0.25 aqueous solutions in 89 and 75% yields respectively.

The *N*-substituted *p*-phenylazobenzenesulfonamides that have been characterized are recorded in Table I. Six of the sulfonamides have been previously reported.[5] Their recorded melting points are listed in Table I. There is a large discrepancy between the melting point values obtained in this study

(1) This paper is based on work presented by W. E. Reynolds and J. L. Mason in partial fulfillment of requirements for undergraduate Honors Course offered in the Department of Chemistry of Central State College.

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TABLE I

AMIDES OF *para*-PHENYLAZOBENZENESULFONIC ACID

Amine used	M. P., °C.[a] Corrected	Yield,[b] %	Yield (%)[c] of amine on Hydrolysis
Primary Aliphatic			
n-Amylamine	97.4– 98.2	47	
Isoamylamine	104.4–105.0	89	38
n-Butylamine	91.4– 92.0	88	94
Isobutylamine	120.6–121.0	71	
sec-Butylamine	123.2–124.4	89	58
tert-Butylamine	159.8–160.3	77	85
Ethylamine	137.2–138.0	62	
Methylamine	156.0–157.3	89	64
n-Propylamine	101.6–102.2	60	
Isopropylamine	119.0–120.6	69	
Secondary Aliphatic			
Di-*n*-amylamine	97.4– 98.4	80	
Di-isoamylamine	118.5–119.3	78	33
Di-*n*-butylamine	99.4–100.0	84	66
Di-isobutylamine	138.7–140.6	78	
Di-*sec*-butylamine	93.6– 95.0	21	
Di-ethylamine	104.6–105.3	76	
Di-methylamine	166.6–168.0	75	80
Di-*n*-propylamine	98.6– 99.2	66	
Di-isopropylamine	138.4–139.4	21	
Primary Aromatic			
o-Aminophenol	178.0–178.9	81	
m-Aminophenol	190.0–191.0	48	
p-Aminophenol	213.0–213.9	32	
Aniline	156.0–156.8 (Lit. 152)	89	
m-Bromoaniline	168.0–169.8	38	
p-Bromoaniline	188.0–188.9	40	
o-Chloroaniline	139.0–140.2	35	
p-Chloroaniline	167.0–168.0	60	45
o-Ethoxyaniline	143.0–144.5	58	
m-Ethoxyaniline	132.0–132.9	73	
p-Ethoxyaniline	158.0–159.5	45	
o-Methoxyaniline	122.0–123.0	35	
p-Methoxyaniline	140.0–141.8	44	
1-Naphthylamine	189.0–191.0 (Lit. 156)	61	37
2-Naphthylamine	158.0–159.5 (Lit. 170)	88	37
o-Toluidine	171.2–172.2 (Lit. 138–139)	57	
m-Toluidine	140.0–141.2 (Lit. 168)	53	
p-Toluidine	166.0–166.8 (Lit. 163–164)	79	71
Mixed Secondary			
n-Butylaniline	153.0–154.9	46	
Ethylaniline	144.0–145.2	46	
Isoamylaniline	156.0–157.2	22	
Methylaniline	168.8–168.9	66	
Methyl-*o*-toluidine	141.0–142.0	24	
Methyl-*p*-toluidine	134.0–135.2	52	
Heterocyclic			
Morpholine	217.0–218.0	46	
Piperidine	191.0–191.9	95	

[a] Melting points were taken on a modified Hershberg type apparatus. [b] Yields are on products purified by chromatography. The found analyses agreed with the calculated to within ±0.2% Nitrogen except in 8 cases, and the difference was not greater than ±0.3% except in 4 cases. Microanalyses were performed by the Du Good Chemical Laboratories, St. Louis, Mo. [c] The recovered aliphatic amines were identified as their hydrochlorides. The recovered aromatic amines were identified by mixture melting point.

and those previously reported for the derivatives of *ortho*- and *meta*-toluidine and 1- and 2-naphthylamine. Comparison of these two sets of melting point values indicates that the previous workers may have recorded inversely the melting points of these isomeric sulfonamides. Another possibility is that these derivatives might have been prepared from the amines, contaminated with their isomers, which might have led to the isolation of a mixture of isomeric sulfonamides. These same derivatives have been reported by the previous workers as having a brown color. In this study the crude derivatives were observed to have a brown-yellow color, but this was due to traces of *p*-phenylazobenzenesulfonic acid and some foreign material (See Experimental) which were occluded by the derivatives. These impurities were removed chromatographically to give pure orange-red products.

To some extent the usefulness of a reagent for the identification of an organic compound is dependent upon the ease with which the original compound may be obtained from its derivative. Many alkyl- and arylsulfonyl chlorides have been used for the identification of primary and secondary amines. However, one disadvantage with all of these reagents in actual practice is that once the sulfonamide is obtained, it hydrolyzes with great difficulty to give the original amine.[6]

The *p*-phenylazobenzenesulfonamides are hydrolyzed on refluxing with concentrated hydrochloric acid. In this study no attempt was made to determine the optimum conditions for quantitative hydrolysis of the sulfonamides. The results of the hydrolysis of certain sulfonamides are recorded in Table I.

Chromatographic Adsorption Studies. The Tswett Adsorption method has been applied to the separation of very small quantities (10–20 mg. of each component) of mixtures of these brilliantly colored *N*-substituted *p*-phenylazobenzenesulfonamides. Therefore *p*-phenylazobenzenesulfonyl chloride affords an advantage over the reagents which are commonly used for identification of amines in that it forms colored derivatives which can be separated on the Tswett column in the usual manner. The individual compounds may then be recovered and identified or reconverted into the original colorless amines.

Table II shows the results obtained upon chromatographing nineteen pairs of *N*-alkyl and seventeen pairs of *N*-aryl *p*-phenylazobenzenesulfonamides on mixtures of two parts of silicic acid to one part of celite 535 by weight. The solvents used for developing the chromatograms were Skellysolve B, benzene, mixtures of these two solvents and mixtures of Skellysolve B-ethyl acetate. Sixteen pairs of the alkyl derivatives, ten pairs of the aryl derivatives,

(6) For a study of hydrolysis of sulfonamides see W. Seaman, A. R. Norton, J. T. Woods and H. N. Bank, *J. Am. Chem. Soc.*, **67**, 1571 (1945).

and one pair of heterocyclic derivatives were separated sufficiently to make two zones visible with a colorless zone between. The sulfonamides were recovered from the colored zones in 90 to 95% yield. Six pairs of the aryl derivatives formed a continuous band. Sectioning of this continuous band with sebsequent elution yielded homogeneous top and bottom sections with an intervening section of varying composition. Listed in Table II under the heading "Incompletely Separated" are three pairs of alkyl and one pair of aryl derivatives. These mixtures formed a continuous band, which upon sectioning gave impure materials from the top and bottom sections, which were of different melting points, indicating that a mixture was initially present. The first member of each pair listed in Table II where separation was obtained was the most strongly adsorbed derivative.

The results of the chromatographic studies indicated that resolution of a binary mixture of *N*-alkyl and/or *N,N'*-dialkyl sulfonamides into its compoments could be obtained only if the carbon content of the alkyl portion of the two sulfonamides differed by at least two carbon atoms. With a difference of one carbon atom in the alkyl radicals of the sulfonamides, a continuous band was obtained, except in the case of the binary mixture of *N*-methyl and *N,N'*-dimethyl sulfonamides which gave complete resolution. Materials from the upper and lower parts of the continuous bands showed different melting points, indicating that a mixture was present. Also, the sulfonamides of isomeric aliphatic amines formed a continuous band. However, these mixtures gave no degree of resolution. When the chromatograms of the six possible binary mixtures between *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl sulfonamides were sectioned, the materials isolated from the different sections did not show any variation in melting point.

The chromatography of binary mixtures of the *N*-(ortho-substituted phenyl) sulfonamide mixed with the sulfonamide of the meta or para isomer showed that the sulfonamide of the ortho isomer had a markedly less adsorption affinity than its meta or para isomers. An exception was found in the case of the possible binary mixtures of the sulfonamides of *ortho*, *meta*, and *para*-toluidines. This ortho effect has been observed in previous chromatographic studies[3,4] involving *ortho*-substituted benzenes.

Of the three ternary mixtures studied (See Table II) resolution was obtained for only two. In the two ternary mixtures wherein separation was obtained the derivative of the ortho isomer was least strongly adsorbed and separated from a continuous band of the derivatives of the meta and para isomers. Sectioning of this continuous band yielded the derivative of the para isomer and the derivative of the meta isomer from the top and bottom sections respectively.

It was of further interest to observe the chromatographic separation of a model mixture composed of the *p*-phenylazobenzenesulfonyl derivatives of primary and secondary amines and the corresponding tertiary amine. Table III shows the results obtained by the adsorption of five such mix-

TABLE II

CHROMATOGRAPHIC SEPARATION OF MODEL MIXTURES OF *N*-SUBSTITUTED *p*-PHENYLAZOBENZENESULFONAMIDES

A. Binary mixtures of *N*-alkyl sulfonamides

Separated into zones	
Methyl	*n*-Propyl
Ethyl	*n*-Butyl
Isopropyl	Isoamyl
Dimethyl	Diethyl
Dimethyl	Di-*n*-propyl
Diethyl	Di-*n*-propyl
Diethyl	Di-*n*-butyl
Diisobutyl	Diisoamyl
Methyl	Dimethyl
Ethyl	Diethyl
n-Propyl	Di-*n*-propyl
Isopropyl	Diisopropyl
Isobutyl	Diisobutyl
n-Butyl	Di-*n*-butyl
n-Amyl	Di-*n*-amyl
Isoamyl	Diisoamyl
Incompletely separated	
Methyl	Ethyl
n-Propyl	*n*-Butyl
Ethyl	Propyl

B. Binary mixture of *N*-aryl sulfonamides

Separated into zones	
p-Hydroxyphenyl	*o*-Hydroxyphenyl
p-Ethoxyphenyl	*o*-Ethoxyphenyl
m-Ethoxyphenyl	*o*-Ethoxyphenyl
m-Hydroxyphenyl	*o*-Hydroxyphenyl
p-Chlorophenyl	*o*-Chlorophenyl
Ethyl, phenyl	*n*-Butyl, phenyl
Methyl, phenyl	Ethyl, phenyl
o-Tolyl	Methyl, *o*-Tolyl
Phenyl	Methyl, phenyl
p-Tolyl	Methyl, *p*-Tolyl
Forming continuous band	
p-Bromophenyl	*m*-Bromophenyl
p-Ethoxyphenyl	*m*-Ethoxyphenyl
1-Naphthyl	2-Naphthyl
o-Tolyl	*p*-Tolyl
o-Tolyl	*m*-Tolyl
m-Tolyl	*p*-Tolyl
Incompletely separated	
Methyl, *o*-Tolyl	Methyl, *p*-Tolyl

C. Binary mixture of sulfonyl heterocyclic derivatives

Separated into zones	
Morpholine	Piperidine

D. Ternary mixtures of ortho, meta and para isomers

Topmost zone (continuous)		Bottom zone
Most strongly absorbed	Least strongly absorbed	
p-Ethoxyphenyl	*m*-Ethoxyphenyl	*o*-Ethoxyphenyl
p-Hydroxyphenyl	*m*-Hydroxyphenyl	*o*-Hydroxyphenyl

No separation obtained for a mixture of ortho-, Meta- and Para-tolyl sulfonamides.

tures of the sulfonamides. The *N*-Mono- and, *N,N'*-disubstituted sulfonamides separated on the column into zones with a colorless zone between. The tertiary amine appeared in the effluent. The sulfonamides were obtained in 77 to 95% recovery and identified by mixture melting points. The tertiary amines were isolated from the effluent in 49 to 72% recovery.

TABLE III

CHROMATOGRAPHIC SEPARATION OF MODEL MIXTURES OF *N*-MONO- AND *N,N*-DISUBSTITUTED *p*-PHENYLAZOBENZENESULFONAMIDES AND TERTIARY AMINES

Original Mixture	Column after Development
	15 mm. colorless
20 mg. *n*-butyl	37 mm. orange [16 mg. *n*-butyl (80%)]
	121 mm. colorless
15 mg. Di-*n*-butyl	30 mm. orange [12 mg. di-*n*-butyl (80%)]
	77 mm. colorless
778 mg. tri-*n*-butylamine	Effluent [384 mg. tri-*n*-butylamine (49%)]
	10 mm. colorless
22 mg. isoamyl	23 mm. orange [21 mg. isoamyl (95%)]
	40 mm. colorless
26 mg. diisoamyl	30 mm. orange [20 mg. diisoamyl (77%)]
	197 mm. colorless
197 mg. tri-isoamylamine	Effluent [101 mg. tri-isoamylamine (51%)]
	10 mm. colorless
22 mg. *n*-amyl	24 mm. orange [21 mg. *n*-amyl (95%)]
	43 mm. colorless
20 mg. di-*n*-amyl	29 mm. orange [19 mg. di-*n*-amyl (95%)]
	184 mm. colorless
422 mg. tri-*n*-amylamine	Effluent [tri-*n*-amylamine (wt. not taken)]
	10 mm. colorless
21 mg. phenyl-	43 mm. orange [20 mg. phenyl (95%)]
	45 mm. colorless
21 mg. methyl, phenyl	100 mm. yellow orange [19 mg. methyl, phenyl (90%)]
	130 mm. colorless
1337 mg. dimethylaniline	Effluent [865 mg. dimethylaniline (65%)]
	20 mm. colorless
22 mg. *o*-tolyl	60 mm. orange [21 mg. *o*-tolyl (95%)]
	75 mm. colorless
21 mg. methyl, *o*-tolyl	112 mm. orange [20 mg. methyl, *o*-tolyl (95%)]
	57 mm. colorless
1617 mg. dimethyl-*a*-toluidine	Effluent [1157 mg. Dimethyl-*o*-toluidine (72%)]

Separation and Determination of Primary, Secondary and Tertiary Amines. In this work, we have found that model mixtures composed of the sulfonamides of corresponding primary and secondary amines and the corresponding tertiary amine can be separated into their individual components by chromatographic adsorption. This observation provided the basis for a study of the following method for separating the three classes of amines.

The procedure involves treating a mixture of the three classes of amines with *p*-phenylazobenzenesulfonyl chloride. Only the primary and secondary amines react. When the reaction mixture is distributed between benzene and dilute hydrochloric acid the unreacted tertiary amine forms a water-soluble hydrochloride salt. The aqueous phase is separated and made alkaline to liberate the tertiary amine as the free base which is extracted with benzene, and the amine is recovered upon evaporating the solvent; or the aqueous phase is evaporated to dryness and the tertiary amine is recovered as its hydrochloride. The benzene solution of *p*-phenylazobenzenesulfonic acid, unreacted sulfonyl chloride and the sulfonamides of the primary and secondary amines is chromatographed. The unreacted sulfonyl chloride and/or the free sulfonic acid are strongly adsorbed on the adsorbent, while the monosubstituted sulfonamide and di-substituted sulfonamide are separated into two distinct zones. The sulfonamides are then recovered in the usual manner.

The analyses of six mixtures of the three classes of amines by this method are:

(1) A mixture of 13 mg. methylamine, 19 mg. dimethylamine, 1446 mg. trimethylamine (25% aqueous solutions of the methylamines were used. The weight of each amine is therefore a calculated value) and 251 mg. sulfonyl chloride was treated as described above. Trimethylamine hydrochloride [462 mg. (20%)] was recovered from the acid extract. The top 4 mm. of the chromatogram was an orange zone from which was isolated *p*-phenylazobenzenesulfonic acid. Below a 7 mm. colorless zone was found a 32 mm. orange zone which yielded 65 mg. (55%) methyl sulfonamide. Following the latter a 25 mm. colorless zone was found. Below this, a 108 mm. orange zone was found from which 113 mg. (90%) dimethyl sulfonamide was recovered. The bottom portion (137 mm.) of the column was colorless.

(2) A mixture of 23 mg. ethylamine, 24 mg. diethylamine, 5030 mg. triethylamine and 252 mg. sulfonyl chloride was treated as described above. Triethylamine hydrochloride [4342 mg.(64%)] was recovered from the acid extract. The chromatogram was similar to the one described in part one: 3 mm. orange zone which yielded the sulfonic acid, 10 mm. colorless zone, 42 mm. orange zone which yielded 138 mg. (95%) ethyl sulfonamide, 15 mm. colorless zone, 60 mm. orange zone which yielded 57 mg. (55%) diethyl sulfonamide, and a 203 mm. colorless zone.

(3) A mixture of 25 mg. *n*-butylamine, 45 mg. di-*n*-butylamine, 5813 mg. tri-*n*-butylamine and 233

mg. sulfonyl chloride was treated as described above. Tri-*n*-butylamine hydrochloride [6336 mg. (91%)] was recovered from the acid extract. The chromatogram was similar to the one described in part one: 9 mm. orange zone which yielded the sulfonic acid, 11 mm. colorless zone, 75 mm. orange zone which yielded 98 mg. (85%) *n*-butyl sulfonamide, 145 mm. colorless zone, 85 mm. orange zone combined with some colored material which was washed into the effluent yielded 115 mg. (88%) di-*n*-butyl sulfonamide.

(4) A mixture of 66 mg. isoamylamine, 104 mg. diisoamylamine, 5140 mg. triisoamylamine and 428 mg. sulfonyl chloride was treated as described above. Triisoamylamine hydrochloride [5117 mg. (89%)] was recovered from the acid extract. The chromatogram was similar to the one described in part one: 14 mm. orange zone which yielded the sulfonic acid, 32 mm. colorless zone, 52 mm. orange zone which yielded 201 mg. (79%) isoamyl sulfonamide, 41 mm. colorless zone, 69 mm. orange zone which yielded 212 mg. (79%) diisoamyl sulfonamide and 183 mm. colorless zone.

(5) A mixture of 25 mg. aniline, 23 mg. methylaniline, 1711 mg. dimethylaniline, and 147 mg. sulfonyl chloride was treated as described above. Dimethylaniline [1479 mg. (87%)] was recovered from the acid extract. The chromatogram was similar to the one described in part one: 30 mm. orange zone which yielded the sulfonic acid, 10 mm. colorless zone, 60 mm. orange zone which yielded 87 mg. (96%) phenyl sulfonamide, 120 mm. colorless zone, 105 mm. orange zone which yielded 51 mg. (69%) methyl, phenyl sulfonamide, and 10 mm. colorless zone.

(6) A mixture of 21 mg. *o*-toluidine, 22 mg. methyl-*o*-toluidine, 2888 mg. dimethyl-*o*-toluidine and 109 mg. sulfonyl chloride was treated as described above. Dimethyl-*o*-toluidine [1850 mg. (64%)] was recovered from the acid extract. The chromatogram was similar to the one described in part one: 20 mm. colorless zone, 75 mm. orange zone which yielded 58 mg. (85%) *o*-tolyl sulfonamide, 85 mm. colorless zone, 120 mm. yellowish orange zone which yielded 44 mg. (66%) methyl, *o*-tolyl sulfonamide, and 18 mm. colorless zone.

The yields of the monosubstituted sulfonamides ranged from 55 to 96% with an average value of 83%. The yields of the disubstituted sulfonamides ranged from 55 to 90% with an average value of 75%. The tertiary amines were recovered in yields ranging from 20 to 91% with an average value of 69%. The quantitative separation of the three classes of amines was not of paramount interest in this study. However, the recoveries of the different classes of amines from the mixtures are satisfactory for identification purposes.

The method proposed herein for the separation of the three classes of amines appears to offer promise for the quantitative separation of mixtures of both aliphatic and aromatic amines. A quantitative study of the separation of mixtures of the three classes of amines is now under investigation. This method, also, appears to have advantages over the commonly used Hinsberg Method.[7]

EXPERIMENTAL

Reagents. Amines of commercially available grades were used without further purification.

p-Phenylazobenzenesulfonyl chloride was prepared as described by Desai and Mehta.[6]

The adsorbent used in preparing the chromatographic columns was a mixture of silicic acid (Mallinckrodt, prepared by the method of Ramsey and Patterson) and Celite-535 (Johns-Manville).

The solvents Skellysolve B and A.C.S. grade benzene were redistilled and absolute ethyl alcohol and A.C.S. grade ethyl acetate were used as purchased.

Preparation of N-substituted p-phenylazobenzenesulfonamides. A mixture of *p*-phenylazobenzenesulfonyl chloride (approximately 100 mg.), amine (10% by weight excess), and 3 to 6 ml. of pyridine was refluxed for 1 hr. The clear red solution was poured with stirring into ice and 50 ml. of 10% sodium bicarbonate solution. The derivatives of the aliphatic amines, aniline and methylaniline crystallized immediately, and the derivatives of the other aromatic amines crystallized on further cooling. The crystalline product was filtered, washed with water, 1% hydrochloric acid, water, and then air dried. The crude product was dissolved in either Skellysolve B, benzene or a mixture of the two and chromatographed on a mixture of silicic acid–celite (2 to 1 by weight) on which any free acid and/or unreacted acid chloride was strongly adsorbed. The sulfonamide was desorbed with absolute ethyl alcohol and the solvent removed. The colored solid (orange to red) was then recrystallized. The derivatives of the aliphatic amines were recrystallized from Skellysolve B. The derivatives of the aromatic amines were recrystallized from ethyl alcohol–water mixtures, using as little water as possible. The derivatives crystallized as fluffy solids, plates or fine needles.

Chromatography of the crude aromatic amine derivatives usually gave three colored zones a strongly adsorbed acid zone and two zones separated by a colorless zone. Of the latter two colored zones the lower one gave sharp melting points and good analysis, whereas the higher one gave less than 10 mg. of tacky or solid material of indefinite melting point. This material was considered to be derived from an impurity of the original amine.

Acid Hydrolysis of the Sulfonamides. A typical acid hydrolysis was conducted as described below. A mixture of each sulfonamide (methyl, 112 mg.; dimethyl, 184 mg.; *n*-butyl, 188 mg.; di-*n*-butyl, 91 mg.; *tert*-butyl, 102 mg.; *sec*-butyl, 120 mg.; isoamyl, 179 mg.; di-isoamyl, 132 mg.; p-chlorophenyl, 102 mg.; 2-naphthyl, 96 mg.; 1-naphthyl, 105 mg.; *p*-tolyl, 114 mg.) with 50 ml. of concentrated hydrochloric acid in the case of an aliphatic amine and with 10 ml. of concentrated hydrochloric acid and 10 ml. of dioxane in the case of an aromatic amine was refluxed for approximately 6 hr. The dioxane was used with the aromatic amines to effect a homogeneous reaction mixture. The reaction mixture was poured into 100 ml. of distilled water and filtered to remove a negligible amount (1 to 3 mg.) of dark material suspended in the clear red solution. This material did not melt under 300°.

The filtered reaction mixture from the hydrolysis of the sulfonamides of the aliphatic amines was evaporated to dryness *in vacuo* to give a white residue with reddish tinge. The solid or oily residue was dissolved in 95% ethanol and the ethanol solution treated with norit to give a clear, color-

(7) O. Hinsberg, *Ber.*, **23**, 2961 (1890).

less solution. The solvent was removed *in vacuo* under a stream of nitrogen to give the amine hydrochloride (see Table I for % recovery).

The filtered reaction mixture from the hydrolysis of the sulfonamides of the aromatic amines was made basic with 10% sodium hydroxide and then extracted with several portions of benzene. The benzene extracts were combined and dried over anhydrous sodium sulfate, and then treated with norit. The solvent removed *in vacuo* under a stream of nitrogen and the aromatic amine so obtained was identified by mixture melting point (See Table I for % recovery).

Chromatographic Separations of Model Mixtures. A typical chromatographic separation was conducted as described below. A tube 20 mm. × 400 mm. was connected to a suction flask. A 2 to 1 mixture by weight of silicic acid and celite was prepared for use as the adsorbent. The tube was packed to a height of approximately 300 mm. with the adsorbent by adding it batchwise while tapping simultaneously the opposite sides of the column with two cork rings. Then full suction of the water aspirator was applied to the suction flask for about 2 minutes. The adsorbent was then washed with 100 ml. Skellysolve B, 100 ml. of a 50–50 mixture of Skellysolve B and ethyl acetate, and finally 100 ml. of Skellysolve B.

A binary mixture of sulfonamides (10 to 20 mg. of each component) was dissolved in the minimum volume of benzene and then adsorbed on the column. The chromatogram was developed with Skellysolve B, then solutions of 5% up to 10% of benzene in Skellysolve B, and finally solutions of 1% up to 4% of ethyl acetate in Skellysolve B. The zones were dug out of the column by a long narrow spatula and desorbed by shaking with absolute ethanol. When a continuous band was obtained, the band was arbitrarily dug out in several sections. The pure components were obtained from the top and bottom sections and the intervening section was a mixture. The eluents were concentrated, filtered into a tared flask, and the last traces of solvent removed *in vacuo* under a stream of nitrogen. The weights and melting points of the residues were determined.

The ternary mixtures of the *N*-substituted sulfonamides of ortho, meta and para isomers of the aromatic amines were chromatographed by the same general procedure as described above. The chromatogram showed two colored zones separated by a colorless zone. The sulfonamide of the ortho isomer was isolated from the bottom zone. The top zone contained the sulfonamides of the meta and para isomers which upon sectioning as described above gave pure components from the top and bottom sections.

The mixtures of *N*-mono- and *N,N'*-disubstituted sulfonamides and tertiary amines were chromatographed by the same general procedure as described above. The chromatograms are described in Table III. It was assumed that on developing the chromatogram by washing with 50 ml. of Skellysolve B, 100 ml. of 2% ethyl acetate in Skellysolve B and 200 ml. of 4% ethyl acetate in Skellysolve B that the tertiary amine had been completely washed into the effluent. The tertiary amine was then recovered from the effluent by removal of the solvent. The mono- and di-substituted sulfonamides separated into two distinct colored zones with a colorless zone between. The mono- and di-substituted sulfonamides were isolated from the top and bottom zones respectively. They were identified by mixture melting point.

Analysis of Mixtures of Amines. A mixture of primary, secondary, and tertiary amine and the molar quantity of *p*-phenylazobenzenesulfonyl chloride required for reaction with the primary and secondary amines was refluxed for one hour. Homogeneous reaction mixtures were obtained in all cases except with the mixture of aqueous solutions of methyl amines.

The red-colored reaction mixture was cooled and dissolved in benzene. The benzene layer was extracted with several portions of 6*N* hydrochloric acid and the aqueous layers were collected. The benzene layer was washed with water which was added to the aqueous layers. The benzene layer was than washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and the benzene solution was concentrated. The benzene concentrate of the sulfonamides was saved for subsequent chromatography.

In the analysis of aliphatic amines the aqueous layer was evaporated to dryness *in vacuo*. The residue was dissolved in 95% ethyl alcohol, treated with norit, filtered into a tared flask, concentrated and the last traces of solvent removed *in vocuo* under a stream of nitrogen. The residue was the hydrochloride of the aliphatic tertiary amine.

In the analysis of mixtures of aromatic amines the aqueous layer was made basic with 10% sodium hydroxide. The aqueous solution was extracted with several portions of benzene. The benzene extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, treated with norit, filtered, and the solvent removed *in vacuo* under a stream of nitrogen. The residue was confirmed as the aromatic amine through picrate formation.

The benzene concentrate of the sulfonamides of the primary and secondary amines was chromatographed in the manner previously described for the chromatographic separation of binary mixtures. The mono- and di-substituted sulfonamides separated into two distinct colored zones with a colorless zone between. The mono- and di-substituted sulfonamides were isolated from the top and bottom zones respectively. They were identified by mixture melting point.

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WILBERFORCE, OHIO

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

Syntheses of Dimethoxybenzimidazoles, Dihydroxybenzimidazoles and Imidazo-*p*-benzoquinones

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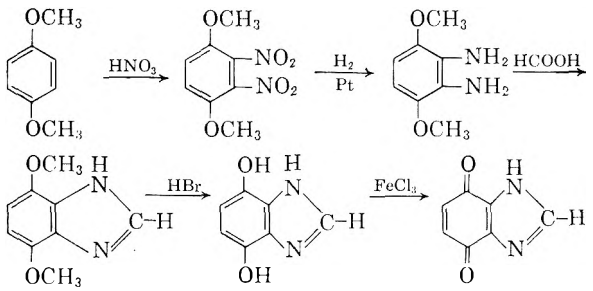
The syntheses of a number of 4,7- and 5,6-dimethoxybenzimidazoles and of the corresponding dihydroxy derivatives are reported. Several of the 4,7-dihydroxy compounds have been converted to quinones.

Imidazole derivatives of 1,4-naphthoquinone[1] have been demonstrated to possess antimetabolite activity against vitamin B_{12}-requiring *E. coli* 113-3, folic acid-requiring *L. casei* and purine-requiring *E. coli B* 96.[2] These activities have prompted us to extend this work to imidazo-*p*-benzoquinones and related compounds. This paper describes some of this work.

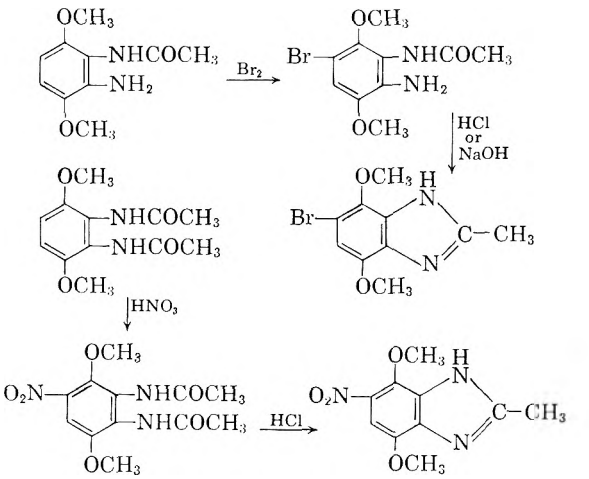
An obvious approach to the syntheses of such compounds is through the preparation of suitable dimethoxybenzimidazoles. 1,4-Dimethoxybenzene and 1,2-dimethoxybenzene were the starting materials for these preparations. For example:



1,2-Dimethoxybenzene was treated in a similar manner.

The nitration of 1,4-dimethoxybenzene was carried out by the methods of Habermann[3] and of Nietzki and Rechberg.[4] The 2,3-diamino-1,4-dimethoxybenzene oxidized rapidly in air and it was found necessary to convert it to the hydrochloride as soon as possible. The diamine was converted to 4,7-dimethoxybenzimidazole by Phillips' procedure.[5] A number of 2-substituted 4,7-dimethoxybenzimidazoles were prepared by using other acids in place of formic acid (see Table I). 2-Carboxyethyl-4,7-dimethoxybenzimidazole was prepared from the diamine and succinic anhydride by the method of Chatterjee.[6] The corresponding methyl ester and hydrazide were also prepared.

To introduce other substituents into the benzene ring, it was found most convenient to introduce them before ring closure to the imidazole. For example:



It is interesting to note that the diacetamido derivative could not be brominated whereas the monoacetamido compound undergoes bromination under mild conditions. Nitration of the diacetamido derivative proceeded normally. The nitro group may also be introduced by direct nitration of the benzimidazole. For example, 4,7-dimethoxybenzimidazole was nitrated to form 5-nitro-4,7-dimethoxybenzimidazole. The latter was reduced to the corresponding amino compound which was isolated as its hydrochloride.

4,7-Dimethoxybenzimidazole was converted to the corresponding dihydroxy derivative by heating with 48% hydrobromic acid. When the 2-position is alkylated, the ether linkages are not cleaved, under similar conditions, due to the insolubility of the compound to be cleaved. In these cases, cleavage was effected by heating with concentrated hydrochloric acid in sealed tubes. In general, the hydroquinones could not be isolated as the free bases. Their hydrohalides were obtained in solid form but only in two cases were analytically pure samples obtained. The impure hydrohalides may be oxidized directly to the corresponding quinones (Table II).

1,2-Dimethoxybenzene, the starting material for 5,6-dimethoxybenzimidazole, was nitrated in two

(1) J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **76**, 4148 (1954).

(2) D. B. McNair Scott, Dept. of Physiology, Medical School of the University of Pennsylvania, private communication.

(3) J. Habermann, *Ber.*, **11**, 1037 (1878).

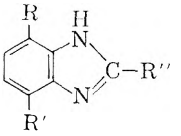
(4) R. Nietzki and F. Rechberg, *Ber.*, **23**, 1216 (1890).

(5) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(6) B. Chatterjee, *J. Chem. Soc.*, 2965 (1929).

TABLE I

4,7-DISUBSTITUTED BENZIMIDAZOLES

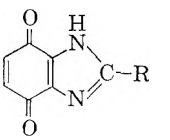


R	R′	R″	Yield, %	M.P. °C (dec.)	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
OCH_3	OCH_3	H	88	218–222	$C_9H_{10}N_2O_2$	60.66	60.54	5.66	5.44	15.72	15.89
OCH_3	OCH_3	CH_3	90[e]	224–226	$C_{10}H_{12}N_2O_2$	62.49	62.51	6.30	6.42	14.58	14.55
OCH_3	OCH_3	C_2H_3	57[f]	190–193	$C_{11}H_{14}N_2O_2$	64.05	63.91	6.84	6.98	13.58	13.42
OCH_3	OCH_3	n-C_3H_7	50[g]	183–189	$C_{12}H_{16}N_2O_2$	65.43	65.59	7.33	7.25	12.72	12.55
OCH_3	OCH_3	i-C_5H_{11}	23[e]	157–160	$C_{14}H_{20}N_2O_2$	67.71	67.57	8.12	8.39	11.28	11.37
OCH_3	OCH_3	CH_3OCH_3	69[h]	154–157	$C_{11}H_{14}N_2O_3$	59.44	59.26	6.35	6.48	12.61	12.47
OCH_3	OCH_3	$HOCH_2$	72[h]	200–202	$C_{10}H_{12}N_2O_3$	57.63	57.42	5.81	5.71	13.45	13.26
OCH_3	OCH_3		90	178–180	$C_{14}H_{19}N_3O_3$	60.63	60.42	6.91	7.08	15.15	15.21
OCH_3	OCH_3	$(CH_3)_2COOH$	40[a]	[d]	$C_{12}H_{15}N_2O_4Cl$	50.26	50.24	5.27	5.36	9.77	9.79
OCH_3	OCH_3	$(CH_3)_2COOCH_3$	65	154–157	$C_{13}H_{16}N_2O_4$	59.08	58.98	6.10	5.87	10.60	10.54
OCH_3	OCH_3	$(CH_3)_2CONHNH_2$	87	188–196	$C_{12}H_{16}N_4O_3$	54.53	54.34	6.10	6.13	21.20	21.18
OH	OH	H	100[b]	285–325	$C_7H_7N_2O_2Br$	36.38	36.59	3.01	3.24	12.12	12.07
OH	OH	CH_3	60[c]	297–299	$C_8H_9N_2O_2Cl$	47.89	48.08	4.52	4.54	13.97	13.86
OH	OH	$(CH_2)_2COOCH_3$	90	213–219	$C_{11}H_{12}N_2O_4$	55.96	55.93	5.12	5.12	11.82	11.86

[a] As hydrochloride. Chlorine calcd., 12.37; Found, 12.17. [b] As hydrobromide. Bromine calcd., 34.58; Found, 34.60. [c] As hydrochloride. Chlorine calcd., 17.67; Found, 17.50. [d] No definite melting point. [e] Recrystallized from aqueous ethanol. [f] Recrystallized from ethanol. [g] Recrystallized from aqueous ethanol and from chloroform-ethylacetate. [h] Recrystallized from water.

TABLE II

IMIDAZO-*p*-BENZOQUINONES



R	Yield, %	M.P. °C (dec.)	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	92	>340	$C_7H_4N_2O_2$	56.76	56.76	2.72	2.83	18.92	18.97
CH_3	79	250	$C_8H_6N_2O_2$	59.25	59.41	3.73	3.59	17.28	17.26
n-C_3H_7	36	>300	$C_{10}H_{10}N_2O_2$	63.10	63.33	5.27	5.28	14.73	14.64
i-C_5H_{11}	29	164	$C_{12}H_{14}N_2O_2$	66.04	66.21	6.46	6.28	12.84	12.73

steps. The mono nitro derivative was prepared according to the procedure of Cardwell and Robinson.[7] The second nitro group was introduced by using fuming nitric acid.[8] The dinitro compound may be reduced to the corresponding diamine with tin and hydrochloric acid or catalytically over palladium. It had been claimed earlier that only one nitro group was reduced by hydrogen in the presence of palladium.[9] We found no evidence for this observation in the present study.

The 1,2-diamino-4,5-dimethoxybenzene was converted to 5,6-dimethoxybenzimidazole and 2-methyl-5,6-dimethoxybenzimidazole by Phillips' procedure.[5] Both of these compounds are water soluble. Attempts to prepare 2-ethyl- and 2-propyl-5,6-dimethoxybenzimidazoles, by Phillips' method, failed. Extensive decomposition occurred. Similar results were obtained when the diamine was treated with propionyl chloride in pyridine solution. The reaction of the diamine with glycolic acid, by Phillips' method, gave the expected 2-hydroxymethyl-5,6-dimethoxybenzimidazole. The latter compound was converted to the corresponding 2-chloromethyl compound by thionyl chloride. The 2-chloromethyl derivative could not be obtained by treating the diamine with chloroacetic acid.

2-Chloromethyl-5,6-dimethoxybenzimidazole was

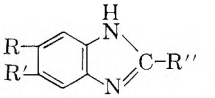
(7) D. Cardwell and R. J. Robinson, *J. Chem. Soc.*, 107, 256 (1915).

(8) H. Vermeulen, *Rec. trav. chim.*, 48, 969 (1929).

(9) K. Frisch and M. T. Bogert, *J. Org. Chem.*, 8, 331 (1943).

TABLE III

5,6-DISUBSTITUTED BENZIMIDAZOLES



R	R′	R″	Yield %	M.P. °C (dec.)	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
OCH_3	OCH_3	H	93	179–183	$C_9H_{10}N_2O_2$	60.66	60.41	5.66	5.59	15.72	15.79
OCH_3	OCH_3	CH_3	65[e]	168–172	$C_{10}H_{12}N_2O_2$	62.49	62.49	6.30	6.21	14.58	14.40
OCH_3	OCH_3	CH_2OH	78[f]	240–241	$C_{10}H_{12}N_2O_3$	57.69	57.54	5.81	5.72	13.46	13.21
OCH_3	OCH_3	CH_3Cl[a]	62	[d]	$C_{10}H_{12}N_2O_2Cl_2$	45.64	45.67	4.60	4.38	10.65	10.49
OCH_3	OCH_3	$CH_2N(C_4H_9)_2$	60	95–97	$C_{18}H_{29}N_3O_2$	67.68	67.59	9.15	8.91	13.15	13.06
OCH_3	OCH_3	$CH_3N(CH_2CH_2Cl)_2$[b]	56	182	$C_{14}H_{20}N_3O_2Cl_3$	45.56	45.46	5.44	5.36	11.39	11.61
OH	OH	H[c]	98	>300	$C_7H_7N_2O_2Br$	36.38	36.50	3.05	2.90	12.13	12.31

[a] As hydrochloride. Chlorine calcd. 26.95; Found 26.73. [b] As hydrochloride. Chlorine calcd. 28.90; Found 28.61. [c] As hydrobromide. Bromine calcd. 34.58; Found 34.31. [d] No definite melting point. [e] Recrystallized from chloroform–petroleum ether and dioxane. [f] Recrystallized from dioxane.

condensed with dibutylamine, morpholine, and diethanolamine, respectively, to form the corresponding 2-aminomethyl compounds. 2-Di(2-hydroxyethyl)aminomethyl - 5,6 - dimethoxybenzimidazole was converted to the corresponding nitrogen mustard by treatment with thionyl chloride. The imidazoles prepared from 1,2-diamino-4,5-dimethoxybenzene are listed in Table III.

EXPERIMENTAL

2,3-Dinitro-1,4-dimethoxybenzene was prepared by a previously described method.[3,4] The crude product was recrystallized from acetic acid.

2,3-Diamino-1,4-dimethoxybenzene. A solution of 22.8 g. (0.135 mole) of 2,3-dinitro-1,4-dimethoxybenzene in 125 ml. of ethanol was hydrogenated with platinum oxide as the catalyst. After removing the catalyst, the filtrate was made strongly acidic by adding concentrated hydrochloric acid. The crude hydrochloride of the product was removed by filtration. The salt was dissolved in water. The solution was made alkaline with sodium hydroxide solution and extracted with chloroform. The extract was reduced to small volume and the product precipitated by the addition of petroleum ether. The product was then recrystallized from water, with the aid of decolorizing carbon and sodium bisulfite, and finally from chloroform and petroleum ether. The yield was 40%, m.p. 85–87°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.14; H, 7.20; N, 16.66. Found: C, 57.01; H, 7.37; N, 16.51.

4,7-Dimethoxybenzimidazole. A solution of 27.4 g. (0.133 mole) of 2,3-diamino-1,4-dimethoxybenzene hydrochloride in 200 ml. of 98% formic acid was refluxed for 2 hr. The solution was cooled and made basic with ammonium hydroxide. The light brown precipitate was removed, recrystallized from ethanol-water with the aid of decolorizing carbon and finally recrystallized from ethanol and chloroform.

2-Alkyl-4,7-dimethoxybenzimidazoles. These compounds were prepared from the corresponding diamine and organic acids by Phillips' method.[5]

2-Chloromethyl-4,7-dimethoxybenzimidazole. 2-Hydroxymethyl-4,7-dimethoxybenzimidazole (9.6 g., 0.046 mole) was refluxed for 2 hr. with 12 ml. of thionyl chloride in 125 ml. of chloroform. The solution was chilled and the hydrochloride of the product precipitated by the addition of ether, yield 11.9 g. (95%), m.p. 228–232°.[10]

2-Morpholinomethyl-4,7-dimethoxybenzimidazole. A solution of 2.63 g. (0.01 mole) of 2-chloromethyl-4,7-dimethoxybenzimidazole and 4.77 g. (0.03 mole) of morpholine in 50 ml. of ethanol was refluxed for 4 hr. The ethanol was removed by distillation and the residue extracted with chloroform. The chloroform extract was treated with decolorizing carbon and dried over magnesium sulfate. The addition of dry hydrogen chloride precipitated the hydrochloride of the product, yield 2.96 g. (95%). The salt was dissolved in water, the solution neutralized with sodium bicarbonate and the free base then extracted with chloroform. Most of the chloroform was removed and petroleum ether added to precipitate the free base.

2-Carboxyethyl-4,7-dimethoxybenzimidazole hydrochloride. A solution of 9.85 g. (0.0586 mole) of 2,3-diamino-4,7-dimethoxybenzene and 11.7 g. (0.117 mole) of succinic anhydride in 110 ml. of xylene was refluxed for 3 hr. The hot xylene was decanted immediately and the residue extracted with hot 4*N* hydrochloric acid. On cooling the extract, the hydrochloride of the product precipitated. It was removed, washed with hot acetone and then recrystallized from 4*N* hydrochloric acid.

The methyl ester was prepared by the usual method used for the esterification of amino acids.

Hydrazide of 2-carboxyethyl-4,7-dimethoxybenzimidazole. Hydrazine hydrate (4.6 g., 0.091 mole) and 1.5 g. (0.0057 mole) of the methyl ester of 2-carboxyethyl-4,7-dimethoxybenzimidazole were dissolved in 10 ml. of methanol and the solution was refluxed for 1 hr. The mixture was poured into ice water to precipitate the hydrazide. The latter was recrystallized from water with the aid of decolorizing carbon.

4,7-Dihydroxybenzimidazole hydrobromide. 4,7-Dimethoxybenzimidazole (3.4 g., 0.019 mole) was refluxed for 1 hr. with 35 ml. of 48% hydrobromic acid. On cooling, the hydrobromide of the dihydroxy compound separated in quantitative yield. The product was purified by recrystallization from ethanol-ether.

2-Methyl-4,7-dihydroxybenzimidazole hydrochloride. 2-Methyl-4,7-dimethoxybenzimidazole (2.7 g., 0.01 mole) and 15 ml. of concentrated hydrochloric acid were heated in a sealed Pyrex tube for 20 hr. at 100°. After cooling, the tube was opened and the contents filtered. The hydrochloride

(10) J. M. Cohen, Doctoral Dissertation, University of Pennsylvania, 1958.

was recrystallized from ethanol-ether, with the aid of decolorizing carbon.

Methyl ester of 2-carboxyethyl-4,7-dihydroxybenzimidazole. 2-Carboxyethyl-4,7-dimethoxybenzimidazole (5.04 g., 0.0202 mole) was heated in a sealed Pyrex tube with 25 ml. of concentrated hydrochloric acid for 24 hr. at 100°. A 66% yield of the crude hydrochloride was obtained. Since we were not successful in purifying the product, we converted it to its methyl ester. The hydrochloride of the latter was obtained in quantitative yield. It was dissolved in water and the solution neutralized with sodium bicarbonate to precipitate the free base. The latter was recrystallized from dioxane–petroleum ether.

2-Acetamido-3-amino-1,4-dimethoxybenzene. 2,3-Diamino-1,4-dimethoxybenzene (13.2 g., 0.064 mole) was dissolved in 170 ml. of water at 35°. The solution was treated with charcoal and filtered. To this solution was added 6.2 ml. (0.065 mole) of acetic anhydride followed by the addition of 5.3 g. (0.065 mole) of sodium acetate in 30 ml. of water. The acetamido derivative separated on standing. It was recrystallized from ethanol with the aid of decolorizing carbon, yield 53%, m.p. 143–145°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.12; H, 6.71; N, 13.13. Found: C, 57.28; H, 6.63; N, 13.30.

2,3-Diacetamido-1,4-dimethoxybenzene. Acetic anhydride (2.28 ml., 0.0242 mole) was added to 2.43 g. (0.0119 mole) of 2,3-diamino-1,4-dimethoxybenzene in 50 ml. of water, followed by the addition of 1.96 g. (0.024 mole) of sodium acetate in 15 ml. of water. The diacetamido derivative separated on standing. It was recrystallized from ethanol, yield 37%, m.p. 203–213° dec.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 56.96; H, 6.61; N, 11.30.

2-Acetamido-3-amino-6-bromo-1,4-dimethoxybenzene. 2-Acetamido-3-amino-1,4-dimethoxybenzene (2.1 g., 0.01 mole) was dissolved in 75 ml. of dioxane and a solution of 1.6 g. (0.01 mole) of bromine in 16 ml. of dioxane was slowly added. The hydrobromide of the bromo compound separated from the reaction mixture. The crystals were dissolved in water and the solution treated with sodium bicarbonate. The precipitate which formed was removed, dried, and recrystallized from chloroform–petroleum ether, yield 70%, m.p. 164–167°.

Anal. Calcd. for $C_{10}H_{13}N_2O_3Br$: C, 41.54; H, 4.53; N, 9.69; Br, 27.64. Found: C, 41.35; H, 4.35; N, 9.89; Br, 27.85.

2,3-Diacetamido-6-nitro-1,4-dimethoxybenzene. 2,3-Diacetamido-1,4-dimethoxybenzene (2.52 g., 0.01 mole) was dissolved in 15 ml. of acetic acid and 25 ml. of concentrated sulfuric acid was slowly added. This solution was cooled to 5° and 0.9 g. (0.01 mole) of concentrated nitric acid in 0.7 g. of concentrated sulfuric acid was added, keeping the temperature between 0–10°. After standing for 1 hr., the solution was poured into ice water and neutralized to *p*H 7. The precipitate which formed was removed and recrystallized from ethanol, yield 66%, m.p. 265–268 dec.

Anal. Calcd. for $C_{12}H_{15}N_3O_6$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.46; H, 4.98; N, 14.29.

2-Methyl-5-bromo-4,7-dimethoxybenzimidazole. This compound was prepared from 2-acetamido-3-amino-6-bromo-1,4-dimethoxybenzene by Phillips' method.[5] The product was recrystallized from benzene and from chloroform–petroleum ether, yield 89%, m.p. 177–181°.

Anal. Calcd. for $C_{10}H_{11}N_2O_2Br$: C, 44.30; H, 4.09; N, 10.33; Br, 29.47. Found: C, 44.27; H, 4.10; N, 10.24; Br, 29.60.

This compound was also obtained when the 2-acetamido-3-amino compound was heated with 10% sodium hydroxide in aqueous ethanol.

2-Methyl-5-nitro-4,7-dimethoxybenzimidazole. 2,3-Diacetamido-5-nitro-1,4-dimethoxybenzene (6.2 g., 0.0208 mole) was dissolved in 100 ml. of 4*N* hydrochloric acid and refluxed for 2 hr. The cooled solution was made slightly basic. The precipitate which formed was removed, dried, and extracted with chloroform. The extracted product was recrystallized from benzene and from dioxane–petroleum ether, yield 80%, m.p. 204–205°.

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.71. Found: C, 50.44; H, 4.55; N, 17.63.

5-Nitro-4,7-dimethoxybenzimidazole. 4,7-Dimethoxybenzimidazole (1.78 g., 0.01 mole) was suspended in 15 ml. of acetic acid and 25 ml. of concentrated sulfuric acid was gradually added, keeping the temperature below 40°. The solution was cooled to 0–10° and a mixture of 0.9 g. (0.01 mole) of concentrated nitric acid and 0.7 g. of concentrated sulfuric acid was added. After 0.5 hr. the solution was allowed to come to room temperature and then poured into ice water and the *p*H adjusted to 5. The precipitate which formed was recrystallized from ethanol and ethanol-water, yield 86%, m.p. 210°.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.82. Found: C, 48.60; H, 4.22; N, 19.04.

5-Amino-4,7-dimethoxybenzimidazole dihydrochloride. 5-Nitro-4,7-dimethoxybenzimidazole in ethanol was hydrogenated in the presence of a palladium-charcoal catalyst. The catalyst was removed and concentrated hydrochloric acid added to the filtrate to precipitate the product as its dihydrochloride. The latter was recrystallized from ethanol-water with the aid of decolorizing carbon, yield 95%, m.p. 230–231°.

Anal. Calcd. for $C_9H_{13}N_3O_2Cl_2$: C, 40.62; H, 4.93; N, 15.79; Cl, 26.65. Found: C, 40.80; H, 4.73; N, 15.68; Cl, 26.50.

Imidazo-p-benzoquinone. 4,7-Dihydoxybenzimidazole hydrobromide (3.7 g., 0.016 mole) was dissolved in water and an excess of ferric chloride added. After standing for 2 hr., the yellow product was collected by filtration and recrystallized from dimethylformamide.

2-Methylimidazo-p-benzoquinone. 2-Methyl-4,7-dihydroxybenzimidazole (1.15 g., 0.0057 mole) was dissolved in 30 ml. of water and 0.63 g. (0.0063 mole) of chromic anhydride in 5 ml. of water was added to the solution. After standing for 2 hr., the yellow product was removed by filtration. It was recrystallized from acetic acid, with the aid of decolorizing carbon, and twice from ethylene glycol monomethyl ether.

2-Propylimidazo-p-benzoquinone. This compound was prepared from crude 2-propyl-4,7-dihydroxybenzimidazole hydrochloride by oxidation with chromic anhydride. The crude quinone was extracted with benzene and finally recrystallized from benzene.

2-Isoamylimidazo-p-benzoquinone. Crude 2-isoamyl-4,7-dihydroxybenzimidazole hydrochloride was used for this preparation and chromic anhydride was the oxidizing agent. The yellow product was recrystallized from dioxane–petroleum ether.

4-Nitro-1,2-dimethoxybenzene. 1,2-Dimethoxybenzene (23 g., 0.018 mole) was added dropwise to a mixture of 10 ml. of concentrated nitric acid and 20 ml. of water, between 15–30°. After 15 min., the mixture was poured into ice water. The precipitate was removed, washed and dried, yield 100%, m.p. 96–99° (crude product).

4,5-Dinitro-1,2-dimethoxybenzene. 4-Nitro-1,2-dimethoxybenzene (33 g., 0.14 mole) was added to 115 ml. of fuming nitric acid, keeping the temperature at 0°. After 0.5 hr., the mixture was poured into ice water. The precipitate was removed, washed and dried, yield 38.9 g. (95%), m.p. 125–132° (crude product).[11]

4,5-Diamino-1,2-dimethoxybenzene. The corresponding dinitro compound was hydrogenated, in the presence of a palladium-on-carbon catalyst, in ethanol solution. After removing the catalyst, the diamine was obtained by removing the ethanol *in vacuo*, m.p. 131°.[9]

5,6-Dimethoxybenzimidazole. 4,5-Diamino-1,2-dimethoxybenzene was treated with 98% formic acid as in the prep-

(11) The preparations of the last two compounds are included because difficulties were encountered with the previously described preparations.

aration of 5,7-dimethoxybenzimidazole. The product was recrystallized from dioxane with the aid of decolorizing carbon.

2-Methyl-5,6-dimethoxybenzimidazole and 2-hydroxymethyl-5,6-dimethoxybenzimidazole were prepared by Phillips' method.[5]

2-Chloromethyl-5,6-dimethoxybenzimidazole hydrochloride. A mixture of 8.19 g. (0.0393 mole) of 2-hydroxymethyl-5,6-dimethoxybenzimidazole and 15 ml. of thionyl chloride was refluxed for 4 hr. The mixture was cooled and the solid removed and washed with chloroform. It was recrystallized from ethanol with the aid of decolorizing carbon.

2-Di-n-butylaminomethyl-5,6-dimethoxybenzimidazole. A solution of 2.63 g. (0.01 mole) of 2-chloromethyl-5,6-dimethoxybenzimidazole hydrochloride and 3.78 g. (0.03 mole) of di-*n*-butylamine in 5 ml. of ethanol was refluxed for 3 hr. The alcohol was removed by evaporation and the residue treated with water. The water solution was extracted with chloroform. The chloroform was removed and the residue dissolved in ether. The addition of petroleum ether precipitated an oil which solidified on cooling. This product was purified by forming its hydrochloride in carbon tetrachloride solution. The salt was recrystallized from ethanol and then converted to the base by treatment with sodium carbonate solution. The free base was recrystallized from carbon tetrachloride–petroleum ether.

2-Di(β-chloroethyl) aminomethyl-5,6-dimethoxybenzimidazole. 2-Chloromethyl-5,6-dimethoxybenzimidazole hydrochloride (3.22 g., 0.0123 mole) and 3.9 g. (0.070 mole) of diethanolamine were dissolved in 40 ml. of ethanol and the solution was refluxed for 3 hr. The ethanol was removed *in vacuo* and 100 ml. of chloroform added. A small upper layer formed and was discarded. Ten ml. of thionyl chloride was added to the chloroform layer and the solution was refluxed for 1 hr. After cooling, the precipitate was removed by filtration. It was recrystallized from ethanol with the aid of decolorizing carbon.

5,6-Dihydroxybenzimidazole Hydrobromide. 5,6-Dimethoxybenzimidazole (1 g., 0.0056 mole) was dissolved in 25 ml. of 48% hydrobromic acid and the solution was refluxed for 1 hr. On cooling, the product crystallized. It was recrystallized from ethanol–petroleum ether.

PHILADELPHIA, PA.

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

Preparation of Pyrido-(2,3)-pyrazines, Pyrido-(3,4)-pyrazines and Imidazo-(b)-pyridines

MERVYN ISRAEL[1] AND ALLAN R. DAY

Received May 18, 1959

A number of imidazopyridines and pyridopyrazines have been prepared. Imidazo-(b)-pyridines having methyl groups and/or halogen were converted to mono *N*-oxides by the action of 1.2 *M* peracetic acid. Electron attracting substituents prevented *N*-oxidation. The pyridopyrazines failed to give *N*-oxides under a variety of conditions.

A number of benzimidazoles and quinoxaline derivatives have been found to possess antimetabolite or bactericidal activity. The activity of these compounds is somewhat dependent on the nature and positions of substituent groups. Much less is known about the imidazopyridines and pyridopyrazines. It seemed desirable to prepare a number of substituted imidazopyridines and pyridopyrazines for testing purposes. Diaminopyridines were the starting materials for these preparations.[2]

2-Amino-5-chloropyridine was nitrated to form 2-amino-3-nitro-5-chloropyridine. The latter was reduced most efficiently with sodium dithionate to the corresponding 2,3-diamino compound. The diamine was converted to 6-chloroimidazo-(b)-pyridine by refluxing with formic acid and to 7-chloropyrido-(2,3)-pyrazine and 2,3-dimethyl-7-chloropyrido-(1,3)-pyrazine by treatment with glyoxal and diacetyl respectively. The diphenyl derivative was made from the diamine and benzil.

When 2-amino-3-nitro-5-chloropyridine was reduced with stannous chloride in concentrated hydrochloric acid, a dichlorinated diamine was isolated. This product was assumed to be 5,6-dichloro-2,3-diaminopyridine. It was converted to the corresponding pyridopyrazines with glyoxal and diacetyl.

2-Amino-4-methylpyridine was brominated in alcohol solution to give 2-amino-4-methyl-5-bromopyridine. The latter was nitrated to the corresponding 3-nitro compound which was then reduced with stannous chloride to 2,3-diamino-4-methyl-5-bromopyridine. The diamine was converted to 2-hydroxy-6-bromo-7-methylimidazo-(b)-pyridine by fusion with urea and to 2-mercapto-6-bromo-7-methylimidazo-(b)-pyridine by treatment with carbon disulfide in alcoholic potassium hydroxide solution. 6-Bromo-7-methylimidazo-(b)-pyridine was obtained from the diamine by heating with formic acid. This imidazo compound was oxidized to 6-bromo-7-imidazo-(b)-pyridinecarboxylic acid. 2,3-Diamino-4-methyl-5-bromopyridine was also treated with glyoxal, diacetyl and benzil, respectively, to obtain the corresponding pyridopyrazines.

The preparation of 2,3-diamino-5-bromo-6-methylpyridine from 2-amino-6-methylpyridine was completely analogous to that just described for the 4-methyl isomer. The 2,3-diamino-5-bromo-6-methylpyridine was converted to the corresponding

(1) DuPont Teaching Fellow, 1957–1958.

(2) The new compounds that were prepared during this investigation are being tested at the University of Pennsylvania. The results will be reported later.

2-hydroxy and 2-mercapto-5-methyl-6-bromoimidazo-(b)-pyridines as described for the 4-methyl isomer. Reactions with glyoxal, diacetyl and benzil gave the corresponding pyridopyrazines. Attempts to oxidize the methyl group in 5-methyl-6-bromoimidazo-(b)-pyridine to the carboxyl group were not successful. This methyl group, which is alpha to the pyridine nitrogen atom, is very resistant to oxidation.

2-Amino-4,6-dimethylpyridine was converted to 2,3 - diamino - 4,6 - dimethyl - 5 - bromopyridine by methods similar to those just described except that it was necessary to acetylate the 2-amino compound prior to bromination. Formic acid, glyoxal and diacetyl converted 2,3-diamino-4,-6-dimethyl-5-bromopyridine to the corresponding imidazole and pyrazines. When 5,7-dimethyl-6-bromoimidazo-(b)-pyridine was oxidized with potassium permanganate, the corresponding 5,7-dicarboxylic acid was obtained.

Attempts to form pyrazines from 2,3-diaminopyridine-5-sulfonic acid were unsuccessful. The imidazopyridine sulfonic acid was reported earlier.[3]

4-Aminopyridine was the starting material for another series of pyrazines. It was nitrated and reduced to form both 3,4-diamino-5-nitropyridine and 3,4,5-triaminopyridine by modifications of previously described procedures.[3] The latter was treated with glyoxal, methylglyoxal and diacetyl to form the corresponding pyrido-(3,4)-pyrazines. With methyl glyoxal, a mixture of two isomers was obtained, 2-methyl- and 3-methyl-8-aminopyrido-(3,4)-pyrazines. The 3,4-diamino-5-nitropyridine did not form pyrazines with glyoxal or methyl glyoxal and only a very low yield of 2,3-dimethyl-8-nitropyrido-(3,4)-pyrazine was obtained from the reaction with diacetyl.

In addition to the compounds noted above, five *N*-oxides of imidazo-(b)-pyridines were also prepared. Imidazo-(b)-pyridines, substituted with halogen and/or methyl groups, readily formed mono *N*-oxides when treated with peracetic acid. The *N*-oxide function has been assigned to the pyridine nitrogen rather than to a nitrogen atom in the imidazole ring for two reasons: (1) the ability of pyridines to form *N*-oxides is well known; and (2) benzimidazole under similar conditions was found to be unaffected. *N*-Oxides of imidazopyridines containing strong deactivating groups could not be prepared. Both imidazo-(b)-pyridine-6-sulfonic acid and 7-nitroimidazo-(c)-pyridine failed to form *N*-oxides.

The mono *N*-oxide of 7-bromopyrido-(2,3)-pyrazine was reported in 1948.[4] Attempts to prepare the di-*N*-oxide failed. In the present investigation, attempts were made to prepare *N*-oxides of the pyridopyrazines reported here. Although various conditions were used, the attempts were unsuccessful.

EXPERIMENTAL

2-Amino-3-nitro-5-chloropyridine (I). 2-Amino-5-chloropyridine was nitrated by the method of Vaughan, Krapcho and English.[5] The yield was 70%, m.p. 191–192°.

2,3-Diamino-5-chloropyridine (II). The 5-nitro compound was reduced with sodium dithionate.[5] The yields were 45-50%, m.p. 172–173°.

6-Chloroimidazo-(b)-pyridine (III). 2,3-Diamino-5-chloropyridine was refluxed with formic acid.[5] The yield was 74%, m.p. 237–238°.

7-Chloropyrido-(2,3)-pyrazine (IV). A solution of 2.9 g. (0.02 mole) of 2,3-diamino-5-chloropyridine and 5 g. (0.025 mole) of 30% aqueous glyoxal in 25 ml. of 50% aqueous ethanol was refluxed for 20 minutes. Water was added to the hot solution until it became cloudy. On cooling, the product separated and was removed by filtration. It was recrystallized from ligroin.

2,3-Dimethyl-7-chloropyrido-(2,3)-pyrazine (V). This preparation was similar to that of IV except that diacetyl was used in place of glyoxal. The product was recrystallized from ligroin and finally from 30% ethanol.

2,3-Diphenyl-7-chloropyrido-(2,3)-pyrazine (VI). 2,3-Diamino-5-chloropyridine (4.0 g., 0.028 mole) was refluxed with 6.0 g. (0.028 mole) of benzil in 60 ml. of benzene for 1 hr. The solution was dried over anhydrous magnesium sulfate and the benzene removed under reduced pressure. The residue was recrystallized from ligroin and then from ethanol. The product was obtained as pale yellow needles.

2,3-Diamino-5,6-dichloropyridine (VII). To a solution of 76.8 g. (0.4 mole) of anhydrous stannous chloride in 200 ml. of concentrated hydrochloric acid was added 17.4 g. (0.1 mole) of 2-amino-3-nitro-5-chloropyridine in small portions. Finally, the solution was refluxed for 30 minutes. After cooling, the solution was made strongly basic with 40% sodium hydroxide solution. The mixture was stirred for 2 hr. at 90° and the yellow precipitate removed by filtration and washed with ice water. Extraction with hot water gave a white product which was then recrystallized from water, yield 32%, m.p. 167°.

Anal. Calcd. for $C_5H_5N_3Cl_2$: C, 33.70; H, 2.80; N, 23.59; Cl, 39.88. Found: C, 33.50; H, 2.94; N, 23.42; Cl, 39.54.

6,7-Dichloropyrido-(2,3)-pyrazine (VIII). This compound was prepared from VII by the same procedure that was used for compound IV. The crude product was recrystallized from 30% ethanol.

2,3-Dimethyl-6,7-dichloropyrido-(2,3)-pyrazine (IX). Diacetyl was used in place of glyoxal in this preparation, otherwise the method was the same as for compound IV. The crude product was recrystallized from 50% ethanol.

2,3-Diamino-4-methyl-5-bromopyridine (X). The starting compound for this preparation was 2-amino-4-methylpyridine. The procedure which was used is reported in reference 3. Only one modification is reported here. After the stannous chloride reduction of 2-amino-3-nitro-4-methyl-5-bromopyridine, the solution was cooled to precipitate the double tin salt of the diamine. The latter was removed and dissolved in boiling 0.3 N hydrochloric acid. Hydrogen sulfide was passed into the solution to precipitate the tin as sulfide. After removing the latter, the filtrate was adjusted to a pH of 9–10. On cooling, the diamine separated as fine crystals, yield 55–57%, m.p. 161–162°.

2-Hydroxy-6-bromo-7-methylimidazo-(b)-pyridine (XI). A mixture of 4.04 g. (0.02 mole) of 2,3-diamino-4-methyl-5-bromopyridine and 1.2 g. (0.02 mole) of urea was fused at 180° until no more ammonia was given off. The brown solid was dissolved in 50 ml. of hot dimethyl formamide and after

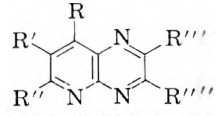
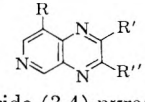
(3) H. Graboyes and A. R. Day, *J. Am. Chem. Soc.*, 79, 6421 (1957).

(4) V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

(5) J. R. Vaughan, Jr., J. Krapcho and J. P. English, *J. Am. Chem. Soc.*, 71, 1885 (1949).

TABLE I

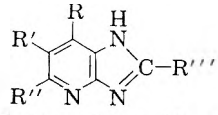
PYRIDOPYRAZINES

	R	R′	R″	R‴	R⁗	Formula	Yield, %	M.P. °C.	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Bromine Calcd.	Bromine Found
																		
									Pyrido-(2,3)-pyrazines									
IV	H	Cl	H	H	H	$C_7H_4N_3Cl$	51	159–160.5	50.77	50.84	2.45	2.58	25.37	25.25	21.40	21.32		
V	H	Cl	H	CH_3	CH_3	$C_9H_8N_3Cl$	72	152	55.82	55.67	4.14	4.20	21.70	21.51	18.31	18.12		
VI	H	Cl	H	C_6H_5	C_6H_5	$C_{19}H_{12}N_3Cl$	60	159-161	71.80	71.55	3.81	3.72	13.22	13.04	11.15	10.93		
VIII	H	Cl	Cl	H	H	$C_7H_3N_3Cl_2$	55	162–164d	42.05	41.88	1.51	1.59	21.01	21.09	35.46	35.71		
IX	H	Cl	Cl	CH_3	CH_3	$C_9H_7N_3Cl_2$	66	197–199d	47.39	47.60	3.09	3.03	18.43	18.52	31.10	30.96		
XIV	CH_3	Br	H	H	H	$C_8H_6N_3Br$	82	204–206	42.88	43.07	2.70	2.64	18.76	18.87			35.67	35.76
XV	CH_3	Br	H	CH_3	CH_3	$C_{10}H_{10}N_3Br$	90	141.5–143	47.62	47.43	4.00	3.89	16.67	16.54			31.71	32.00
XVI	CH_3	Br	H	C_6H_5	C_6H_5	$C_{20}H_{14}N_3Br$	18	199.5–201	63.84	63.98	3.75	3.87	11.17	11.14			21.24	21.47
XXII	H	Br	CH_3	H	H	$C_8H_6N_3Br$	47	165–166d	42.88	43.04	2.70	2.90	18.76	18.65			35.67	35.62
XXIII	H	Br	CH_3	CH_3	CH_3	$C_{10}H_{10}N_3Br$	84	161–162	47.62	47.53	4.08	4.10	16.67	16.43			31.71	31.81
XXIV	H	Br	CH_3	C_6H_5	C_6H_5	$C_{20}H_{14}N_3Br$	60	160d	63.84	64.02	3.75	3.79	11.17	10.99			21.24	21.31
XXV	CH_3	Br	CH_3	H	H	$C_9H_8N_3Br$	42	174–174.5d	45.39	45.24	3.39	3.57	17.65	17.58			33.57	33.46
XXVI	CH_3	Br	CH_3	CH_3	CH_3	$C_{11}H_{12}N_3Br$	68	166–167	49.63	49.61	4.55	4.67	15.79	15.82			30.02	29.93
																		
									Pyrido-(3,4)-pyrazines									
XXVIII	NO_2	CH_3	CH_3			$C_9H_8N_4O_2$	28	109.5–110	52.94	52.81	3.95	3.91	27.44	27.24				
XXIX	NH_2	H	H			$C_7H_6N_4$	54	149–150	57.55	57.56	4.14	4.13	38.36	38.46				
XXX	NH_2	CH_3	CH_3			$C_9H_{10}N_4$	65	187–189	62.05	62.06	5.79	5.76	32.17	32.03				
XXXI	NH_2	CH_3(H)	CH_3(H)[a]			$C_8H_8N_4$	62	137–162	59.99	59.88	5.04	5.15	34.97	34.78				

[a] Mixture of 2-methyl and 3-methyl isomers.

TABLE II

IMIDAZOPYRIDINES

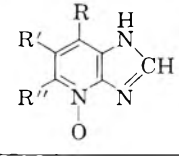


Imidazo-(b)-pyridines

	R	R′	R″	R‴	Formula	Yield, %	M.P., °C.	Analyses									
								Carbon		Hydrogen		Nitrogen		Bromine		Sulfur	
								Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XI	CH_3	Br	H	OH	$C_7H_6N_3BrO$	57	>300	36.86	36.61	2.65	2.86	18.42	18.44	35.04	35.26		
XIII	CH_3	Br	H	SH	$C_7H_6N_3BrS$	73	>300	34.43	34.59	2.48	2.30	17.22	17.11	32.74	32.64	13.13	12.97
XVII	COOH	Br	H	H	$C_7H_4N_3BrO_2$	61	254–255d	34.73	34.66	1.67	1.84	17.36	17.20	33.00	32.80		
XVIII	$COOCH_2CH_2OH$	Br	H	H	$C_9H_8N_3BrO_3$	47	208–209	37.78	37.64	2.82	2.69	14.69	14.62	27.94	28.02		
XIX	H	Br	CH_3	OH	$C_7H_6N_3BrO$	73	>300	36.86	37.07	2.65	2.40	18.42	18.57	35.04	35.27		
XXI	H	Br	CH_3	SH	$C_7H_6N_3BrS$	68	>300	34.43	34.28	2.48	2.45	17.22	17.06	32.74	32.52	13.13	13.08
XXVII	COOH	Br	COOH	H	$C_8H_4N_3BrO_4$	58	244d	33.58	33.30	1.41	1.62	14.69	14.68	27.94	27.78		

TABLE III

IMIDAZO-(b)-PYRIDINE N-OXIDES



	R	R′	R″	Formula	Yield, %	M.P., °C.	Analyses									
							Carbon		Hydrogen		Nitrogen		Chlorine		Bromine	
							Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XXXII	H	Br	H	$C_6H_4N_3BrO$	51	254d	33.66	33.61	1.88	1.66	19.36	19.48			37.35	37.51
XXXIII	H	Cl	H	$C_6H_4N_3ClO$	63	>300	42.27	42.27	2.38	2.36	24.77	25.00	20.90	20.67		
XXXIV	CH_3	Br	H	$C_7H_6N_3BrO$	90	263–264d	36.86	36.68	2.65	2.48	18.43	18.22			35.04	35.24
XXXV	H	Br	CH_3	$C_7H_6N_3BrO$	60	263d	36.86	36.80	2.65	2.85	18.43	18.31			35.04	35.31
XXXVI	CH_3	Br	CH_3	$C_8H_8N_3BrO$	75	246d	39.70	39.46	3.33	3.30	17.36	17.09			33.01	32.79

treatment with decolorizing carbon the product was precipitated by the addition of water. It was then recrystallized from *n*-amyl alcohol.

1-N-Acetyl-2-acetoxy-6-bromo-7-methylimidazo-(b)-pyridine (XII). 2-Hydroxy-6-bromo-7-methylimidazo-(b)-pyridine (1.14 g.) was refluxed for 30 minutes with 25 ml. of acetic anhydride containing one drop of concentrated sulfuric acid. The product crystallized on cooling and was purified by recrystallization from acetic anhydride. The yield was 90%, m.p. 197–198°.

Anal. Calcd. for $C_{11}H_{10}N_3BrO_3$: C, 42.33; H, 3.23; N, 13.47; Br, 25.61. Found: C, 42.26; H, 3.28; N, 13.40; Br, 25.47.

2-Mercapto-6-bromo-7-methylimidazo-(b)-pyridine (XIII). 2,3-Diamino-4-methyl-5-bromopyridine (2.02 g., 0.01 mole) was dissolved in 30 ml. of ethanol. To this solution was added 0.1 g. of potassium hydroxide and 0.8 g. of carbon disulfide. The solution was heated on the steam bath for 1 hr., during which time a yellow solid precipitated. The product was removed and recrystallized from dimethyl formamide–water.

7-Bromo-8-methylpyrido-(2,3)-pyrazine (*XIV*). Compound XIV was prepared from 2,3-diamino-4-methyl-5-bromopyridine by the procedure described for making compound IV. The product was recrystallized from 40% aqueous ethanol.

2,3,8-Trimethyl-7-bromopyrido-(2,3)-pyrazine (*XV*). Compound XV was prepared from 2,3-diamino-4-methyl-5-bromopyridine by the method described for making compound V. The product was recrystallized from 50% aqueous ethanol.

2,3-Diphenyl-7-bromo-8-methylpyrido-(2,3)-pyrazine (XVI). A mixture of 3.2 g. (0.016 mole) of 2,3-diamino-4-methyl-5-bromopyridine and 3.3 g. (0.016 mole) of benzil in 100 ml. of 50% aqueous ethanol was refluxed for 6 hr. After cooling, the product was removed and recrystallized from ethanol with the aid of decolorizing carbon.

6-Bromo-7-carboxyimidazo-(b)-pyridine (XVII). 6-Bromo-7-methylimidazo-(b)-pyridine[3] (2.12 g., 0.01 mole) was partially dissolved in 150 ml. of boiling water containing 1 g. of sodium carbonate. Four grams (0.025 mole) of powdered potassium permanganate was added, in small portions, to the refluxing solution. After 1 hr. the manganese dioxide was removed and the filtrate concentrated to one third the original volume under reduced pressure. Acidification of this solution, with 10% hydrochloric acid, gave a precipitate which was removed and recrystallized from 50% aqueous ethylene glycol.

β-Hydroxyethyl 6-bromo-7-imidazo-(b)-pyridine carboxylate (XVIII). 6-Bromo-7-carboxyimidazo-(b)-pyridine (0.63 g., 0.0026 mole) was suspended in 20 ml. of ethylene glycol which had been previously saturated with dry hydrogen chloride at 10°. The mixture was slowly heated to reflux temperature. The solid dissolved gradually over a period of 3 hr. After cooling, an equal volume of water was added and the pH adjusted to 7.0. On standing overnight, at −10°, the ester crystallized. The product was recrystallized from a small volume of water.

2-Hydroxy-5-methyl-6-bromoimidazo-(b)-pyridine (XIX). Compound XIX was prepared from 2,3-diamino-5-bromo-6-methylpyridine[2] by the method described for XI. The purification procedure, however, was not the same. The brown residue was dissolved in hot 10% sodium hydroxide. The solution was treated with decolorizing carbon and filtered. The addition of 15 ml. of 40% sodium hydroxide, to the cooled filtrate, precipitated the product as its disodium salt. The latter was dissolved in water and the solution acidified with hydrochloric acid to precipitate the product. It was recrystallized from dimethyl formamide–water.

1-N-Acetyl-2-acetoxy-5-methyl-6-bromoimidazo-(b)-pyridine (XX). The preparation of XX from XIX was the same as that described for compound XII. The yield was almost quantitative, m.p. 178°.

Anal. Calcd. for $C_{11}H_{10}N_3BrO_3$: C, 42.33; H, 3.23; N, 13.47; Br, 25.61. Found: C, 42.40; H, 3.07; N, 13.48; Br, 25.35.

2-Mercapto-5-methyl-6-bromoimidazo-(b)-pyridine (XXI). Compound XXI was prepared by the method used for making XIII. The product was recrystallized from ethylene glycol.

6-Methyl-7-bromopyrido-(2,3)-pyrazine (XXII) *and 2,3,6-Trimethyl-7-bromopyrido-(2,3)-pyrazine* (XXIII). Compounds XXII and XXIII were prepared from 2,3-diamino-5-bromo-6-methylpyridine by the procedures described for making compounds IV and V respectively.

2,3-Diphenyl-6-methyl-7-bromopyrido-(2,3)-pyrazine (XXIV). 2,3-Diamino-5-bromo-6-methyl-pyridine (4.04 g., 0.02 mole) and an equimolar amount (4.5 g.) of benzil were dissolved in 40 ml. of ethanol and the solution refluxed for 1 hr. The solution was evaporated, the residue taken up in chloroform, and the solution dried over anhydrous magnesium sulfate. After the chloroform was removed, the residue was recrystallized from ligroin.

6,8-Dimethyl-7-bromopyrido-(2,3)-pyrazine (XXV). 2,3-Diamino-4,6-dimethyl-5-bromopyridine[3] (2.2 g., 0.01 mole) and 2 g. of 30% glyoxal solution (1 equivalent of glyoxal) in 25 ml. of water were heated at 80° for 25 minutes. Crystallization occurred on cooling. The product was recrystallized from ligroin.

2,3,6,8-Tetramethyl-7-bromopyrido-(2,3)-pyrazine (*XXVI*). This compound was prepared from the corresponding diamine by the procedure used for making V. The product was recrystallized from ligroin.

5,7-Dicarboxy-6-bromoimidazo-(b)-pyridine (XXVII). 5,7-Dimethyl-6-bromoimidazo-(b)-pyridine (3 g., 0.0133 mole) was partially dissolved in 200 ml. of boiling water containing 2.5 g. of sodium carbonate. Powdered potassium permanganate (11 g., 0.07 mole) was added in small portions and the solution was refluxed for 2 hr. The manganese dioxide was removed and the filtrate was evaporated to a volume of 60 ml. under reduced pressure. The addition of concentrated hydrochloric acid precipitated a pale yellow solid. The latter was recrystallized from 40% aqueous ethylene glycol to give pale yellow needles.

2,3-Dimethyl-8-nitropyrido-(3,4)-pyrazine (XXVIII). 3,4-Diamino-5-nitropyridine[3] (6.2 g., 0.04 mole) was dissolved in 100 ml. of hot water. The addition of 4 ml. of diacetyl (0.045 mole) produced a very dark solution. After cooling, the solution was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, clarified with charcoal, and evaporated to dryness. The residue was extracted with hot ligroin. Yellow crystals separated from the extract on cooling. The product was recrystallized once from cyclohexane and three times from a minimum amount of ethanol and was obtained as yellow needles.

8-Aminopyrido-(3,4)-pyrazine (XXIX). A solution of 5.8 g. (0.025 mole) of 3,4,5-triaminopyridine trihydrochloride[3] in water was neutralized with sodium bicarbonate. The solution was warmed to 60° and 5 g. of 30% glyoxal solution (0.025 mole glyoxal) and 5.2 g. of sodium bisulfite (0.05 mole) were added. The cooled solution was made strongly alkaline with 20% aqueous sodium hydroxide and extracted with chloroform. The extract was dried over anhydrous potassium carbonate and the chloroform then removed. The residue was recrystallized from a large volume of ligroin to give orange needles.

2,3-Dimethyl-8-aminopyrido-(3,4)-pyrazine (XXX). An aqueous solution of 7 g. (0.03 mole) of 3,4,5-triaminopyridine trihydrochloride was neutralized with sodium bicarbonate and a slight excess of diacetyl (2.7 ml.) was added. The solution was warmed at 80° for 10 minutes. The solution was made strongly alkaline with 10% sodium hydroxide solution and on cooling brown crystals separated. The product was recrystallized from water and obtained as yellow needles.

2-Methyl and 3-Methyl-8-aminopyrido-(3,4)-pyrazines (XXXI). To a solution of 4.67 g. (0.02 mole) of 3,4,5-triaminopyridine trihydrochloride in 40 ml. of water at 60° was added a solution of 6 g. of 30% aqueous methyl glyoxal solution and 6.25 g. of sodium bisulfite in 30 ml. of water.

The solution was warmed at 60° for 30 minutes, treated with decolorizing carbon and filtered. The filtrate was extracted with chloroform. After drying over anhydrous potassium carbonate, the chloroform was removed under reduced pressure. The yellow residue melted at 137–162°. Repeated recrystallization from ligroin failed to change the melting point. A mixture of two isomers was assumed but no method has been found to separate them as yet.

N-Oxides of Imidazo-(b)-pyridines. 6-Bromoimidazo-(b)-pyridine-4-N-oxide (XXXII). A 1.2 M solution of peracetic acid was made according to the procedure of Byers and Hickenbottom.[6] 6-Bromoimidazo-(b)-pyridine[3] (3.96 g., 0.02 mole) was suspended in an equivalent amount of freshly prepared 1.2 M peracetic acid (17 ml.). The suspension was warmed at 50°. The solid dissolved and after 20 minutes a white solid precipitated. The latter was removed, dried and recrystallized from glacial acetic acid.

6-Chloroimidazo-(b)-pyridine-4-N-oxide (XXXIII). The *N*-oxide was prepared from 6-chloroimidazo-(b)-pyridine[3] by the procedure used for XXXII except that the suspension was warmed at 70° for 30 min.

6-Bromo-7-methylimidazo-(b)-pyridine-4-N-oxide (XXXIV). The preparation of this compound from 6-bromo-7-methylimidazo-(b)-pyridine[3] was similar to that used for XXXIII.

5-Methyl-6-bromoimidazo-(b)-pyridine-4-N-oxide (XXXV). No precipitate formed when 5-methyl-6-bromoimidazo-(b)-pyridine was warmed with the peracetic acid solution at 70° for 30 minutes. The solution was concentrated to half volume under reduced pressure. The product so obtained was purified by dissolving in glacial acetic acid and adding ether to precipitate the *N*-oxide.

5,7-Dimethyl-6-bromoimidazo-(b)-pyridine-4-N-oxide (XXXVI). The preparation of XXXVI, from the corresponding diamine,[3] was similar to that used for compound XXXII. It was purified in the same manner as XXXV.

(6) A. Byers and W. J. Hickenbottom, *J. Chem. Soc.*, 284, (1948).

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID COMPANY]

Reaction of Phosphine with Isocyanates

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Received March 30, 1959

Phosphine reacts with three isocyanates to give derivatives of a new class of organophosphorus compounds, the tricarbamoylphosphines. Information about the hydrolytic and thermal stability of these materials is presented.

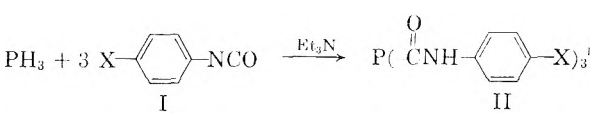
As part of a general study of the reactions of phosphine with carbonyl-containing compounds,[1a,b] we have investigated the reaction of phosphine with isocyanates.

Few reports are to be found in the literature dealing with the reaction of an isocyanate with a substance having a P—H bond. Reetz *et al.* found that dialkyl phosphonates and isocyanates react in the absence of catalyst at temperatures of about 135° to give low yields of carbamoylphosphonates.[2]

Higher yields have been obtained in this reaction by the use of basic catalysts.[3–6] Other reactions of this type which give monocarbamoyl derivatives have been carried out with a monoalkylphosphinic acid,[6] an alkyl monoalkylphosphinate,[7] a dialkyl thionophosphonate,[7] and a secondary phosphine.[1b]

Although no reactions of isocyanates and phosphine have been reported, Hunter has described an unsuccessful attempt to react phosphine with phenyl isothiocyanate.[8]

In the present work we have found that phosphine reacts with isocyanates to give derivatives of a novel type of organophosphorus compound, tricarbamoylphosphine.



I II

a. X = H
b. X = Cl
c. X = NO_2

The reactions were conducted under mild conditions (room temperature and 2–4 atmospheres of phosphine) for periods ranging from 4 hours to 4 days. The yields were 13, 55, and 100% of IIa, IIb, and IIc, respectively, based on the isocyanate charged. Judging from the yields obtained, the reactivities of the isocyanates employed were in the same order, in terms of the electronegativity of

(1) For previous reports in this field see: (a) Abstracts of Papers presented at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958, p. 97P. (b) *J. Am. Chem. Soc.*, **80**, 6454 (1958).

(2) T. Reetz, D. H. Chadwick, E. E. Hardy, and S. Kaufman, *J. Am. Chem. Soc.*, **77**, 3813 (1955).

(3) R. B. Fox and D. L. Venezky, *J. Am. Chem. Soc.*, **78**, 1661 (1956).

(4) A. N. Pudovik and A. V. Kuznetsova, *Zhur. Obshchet Khim.*, **25**, 1369 (1955).

(5) E. C. Ladd and M. P. Harvey, Can. Patent **509,034** (1955).

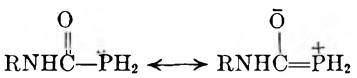
(6) R. B. Fox and W. J. Bailey, Abstracts of Papers presented at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 1956, p. 50–0.

(7) A. N. Pudovik, I. V. Konovalova, and R. E. Krivonosova, *Zhur. Obshchet Khim.*, **26**, 3110 (1956).

(8) R. F. Hunter, *Chem. News*, 50 (1930).

the substituent, as that observed toward other nucleophiles such as amines, *i.e.*, Ic>Ib>Ia.[9]

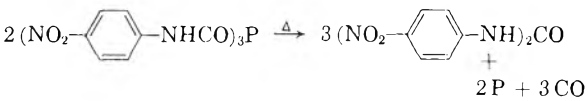
The experimental conditions for these reactions were such that approximately equimolar amounts of phosphine and isocyanate were present initially in the reaction mixtures. In spite of this trisubstituted derivatives of phosphine were the only products observed. In the reaction with phenyl isocyanate the conversion was quite low, but the bulk of the isocyanate was unaltered as indicated by infrared examination. The intermediate mono- and dicarbamoyl phosphines, $RNHCOPH_2$ and $(RNHCO)_2PH$, were not detected. If it is assumed that the tertiary amine catalyst functions in the phosphine reaction in the same way as it is thought to operate in other reactions with isocyanates, *i.e.*, by activating the isocyanate rather than removing a proton in the transition state,[9] two interesting conclusions can be drawn from these observations. First, since the intermediate addition products appear to be more reactive toward isocyanates than phosphine itself, the nucleophilic reactivity of the phosphorus atom is increased by substitution of a carbamoyl group for hydrogen in much the same way as the base strength of phosphine is increased by successive replacement of hydrogen with methyl groups.[10] Secondly, the amide type of resonance with phosphorus is probably not important in these



substances since if it were, one would expect to get monocarbamoyl derivatives such as are obtained under these conditions with ammonia and primary amines.

A limited study of reaction conditions was carried out. It was found that even with *p*-nitrophenyl isocyanate no reaction occurred in the absence of a catalyst such as triethylamine. A stronger base such as pentamethylguanidine did not improve the reaction with phenyl isocyanate, and with metallic sodium present, considerable amounts of isocyanate dimer and trimer were formed. Experiments with *p*-chlorophenyl isocyanate indicated that benzene was superior as a solvent to either acetonitrile or petroleum ether as indicated by the amount of product obtained in a given reaction time. This is similar to the solvent effect found in the reaction of phenyl isocyanate with methanol.[11] Longer reaction times and a higher temperature (60°) failed to improve the conversions obtained with phenyl and *p*-chlorophenyl isocyanate. This is probably due to inactivation of the catalyst rather than an equilibrium situation since the products are stable in the presence of triethylamine; however, this point has not been investigated further.

The tris(arylcarbamoyl)phosphines which have been prepared are thermally stable in the solid state below 200°. At somewhat higher temperatures they melt, evolve gases, and rapidly resolidify. This thermal decomposition was investigated in the case of tris(*p*-nitrophenylcarbamoyl)phosphine, and it was found that in boiling dimethylformamide or nitrobenzene this substance decomposes to give 4,4′-dinitrocarbanilide and elemental phosphorus. The gas collected from the decomposition of a sample in the absence of solvent was found to consist of a mixture of 61% CO and 39% CO_2. The following equation accounts for the major reaction observed:



The tris(arylcarbamoyl)phosphines proved to be of greater stability to hydrolysis than that reported for the monoacyl phosphines.[12] More than 90% of tris(*p*-chlorophenylcarbamoyl)phosphine was recovered unchanged after boiling in aqueous suspension for 16 hours or in 90% aqueous acetic acid solution for 15 minutes. The carbamoylphosphonates are also reported to be more stable to hydrolysis than the acylphosphonates.[2]

The reaction of 2,4-tolylene diisocyanate with phosphine was slow and no definite product was isolated. Phenyl isothiocyanate failed to react with phosphine under the conditions described for the isocyanates. Several attempts to react phosphine with the (iso)cyanic acid liberated from potassium cyanate by acids were unsuccessful. Large amounts of cyanuric acid were isolated in some cases.

EXPERIMENTAL[13]

General procedure for reaction of phosphine with isocyanates. These reactions were carried out using a standard Parr pressure reaction apparatus. Solutions of the isocyanates were prepared in pressure bottles, the catalyst was added, and the bottles were quickly attached to the apparatus. The vessel was evacuated and filled with nitrogen three times and finally filled with phosphine from the reservoir before shaking was started. After the solution was saturated, the reaction was allowed to proceed under 30–60 lb./sq. in. pressure for varying periods of time. In removing the bottle from the apparatus, the evacuation and filling with nitrogen was repeated. No significant rises in temperature were noted. Precipitation of the products was noticed soon after the reactions with *p*-chlorophenyl and *p*-nitrophenyl isocyanate were started.

Reaction with phenyl isocyanate (Ia). A solution of 17.9 g. (0.15 mole) of Ia and 0.5 ml. of triethylamine in 100 ml. of dry benzene was allowed to react with phosphine for 4 days.

(9) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Revs.*, **57**, 47 (1957).

(10) H. C. Brown, *J. Am. Chem. Soc.*, **67**, 503 (1945).

(11) S. Ephraim, A. E. Woodward, and R. B. Mesrobian, *J. Am. Chem. Soc.*, **80**, 1326 (1958).

(12) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, 1950, p. 14.

(13) All melting points are uncorrected. Thanks are due to the microanalytical group of this laboratory for the analyses and to Dr. John E. Lancaster for the infrared spectra.

The solution was then filtered to remove a small amount of insoluble material and concentrated to half its original volume. Fifty ml. of petroleum ether (b.p. 30–60°) was then added and the solid which deposited was collected giving 1.63 g. of material, m.p. 184–186°. Additional petroleum ether (200 ml.) was added to the filtrate and an additional 0.80 g. of material was deposited, m.p. 183–186°. The total yield of tris(phenylcarbamoyl)phosphine (IIa) was 13%. The analytical sample was prepared by recrystallization from acetic acid giving white crystalline material of m.p. 212–213° (resolidifies to an orange solid).

Anal. Calcd. for $C_{21}H_{18}N_3O_3P$: C, 64.45; H, 4.64; N, 10.74; P, 7.92. Found: C, 64.68; H, 4.86; N, 10.73; P, 8.10.

ν_{max}^{Nujol}: 3200 (w), 1665, 1605 (s), 1505, 1470, 1455 (s), 1320, 1255, 1180, 1105 (w), 1080 (w), 910 (w), 895 (w), 880 (w), 750 (s), and 685 cm.$^{-1}$

The petroleum ether–benzene filtrate was evaporated and the residual liquid was examined by infrared spectroscopy. The spectrum was virtually identical with that of phenyl isocyanate.

Reaction with p-chlorophenyl isocyanate (Ib). A solution of 15.4 g. (0.1 mole) of Ib and 0.5 ml. of triethylamine in 100 ml. of dry benzene was reacted with phosphine for 6 hr. The crystalline solid which deposited was collected to give 9.1 g. (55%) of tris(*p*-chlorophenylcarbamoyl)phosphine (IIb) which turned yellow at 235° and melted with immediate resolidification at 245°. An analytical sample was prepared by recrystallization from acetic acid. There was no change in melting point behavior.

Anal. Calcd. for $C_{21}H_{15}Cl_3N_3O_3P$: C, 50.98; H, 3.06; Cl, 21.50; N, 8.49; P, 6.26. Found: C, 50.94; H, 3.22; Cl, 21.23; N, 8.36; P, 6.55.

ν_{max}^{Nujol}: 3200 (w), 1655, 1595 (s), 1535 (s), 1495 (s), 1405, 1305, 1285 (w), 1240, 1170 (w), 1115, 1090, 1015, 875 (w), 825 (s), and 745 cm.$^{-1}$

Reaction with p-nitrophenyl isocyanate (Ic). A solution of 16.4 g. (0.1 mole) of Ic and 1.0 ml. of triethylamine in 100 ml. of dry benzene was reacted with phosphine for 4 hr. The yellow solid was collected and dried giving 17.5 g. (100%) of tris-(*p*-nitrophenylcarbamoyl)phosphine (IIc), m.p. 267–270°. It was insoluble in all common organic solvents. An analytical sample was prepared by extracting the solid with boiling acetone. Two such treatments gave 15.9 g. (91%) of IIc with a single band in the infrared carbonyl region at 1675 cm.$^{-1}$ Five melting point determinations were carried out with this material in a heated bath. In three cases the samples decomposed suddenly in the range of 245–250°. In the other two cases the samples melted at 277–278° (dec.).

Anal. Calcd. for $C_{21}H_{15}N_6O_9P$: C, 47.92; H, 2.87; P, 5.89. Found: C, 47.96; H, 2.96; P, 5.82.

ν_{max}^{Nujol}: 3200 (w), 1675, 1620, 1605, 1555 (s), 1515 (s), 1420, 1345 (s), 1310, 1260, 1190 (w), 1170, 1125, 1115, 885 (w), 860 (s), 810, 755, and 680 (w) cm.$^{-1}$

Thermal decomposition of tris(p-nitrophenylcarbamoyl)-phosphine (IIc). Five g. of IIc was suspended in 25 ml. of dimethylformamide and the mixture was heated until it boiled gently. Smooth decomposition took place, gas was evolved, and the bulk of the solid dissolved. The solution was filtered hot and the amorphous red phosphorus which formed was collected. The filtrate was allowed to cool and 3.1 g. (72%) of 4,4′-dinitrocarbanilide was obtained as shiny pale yellow plates decomposing at 323°. This material gave bright yellow needles having a similar decomposition point when recrystallized from either pyridine or nitrobenzene. Plates were again obtained when the latter was recrystallized from dimethylformamide. The two crystalline forms showed major differences in the infrared (Nujol mull). An authentic specimen was prepared by reacting *p*-nitrophenyl isocyanate and *p*-nitroaniline in refluxing benzene containing a trace of triethylamine. It showed the same behavior in recrystallization as the thermal decomposition product of IIc, and samples from both sources showed decomposition points varying from 320–330°, depending on the rate of heating. The infrared spectra were identical provided the samples were recrystallized from the same solvent. The melting points recorded for this substance vary considerably. One of the more recent reports gives a value of 310.5° (from pyridine).[14] The analysis was carried out with a sample recrystallized from dimethylformamide.

Anal. Calcd. for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.34; N, 18.54. Found: C, 51.48; H, 3.55; N, 18.83.

IIc (1.388 g.) was placed in a small bulb connected to a gas buret filled with mercury and equipped with a leveling bulb. The system was swept with helium and the bulb was heated to 275°. The gas which formed was evolved suddenly and a total of 57.8 ml. (STP) was collected. Mass spectrographic analysis indicated that the gas consisted of 61% carbon monoxide and 39% carbon dioxide.

STAMFORD, CONN.

(14) I. M. Kogan and D. F. Kutepov, *Zhur. Obshchet Khim.*, 21, 1297 (1951).

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

Tetrazole Analogs of Pyridinecarboxylic Acids[1]

J. M. McMANUS[2,3] and ROBERT M. HERBST

Received March 30, 1959

The isomeric 5-tetrazolylpyridines were prepared as anlogs of the pyridine carboxylic acids by interaction of the cyanopyridines with hydrazoic acid. Interaction of 2,6-dicyanopyridine and hydrazoic acid gave the tetrazole analog of dipicolinic acid. Hydrogenation of the tetrazolylpyridines gave the corresponding 5-tetrazolylpiperidines, the analogs of the several isomeric piperidine carboxylic acids.

One of the first instances of vitamin antagonism observed was the interference by pyridine-3-sulfonic acid (I) and its amide (II) with the utilization of niacin (III) and niacinamide (IV) as evidenced by inhibition of staphylococcus growth.[4] Subsequently, 3-acetylpyridine[5] and thiazole-5-

(1) Based on the doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.

(2) White Laboratories Fellow, 1956–1958.

(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(4) H. McIlwain, *Brit. J. Expt. Pathol.*, 21, 136 (1940).

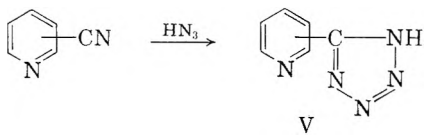
(5) E. Auhagen, *Z. physiol. Chem.*, 274, 48 (1942).

carboxamide[6] were also reported to exhibit nicotinic acid antagonism.

I, R = SO_3H
II, R = SO_2NH_2
III, R = COOH
IV, R = $CONH_2$

In view of the acidic character of the 5-tetrazolyl group, it has been suggested that analogs of biologically active carboxylic acids in which the carboxyl group is replaced by the 5-tetrazolyl group might be antagonistic to the utilization of the corresponding carboxylic acids in biological systems.[7] For this reason the synthesis of the isomeric 5-tetrazolylpyridines (V) was undertaken.

The general procedure developed for the synthesis of 5-aryltetrazoles from nitriles[8] was adapted to the preparation of the tetrazolylpyridines. The isomeric cyanopyridines were heated in *n*-butyl alcohol solution with sodium azide and acetic acid. Although the method requires continuous heating at reflux temperature for 3–4 days, the yields were excellent in each case. After completion of the reaction, replacement of the butyl alcohol by dilution with water and distillation resulted in a clear solution of the sodium salt of the tetrazole. Careful acidification of the solution precipitated the tetrazoles in sufficiently pure form so that a single recrystallization from water provided analytically pure products. After completion of this work, a procedure which permitted a shorter reaction period for the synthesis of 5-substituted tetrazoles involving interaction of nitriles and lithium azide or ammonium azides in dimethylformamide was described.[9]

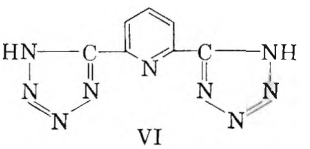


V

All the pyridyltetrazoles are solids that decompose at the melting point. They display typical amphoteric character and precipitate from aqueous acid or alkaline solution upon adjustment of the acidity to about *p*H 5. Their solubility in water, although appreciably lower than that of the pyridine carboxylic acids, decreases in the same order: *i. e.*, 2 isomer > 3 isomer > 4 isomer.

The pyridyltetrazoles are reduced easily in glacial acetic acid solution with hydrogen and platinum oxide catalyst to the respective piperidyltetrazoles. As reduction of the pyridine ring to the piperidyl structure is accompanied by an increase in the strength of the basic function, the physical characteristics of the piperidyltetrazoles differ markedly from those of the pyridyltetrazoles. In addition to amphoteric character the piperidyltetrazoles have higher melting points and greater water-solubility than the corresponding pyridyltetrazoles. Purification is best accomplished by precipitation from a saturated aqueous solution with acetone. The piperidyltetrazoles are easily acetylated with acetic anhydride in acetic acid solution to the expected acetyl derivatives; the latter also serve to characterize the products.

Recently it was reported that pyridine-2,6-dicarboxylic acid is involved in the formation and germination of the spores of a number of bacilli.[10,11] Thus it seemed of interest to prepare the tetrazole analog. 2,6-Di(5-tetrazolyl)pyridine (VI) was prepared easily and in excellent yield by interaction of 2,6-dicyanopyridine with sodium azide and acetic acid in *n*-butyl alcohol. As the tetrazole is only slightly soluble in hot water and rather insoluble in most common organic solvents, purification was best accomplished by precipitation from hot, aqueous alkaline solution by careful addition of hydrochloric acid.



VI

Biological evaluation of the tetrazolylpyridines is still incomplete. On the basis of preliminary tests, the nicotinic acid analog appears to inhibit growth of a number of types of bacteria.[12]

EXPERIMENTAL[13]

5-(2′-Pyridyl)tetrazole. 2-Cyanopyridine (26 g., 0.25 mole), 20 g. (0.33 mole) of glacial acetic acid and 22 g. (0.33 mole) of sodium azide were added to 100 ml. of *n*-butyl alcohol and heated under reflux for 4 days.[14] At this point 5 g. of sodium azide and 10 g. of glacial acetic acid were added and heating continued for 2 days. (In other experiments 3 and 4 day heating periods gave approximately the same yields of product.) The reaction mixture was diluted with about 300 ml. of water and distilled until the *n*-butyl alcohol was removed. The clear aqueous solution was carefully acidified with concentrated hydrochloric acid until precipitation of the tetrazole was complete. The product

(6) H. Erlenmeyer, H. Bloch and H. Kiefer, *Helv. Chim. Acta*, 25, 1066 (1942).

(7) R. M. Herbst, *Essays in Biochemistry*, S. Graff, Ed., John Wiley and Sons, Inc., New York, 1956, p. 141.

(8) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, 22, 1142 (1957).

(9) W. G. Finnegan, R. A. Henry and R. Lofquist, *J. Am. Chem. Soc.*, 80, 3908 (1958).

(10) J. F. Powell, *Biochem. J.*, 54, 210 (1953).

(11) J. F. Powell and R. E. Strange, *Biochem. J.*, 63, 661 (1956).

(12) We are indebted to Dr. J. L. Nemes, Department of Bacteriology, Georgetown University School of Medicine, for preliminary evaluation of some of these compounds.

(13) Microanalyses were done on all compounds by Micro-Tech Laboratories, Skokie, Illinois. Melting points were done in open capillaries and are not corrected.

(14) The entire preparation except the final recrystallization must be done in a well ventilated hood because of the presence of hydrazoic acid.

was obtained as a colorless, crystalline solid from water, yield 33.4 g. (91%), m.p. 211–211.5° with decomposition.[15]

Anal. Calcd. for $C_6H_5N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.7; N, 47.8.

5-(3'-Pyridyl)tetrazole was prepared from 3-cyanopyridine. Using the same quantities of reagents as in the foregoing example, the product was obtained as a colorless, crystalline solid from water, yield 33.3 g. (91%), m.p. 234–235° with decomposition.[15]

Anal. Calcd. for $C_6H_5N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.4; N, 47.7.

5-(4'-Pyridyl)tetrazole was prepared from 4-cyanopyridine in the same way with the same quantities of reagents. It crystallized from water as a colorless solid, yield 34.3 g. (93%), m.p. 253–254° with decomposition.[15]

Anal. Calcd. for $C_6H_5N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.6; N, 47.3.

2,6-Di(5'-tetrazolyl)pyridine. A solution of 27.5 g. (0.21 mole) of 2,6-dicyanopyridine in 100 ml. of *n*-butyl alcohol was refluxed for 2 days with 38.2 g. (0.59 mole) of sodium azide and 38 ml. of glacial acetic acid.[14] At this point another 10 g. of sodium azide and 20 ml. of glacial acetic acid were added. Refluxing continued for 2 days. The crude product, 45.6 g. (99%), was obtained by diluting the reaction mixture with water, distilling and acidifying as in the foregoing examples. The product was purified by dissolving it in aqueous sodium hydroxide and reprecipitating from the hot, colorless solution with acid. The analytical sample was recrystallized from hot water in which the product was only sparingly soluble, m.p. 290° with decomposition.

Anal. Calcd. for $C_7H_6N_8$: C, 39.1; H, 2.3; N, 58.6. Found: C, 39.2; H, 2.6; N, 58.6.

5-(2'-Piperidyl)tetrazole. A suspension of 11 g. of 5-(2'-pyridyl)tetrazole in 150 ml. of glacial acetic acid was shaken with 250 mg. of platinum oxide and hydrogen at an initial pressure of 50 p.s.i. Hydrogenation was complete in 24 hr. After removal of the catalyst by filtration the solution was evaporated to a small volume and diluted with ether to precipitate the product. Purification was effected by dissolving the colorless solid in the minimum amount of warm water, treating with Norit and reprecipitating with acetone, yield 10.5 g. (92%), m.p. 287° with decomposition.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.0; H, 7.1; N, 46.0.

The *acetyl* derivative was prepared by refluxing for 2 hrs. in glacial acetic acid with an equimolar amount of acetic anhydride. After removal of the solvent under reduced pressure, the residue of acetyl derivative was obtained as a colorless, crystalline solid from water, m.p. 135.5–136.5°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.1; H, 6.6; N, 35.6.

For preparative purposes it was advantageous to form the acetyl derivative directly by hydrogenation of the pyridyltetrazole as just described; after removal of the catalyst, acetic anhydride was added to the glacial acetic acid solution and acetylation was completed as just described. The over-all yield from the pyridyltetrazole was 84%.

5-(3'-Piperidyl)tetrazole was obtained in almost quantitative yield as a colorless, crystalline solid by hydrogenation of the pyridyltetrazole in a completely analogous manner, m.p. 296–297° with decomposition. The analytical sample was recrystallized from the minimum amount of water; the remainder of the product was precipitated from water with acetone.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.1; H, 7.3; N, 45.7.

The *acetyl* derivative, prepared as described for the isomer, separated from isopropyl alcohol as a colorless, crystalline solid, m.p. 170–171°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.5; H, 6.7; N, 36.1.

5-(4'-Piperidyl)tetrazole was obtained in 86% yield by hydrogenation of the pyridyltetrazole in a completely analogous manner. The product crystallized from water as dense colorless prisms; it did not decompose below 370° but showed some shrinking and browning at 237°.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.0; H, 7.2; N, 46.0.

The *acetyl* derivative, obtained as described for the isomers, separated from isopropyl alcohol as a colorless, crystalline solid, m.p. 156.5–157.5°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.3; H, 6.8; N, 35.8.

EAST LANSING, MICHIGAN

(15) B. Brouwer-van Straater, D. Solinger, C. van de Westeringh, and H. Veldstra, *Rec. trav. chim.*, 77, 1129 (1958).

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

Tetrazole Analogs of Plant Auxins[1]

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Received March 30, 1959

A group of chlorinated 5-phenoxymethyltetrazoles has been prepared as analogs of the corresponding substituted phenoxyacetic acids. Two methods of synthesis were used to corroborate the structure of the products. The tetrazole analog of the natural plant auxin, 3-indolylacetic acid, in which the carboxyl group is replaced by the acidic tetrazole moiety, has been prepared from the corresponding nitrile. An improved method for the synthesis of phenoxyacetonitriles is described.

The isolation and identification of 3-indolylacetic acid as a natural growth hormone in plants[4] initiated a search for other substances which could elicit this type of activity. Among those synthetic materials shown to stimulate growth was a group of chlorinated compounds derived from phenoxyacetic acid. Varying degrees of activity were demonstrated depending on the number and position of the chlorine atoms in the benzenoid portion of the structure; the most active are 2,4-dichloro-

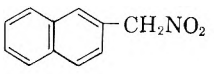
(1) Based on a doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.

(2) White Laboratories Fellow, 1956–1958.

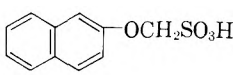
(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(4) F. Kögl, A. J. Haagen-Smit and H. Erxleben, *Z. physiol. Chem.*, 228, 90 (1934).

phenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).[5] The requirement that there be a carboxyl group on the side chain[6] finds exception in that the corresponding aldehydes, nitriles, esters and amides also show, to a certain extent, hormonal activity. Exceptions to the carboxylic acid rule have been shown by active compounds in which the carboxyl group is replaced by a nitro group (I) or a sulfonic acid moiety (II).[7]



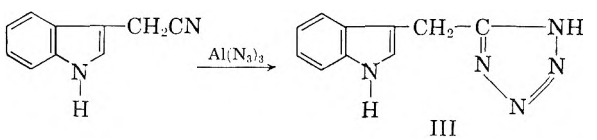
I



II

Because of the acidic nature of 5-mono substituted tetrazoles,[8,9,10,11] it appeared of interest to incorporate a tetrazole nucleus into the chemical structure of an active plant auxin in place of the carboxyl group. In this study the tetrazole analogs of 3-indolylacetic acid and various chlorophenoxyacetic acids were synthesized.

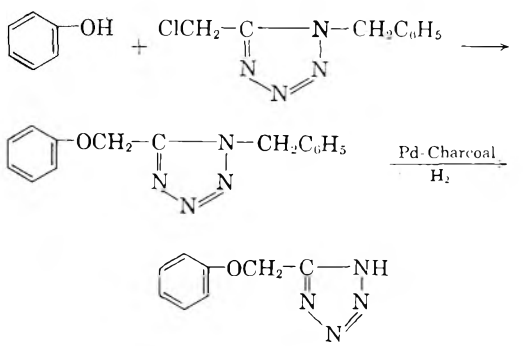
Behringer and Kohl[12] have shown that certain nitriles will react with aluminum azide in tetrahydrofuran to form 5-substituted tetrazoles. The preparation of 5-(3′-indolylmethyl)tetrazole (III) was accomplished by application of this general procedure to 3-indolylacetonitrile. It was found advantageous to modify the isolation technique recommended by these authors. Better results were obtained when the tetrahydrofuran was displaced from the reaction mixture by distillation while constant volume was maintained by simultaneous addition of water. The insoluble aluminum salt of the tetrazole which remained after all the tetrahydrofuran had been removed was decomposed with dilute hydrochloric acid, leaving an aqueous suspension of the tetrazole.



III

The substituted 5-phenoxymethyltetrazoles were synthesized by application of two general procedures: The first involved interaction of nitriles with sodium azide and acetic acid in *n*-butyl alcohol[10]; the second, interaction of nitriles with aluminum azide in tetrahydrofuran.[12] The first procedure was used successfully for the synthesis of 5-phenoxymethyltetrazole and the corresponding 2,4-dichloro- and 2,4,5-trichlorophenoxymethyl analogs from the appropriate nitriles. Attempts to prepare 5-(2′,4′,6′-trichlorophenoxymethyl)tetrazole in this way were not successful; the reaction mixture became very dark because of extensive decomposition, and no definite product was isolated. The interaction of 2-chloro-, 4-chloro-, and 2,4,6-trichlorophenoxyacetonitrile with aluminum azide in refluxing tetrahydrofuran resulted in good yields of the corresponding tetrazoles. After completion of this work an improved technique involving interaction of nitriles with lithium or an ammonium azide in dimethylformamide appeared.[13]

An alternate method used for the preparation of some of the phenoxymethyltetrazoles involved interaction of the appropriately substituted phenol with 1-benzyl-5-chloromethyltetrazole in an alkaline medium, followed by hydrogenolytic removal of the benzyl group with palladium on charcoal and hydrogen. In several instances, namely 5-(2,′4′-dichloro- and 2′,4′,6′-trichlorophenoxymethyl)-1-benzyltetrazole, debenzylation was accompanied by partial dehalogenation and possibly reduction. Isolation of pure compounds of unequivocal structure for comparison with the compounds prepared by other routes was not feasible in these two cases. In other instances compounds identical with those formed from the nitriles were obtained by this method.



The tetrazole analogs are similar to the phenoxyacetic acids in physical properties. All are solids with melting points in the same range as and similar solubilities to the corresponding carboxylic acids. No regular differences in melting points are noted, some are slightly higher some lower than those of the corresponding phenoxyacetic acids.

The nitriles used as intermediates for the phenoxymethyltetrazole syntheses were prepared from the phenol, chloroacetonitrile and potassium carbonate in refluxing acetone. This method of preparation offered a distinct advantage over methods which involved synthesis of the nitrile either from

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TABLE I

PHENOXYACETONITRILES ARYL-OCH_2CN

Aryl	M.P.	Yield, %	Formula	Analyses Calcd. Cl	Calcd. N	Found Cl	Found N
C_6H_5	[a]	82					
2-ClC_6H_4	[b]	44	C_8H_6ClNO	21.2	8.4	21.1	8.1
4-ClC_6H_4	46.5–47.5	93	C_8H_6ClNO	21.2	8.4	21.2	8.2
2,4-$Cl_2C_6H_3$	48.5–49[c]	85	$C_8H_5Cl_2NO$	35.1	6.9	35.2	6.8
2,4,5-$Cl_3C_6H_2$	91.5–92.5	88	$C_8H_4Cl_3NO$	45.0	5.9	44.8	5.8
2,4,6-$Cl_3C_6H_2$	102–103[d]	98	$C_8H_4Cl_3NO$	45.0	5.9	44.9	5.7

[a] B.p. 73–76° at 1 mm., Powell and Adams[18] reported b.p. 132° at 30 mm. [b] B.p. 109° at 1 mm. [c] M.p. 44–46° previously reported.[14] [d] M.p. 103° previously reported.[19]

the acid by way of the acid chloride and amide or from phenoxymethyl chloride and sodium cyanide[14] as these latter methods involved a series of steps. The structure of the phenoxyacetonitriles was established by comparison of physical constants with those recorded in the literature, elemental analysis and, in several cases, by hydrolysis to the known phenoxyacetic acids.

5-(3′-Indolylmethyl)tetrazole appears to stimulate cell elongation in the *Avena* test at concentrations about 200 times as great as those of 3-indolylacetic acid required to produce the same effect. 5(2′,4′-Dichlorophenoxymethyl)tetrazole is inactive but appears to be a competitive antagonist for 2,4-dichlorophenoxyacetic acid in the *Avena* test. Details of these studies are to be published elsewhere.[15]

The preparation of both 5-(3′-indolylmethyl)- and 5-(2′,4′-dichlorophenoxymethyl)tetrazole by somewhat different techniques has just been reported by van de Westeringh and Veldstra.[16]

EXPERIMENTAL[17]

5-(3′-Indolylmethyl)tetrazole. Seven and eight-tenths g. (0.12 mole) of sodium azide and 5.3 g. (0.04 mole) of anhydrous aluminum chloride were refluxed together in 120 ml. of dry tetrahydrofuran for 1 hr. 5.8 g. (0.04 mole) of 3-indolylacetonitrile was added to the mixture and refluxing with stirring continued for 24 hrs. The tetrahydrofuran was then distilled from the reaction mixture while water was added slowly at such a rate that the volume remained constant. After the organic solvent had been removed, the suspended solid was filtered off, resuspended in 250 ml. of water, and treated with sufficient hydrochloric acid to bring the suspension to *p*H 2. After 10 min. stirring, the solid was filtered off and washed with water. Drying gave 6.5 g. of crude product which was recrystallized first from ethylene chloride and then from water, yield 4.5 g. (61%), m.p. 179–180° with decomposition.

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.3; H, 4.8; N, 35.0.

The *monopicrate* crystallized from water, m.p. 131–132°.

Anal. Calcd. for $C_{16}H_{12}N_8O_6$: C, 44.9; H, 2.8; N, 26.2. Found: C, 45.5; H, 3.2; N, 25.8.

Phenoxyacetonitriles. The preparation of phenoxyacetonitrile will serve as a typical example. A mixture of 23.5 g. of phenol, 18.7 g. of chloroacetonitrile and 34.5 g. of anhydrous potassium carbonate in 75 ml. of dry acetone was heated under reflux for 8 hr. The mixture was then poured into 200 ml. of water containing 10 g. of sodium hydroxide and extracted with ether. The ether layer was separated and dried over sodium sulfate, and the ether was removed by distillation. Fractionation of the residual reddish oil gave the product as a colorless, oily liquid, yield 27.2 g. Physical properties, yields, and analytical data for the phenoxyacetonitriles prepared in this way are given in Table I. Except for 2,4,6-trichlorophenoxyacetonitrile, which was recrystallized from absolute ethanol, the solid chlorophenoxyacetonitriles were recrystallized from petroleum ether.

Phenoxyacetic acid. Phenoxyacetonitrile (5.3 g.) was refluxed in 100 ml. of 25% sodium hydroxide solution for 12 hr. The resulting solution was filtered and the filtrate was cooled and acidified with 6*N* hydrochloric acid. The yield of product after recrystallization from water was 4.9 g. (81%), m.p. 98–99°. Sabanejeff and Dworkowitsch[20] report m.p. 97°.

2,4-Dichlorophenoxyacetic acid, m.p. 138.5–139° was obtained from the nitrile in similar manner; previously reported[21] m.p. 138°.

2,4,5-Trichlorophenoxyacetic acid was obtained from the nitrile in similar manner and recrystallized from benzene, m.p. 150.5–152°. Porkorny[21] reported m.p. 153°.

Preparation of Phenoxymethyltetrazoles. 5-Phenoxymethyltetrazole. Procedure Ia. A mixture of 16.3 g. (0.125 mole) of phenoxyacetonitrile, 11 g. (0.165 mole) of sodium azide and 10 g. (0.165 mole) of glacial acetic acid in 60 ml. of *n*-butyl alcohol was heated under reflux for 4 days. Heating was continued for 2 days after addition of 2.5 g. of sodium azide and 5 g. of glacial acetic acid. The reaction mixture was diluted with 200 ml. of water, and the mixture was distilled until the alcohol was removed. Acidification of the residual aqueous solution with dilute sulfuric acid gave the product as a colorless solid, yield 22 g. Recrystallization from water gave the pure product, m.p. 127.5–129°.

(14) H. Barber, R. Fuller, M. Green and H. Zwartouw *J. Appl. Chem. (London)*, **3**, 266 (1953).

(15) We are indebted to Mr. R. H. Hamilton, Dr. A. Kivilaan and Dr. R. S. Bandurski of the Department of Botany at Michigan State University for their enthusiastic cooperation in these studies. Their results will be published separately in *Plant Physiology*.

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(17) Microanalyses were done on all compounds by Micro-Tech Laboratories, Skokie, Ill. Melting points were taken in open capillaries and are not corrected.

(18) S. Powell and R. Adams, *J. Am. Chem. Soc.*, **42**, 646 (1920).

(19) D. Drain, D. Peak, and F. Whitmont, *J. Chem. Soc.*, 2680 (1949).

(20) A. Sabanejeff and P. Dworkowitsch, *Ann.*, **216**, 284 (1883).

(21) R. Porkorny, *J. Am. Chem. Soc.*, **63**, 1768 (1941).

Anal. Calcd. for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31.8. Found: C, 54.5; H, 4.7; N, 31.9.

5-(2'-Chlorophenoxymethyl)tetrazole. Procedure Ib. To a suspension of 16.7 g. (0.1 mole) of 2-chlorophenoxyacetonitrile and 19.5 g. (0.3 mole) of sodium azide in 50 ml. of dry tetrahydrofuran was added a solution of 13.3 g. (0.1 mole) of anhydrous aluminum chloride in 160 ml. of the same solvent. The mixture was refluxed with continuous stirring for 24 hr. The tetrahydrofuran was then distilled from the reaction mixture while water was added slowly at such a rate that the volume of the mixture remained constant. The solid which had separated was filtered off, resuspended in 250 ml. of water and treated with 30 ml. of concentrated hydrochloric acid. After being stirred for 1 hr. the solid was filtered off and dried, yield 18.8 g. of crude product which was recrystallized from toluene, m.p. 134.5–135.5°.

Anal. Calcd. for $C_8H_7ClN_4O$: C, 45.6; H, 3.4; Cl, 16.8; N, 26.6. Found: C, 45.9; H, 3.6; Cl, 16.9; N, 26.6.

5-(4'-Chlorophenoxymethyl)tetrazole. Following *Procedure Ib* a mixture of 16.7 g. (0.1 mole) of 4-chlorophenoxyacetonitrile, 19.5 g. (0.3 mole) of sodium azide, and 13.3 g. (0.1 mole) of anhydrous aluminum chloride in 210 ml. of dry tetrahydrofuran gave 20.6 g. of crude product. Recrystallization from aqueous ethanol gave 13.9 g. (66%) of pure product, m.p. 165–166°.

Anal. Calcd. for $C_8H_7ClN_4O$: C, 45.6; H, 3.4; Cl, 16.8; N, 26.6. Found: C, 45.7; H, 3.6; Cl, 16.8; N, 26.5.

5-(2' 4'-Dichlorophenoxymethyl)tetrazole. Using *Procedure Ia* a mixture of 25.2 g. (0.125 mole) of 2,4-dichlorophenoxyacetonitrile, 11 g. (0.165 mole) of sodium azide, and 10 g. of glacial acetic acid in 60 ml. of *n*-butyl alcohol gave 25.6 g. of crude product which was purified by recrystallization from toluene, m.p. 124.5–125.5°.

Anal. Calcd. for $C_8H_6Cl_2N_4O$: C, 39.2; H, 2.5; Cl, 28.9; N, 22.9. Found: C, 39.4; H, 2.6; Cl, 29.0; N, 23.0.

5-(2',4',5'-Trichlorophenoxymethyl)tetrazole. Following *Procedure Ia* a mixture of 29.6 g. (0.125 mole) of 2,4,5-trichlorophenoxyacetonitrile, 11 g. (0.165 mole) of sodium azide, and 10 g. of glacial acetic acid in 60 ml. of *n*-butyl alcohol gave 25.4 g. of crude product that was purified by recrystallization from toluene, m.p. 163.5–165°.

Anal. Calcd. for $C_8H_5Cl_3N_4O$: C, 34.4; H, 1.8; Cl, 38.1; N, 20.1. Found: C, 34.7; H, 1.8; Cl, 38.3; N, 20.1.

5-(2',4',6'-Trichlorophenoxymethyl)tetrazole. Using *Procedure Ib* 5.8 g. (0.025 mole) of 2,4,6-trichlorophenoxyacetonitrile, 4.8 g. (0.074 mole) of sodium azide, and 2.98 g. (0.025 mole) of anhydrous aluminum chloride in 90 ml. of dry tetrahydrofuran gave 6.6 g. of crude product which was recrystallized first from toluene and then from ethanol, m.p. 164–165°.

Anal. Calcd.: for $C_8H_5Cl_3N_4O$: C, 34.4; H, 1.8; Cl, 38.1; N, 20.1. Found: C, 34.6; H, 2.1; Cl, 37.9; N, 20.0.

Several attempts to prepare this compound using *Procedure Ia* were accompanied by extensive decomposition; no definite product was isolated from the reaction mixtures.

1-Benzyl-5-phenoxymethyltetrazole. A mixture of 8.3 g. (0.04 mole) of 1-benzyl-5-chloromethyltetrazole,[22] 4.7 g. (0.05 mole) of phenol, and 2.7 g. (0.05 mole) of sodium methoxide in 75 ml. of absolute methanol was heated under reflux with stirring for 10 hr. The contents of the flask were then poured into 150 ml. of water, the precipitate was filtered off and recrystallized from aqueous methanol to give 3.8 g. (36%) of the desired product, m.p. 66.5–67°.

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.7; H, 5.3; N, 21.0. Found: C, 67.4; H, 5.4; N, 21.1.

1-Benzyl-5-(2',4'-dichlorophenoxymethyl)tetrazole. Under similar conditions 8.3 g. of 1-benzyl-5-chloromethyltetrazole, 8.15 g. of 2,4-dichlorophenol, and 2.7 g. of sodium methoxide in 75 ml. of absolute methanol gave 12.4 g. of crude product from which, after recrystallization from methanol, 8.6 g. of pure product, m.p. 107.5–108°, was obtained.

Anal. Calcd. for $C_{15}H_{12}Cl_2N_4O$: C, 53.8; H, 3.6; Cl, 21.2; N, 16.7. Found: C, 53.8; H, 3.9; Cl, 21.0; N, 16.8.

1-Benzyl-5-(2',4',6'-trichlorophenoxymethyl)tetrazole. In similar manner 6.9 g. of 1-benzyl-5-chloromethyltetrazole, 8.2 g. of 2,4,5-trichlorophenol, and 2.2 g. of sodium methoxide in 75 ml. of absolute methanol gave 10.6 g. of crude product which on recrystallization from methanol gave 6.4 g. of pure product, m.p. 113.5–114.5°.

Anal. Calcd. for $C_{15}H_{11}Cl_3N_4O$: C, 48.7; H, 3.0; Cl, 28.8; N, 15.2. Found: C, 48.6; H, 3.1; Cl, 28.7; N, 15.3.

1-Benzyl-5-(2',4',6'-trichlorophenoxymethyl)tetrazole. Similarly 6.9 g. of 1-benzyl-5-chloromethyltetrazole, 8.15 g. of 2,4,6-trichlorophenol, and 2.2 g. of sodium methoxide in 75 ml. of absolute methanol gave 12.3 g. of crude product and after recrystallization from methanol, 9.1 g. of pure material, m.p. 112–113°.

Anal. Calcd. for $C_{15}H_{11}Cl_3N_4O$: C, 48.7; H, 3.0; Cl, 28.8; N, 15.2. Found: C, 48.8; H, 3.0; Cl, 28.9; N, 15.0.

Debenzylation of 1-Benzyl-5-phenoxymethyltetrazole. A solution of 2.7 g. (0.01 mole) of 1-benzyl-5-phenoxymethyltetrazole in 100 ml. of absolute ethanol was shaken for 12 hr. with 1 g. of 5% palladium on charcoal at an initial hydrogen pressure of 50 p.s.i. The catalyst was filtered off and the solvent was removed from the filtrate in a vacuum. The residue was treated with dilute sodium hydroxide and filtered. From the alkali insoluble solid, 1.3 g. (49%) of the starting material was recovered. Acidification of the alkaline solution with dilute hydrochloric acid gave a precipitate of 5-phenoxymethyltetrazole, 400 mg. (43%), which was recrystallized from water, m.p. and mixture m.p. 127.5–128.5°.

Debenzylation of 1-benzyl-5-(2',4',5'-trichlorophenoxymethyl)tetrazole. A mixture of 1.8 g. of 1-benzyl-5-(2',4',5'-trichlorophenoxymethyl)tetrazole and 1 g. of palladium on charcoal in 75 ml. of absolute ethanol was shaken for 12 hr. at an initial hydrogen pressure of 50 p.s.i. The catalyst was filtered and washed with warm ethanol. Removal of the solvent from the combined filtrate and washings in a vaccum left a residue which after repeated crystallization from toluene gave 5-(2',4',5'-trichlorophenoxymethyl)tetrazole, m.p. and mixture m.p. 160–162°.

Both 1-benzyl-5-(2',4'-dichloro- and 2',4',6'-trichlorophenoxymethyl)tetrazole were debenzylated in a similar manner, but in neither case was a pure product isolated from the resulting mixture of products. Apparently debenzylation was accompanied by dehalogenation and possibly reduction in varying degrees which would have vitiated this approach as an unequivocal synthesis.

EAST LANSING, MICH.

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

Chemical Structure and Chromatographic Adsorbability of Aromatic Hydrocarbons on Alumina[1,2,3]

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An investigation of structural factors involved in the relative chromatographic adsorbabilities of binary mixtures of aromatic hydrocarbons on alumina was made using elution of the components with petroleum ether or petroleum ether–benzene and analysis of the effluent fractions by evaporation and m.p. determination on the residues. The Law of Inequalities—*i.e.*, if (in adsorbability) A > B and B > C, then A > C—was found to hold. Moreover, adsorbability was found to increase with increasing (a) number of double bonds, (b) approach to coplanarity, (c) symmetry number, (d) extent of conjugation, and (e) number of sterically unhindered methyl or alkylene groups. In two alkylarene series R-Zr, the effect of R in fostering adsorbability was found to be Me (unhindered) > Et ≲ H > *i*-Pr, *tert*-Bu. From the fact that the adsorbability relationships are closely analogous to those found for fostering stability in *bona fide* 1:1 π-type molecular compounds in solution it is proposed that adsorption on alumina also involves π-type complexation where the "active spots" on the alumina are relatively broad electron-attracting areas on to which the electron-donating hydrocarbon substrate is held monomolecularly and preferentially (where such arrangement is sterically possible) in a planar configuration parallel to the surface.

Despite the fact that alumina is a favorite adsorbent for use in chromatographic separations and purifications of aromatic hydrocarbons, the only extensive systematic study which has been reported in an effort to correlate structure or physico-chemical properties of the compounds used with chromatographic adsorbability thereon is the classical research of Winterstein and Schön.[5] These authors, who investigated the diphenylpolyene series and miscellaneous parent arenes of 2–9 rings, concluded that, in general, adsorbability (1) increases with the number of double bonds present (Unsaturation Rule),[6] (2) is greater for an *acene* (a linearly condensed arene) than for an isomeric *phene* (an angularly condensed arene) or a *cata*-condensed compound with the same number of rings (Acene Rule) and (3) is greater for a colored isomer than for a white one. More recently Klemm, Reed, and Lind[7] have noted that of conjugated isomeric biaryls and arylalkenes or of conjugated iso-π-electronic (though not isomeric) aromatic hydrocarbons the most nearly coplanar compound of the group is adsorbed most tenaciously (Coplanarity Rule). We have now undertaken studies on the relative adsorbabilities of various types of aromatic hydrocarbons in an effort to test some of the preceding generalizations further, to search for additional correlations, and to develop, if possible, a rationale for the observed behaviors. In this regard the present paper constitutes a preliminary experimental survey of various series of compounds selected on the bases of ease of handling, availability, and pertinence as well as an interpretative account of other cases described in the literature.[8]

The general procedure was essentially that used by Winterstein and Schön[5] whereby a solution in petroleum ether or benzene–petroleum ether of a mixture of two compounds is added to a column of alumina. The components are subsequently eluted into arbitrary fractions by means of the same solvent, and compositions of the residues remaining from evaporation of these fractions are investigated by melting point determination. The order of increasing adsorbability (same as the order of appearance in the effluent) and a semi-quantitative estimate of the degree of separation of the components are thus obtained. The analytical method, to be sure, has the limitation that it operates best for mixtures of solid components with rather widely separated melting points and, of course, is inapplicable to mixtures of liquid components. To avoid possible difficulties due to the overriding of one component by another or to flooding of the column, the ratio of the weights of the components used was kept close to 1:1 and the total combined weights of adsorbates charged to the column was kept small. At least under such circumstances (deviations therefrom were not investigated) orders of adsorbability were reproducible. The

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(2) Part II in the series on Correlation of Structure with Chromatographic Adsorbability. For part I see ref. 7. For part III see L. H. Klemm and D. Reed, *J. Chromatography*, in press.

(3) Abstracted (in part) from the M.S. theses of L. A. Miller and B. T. Ho, University of Oregon, June, 1959.

(4) Research assistant, 1957–1959.

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(6) The same generalization has been noted for carotinoids on various adsorbents. See P. Karrer and E. Jucker, *Carotinoide*, Birkhäuser, Basel, 1948, p. 31.

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(8) No exhaustive survey of recent literature is claimed. On the other hand, all apparently potential leads gleaned from the common chromatographic books and reviews have been carefully followed. Especially useful in this regard were ref. 20 and L. Zechmeister, *Progress in Chromatography* 1938–1947, Chapman and Hall, London, 1950.

TABLE I. RELATIVE CHROMATOGRAPHIC ADSORBABILITIES OF AROMATIC HYDROCARBONS ON ALUMINA COLUMNS

Run No.	Components Used in Mixture[a] Name	M.P., °C.	Wt. of each (mg.)	Size of Column[b]	Length of Run (Hr.)	Melting Ranges (°C.) of Selected Fractions of Effluent[c] First fraction[d]	Intermediate fraction[e]	Last fraction[f]	Extent of Separation[g]
1	9-Phenylanthracene	151.5–152.5	150	A	16	149–152	117–141	105–110	Fair
	1-Phenylanthracene	113–114.5							
2[h]	1-Phenylanthracene	113–114.5	100	A	(8)	111–113.5	—[i]	209–212	Complete
	2-Phenylanthracene	211.5–212.5							
3	1,1′-Binaphthyl	157–158	100	A	4.2	156.5–157.5	100–128	70–73	Good
	1,2′-Binaphthyl	74.5–76							
4	1-(1-Naphthyl)cyclopentene (III)	<25	200	A	3.7	<25	51–73	83–85.5	Fair
	1-(2-Naphthyl)cyclopentene (I)	85–86							
5	1-Vinylnaphthalene	<25	200	A	4.0	<25	45–57	59–62	Fair
	2-Vinylnaphthalene	66–67							
6	Biphenyl	69–71	100	A	3.4	70–71	(Faint film)	114–116	Complete
	Fluorene	113.5–115							
7	Naphthalene	80.5–81.5	75	A	12.6	80.5–81.5	63.5–66	96–98	Very good
	2-Vinylnaphthalene	66–67							
	Phenanthrene	97.5–99							
8	Anthracene	210–211	80	A	15	206–209	128–173	142–148	Fair
	Pyrene	149–150							
9	1,2,3,4-Tetrahydronaphthalene	<25	100	A	1.8	<25	<25	79–81	Complete
	Naphthalene	80–81							
10	Naphthalene	80–81	150	A	(2.6)	79–81	—[i]	156–157	Complete
	1,1′-Binaphthyl	157–158							
11	Naphthalene	80–81	150	A	2.4	78–81	<25	<25	Very good
	1-Phenylnaphthalene	<25							
12	Anthracene	209–210	130	A	15	206–210	138–174	140–150	Fair
	9-Phenylanthracene	151.5–152.5							
13	1-(1-Naphthyl)cyclopentene (III)	<25	150	A	3.7	<25	(Oily solid)[j]	101–102	Good
	2-Phenylnaphthalene	101.5–102							
14	1-(1-Naphthyl)cyclopentene (III)	<25	150	A	3.2	<25	47–55	58–60	Fair
	1-(2-Naphthyl)cyclohexene (IV)	60–61							
15[q]	Benzo[*c*]phenanthrene	67–68.5	50	A	(3.4)	52–59	50–135	194–195	{Virtually none / Very good
	Pyrene	149–150							
	Triphenylene	195–196							
16	Chrysene	247–248	30	A	52	—[k]	—	—[k]	Complete
	Naphthacene	324–328	15						
17	Triphenylene	195–196	75	A	58	190–193.5	172–209	214–232	Fair
	Chrysene	247–248							
18	Benz[*a*]anthracene[l]	158.5–159.5	50	A	64	168–184	175–199	182–208	Poor
	Chrysene	247–248							
19	Benz[*a*]anthracene	158.5–159.5	15	A	55	—[k]	—	—[k]	Complete
	Naphthacene	324–328							
20	3-(2-Naphthyl)cyclopentene (II)	<25	200	B	5	<25	68–78	82–85	Good
	1-(2-Naphthyl)cyclopentene (I)	84.5–86							
21	3-(2-Naphthyl)cyclohexene (V)	<25	200	B	4	<25	(Oily solid)[j]	57.5–59	Good
	1-(2-Naphthyl)cyclohexene (IV)	56–58							

TABLE I (*Continued*)

Run No.	Components Used in Mixture[a] Name	M.P., °C.	Wt. of each (mg.)	Size of Column[b]	Length of Run (Hr.)	Melting Ranges (°C.) of Selected Fractions of Effluent[c] First fraction[d]	Intermediate fraction[e]	Last fraction[f]	Extent of Separation[g]
22	Pentamethylbenzene	53–55	100	C	4.6	45–49	55–91	160–164	Poor
	Hexamethylbenzene	163–165							
23	Durene	79–81	300	C	5.5	76–80	101–150	162–164	Fair
	Hexamethylbenzene	163–165							
24	Durene	79–81	100	C	3.8	68–77	43–49	53.5–57	Fair
	Pentamethylbenzene	53–55							
25	Mesitylene	<25	300	C	2.2	<25	<25	79–80	Good
	Durene	79–81							
26	Naphthalene	80–81	100	A	2.3	78–81	91.5–94	92.5–94	Good
	Acenaphthene	93.5–95.5							
27	2-Vinylnaphthalene	66–67	100	A	3.3	65–67	59–68	78–83	Fair
	1-(2-Naphthyl)cyclopentene (I)	85–86							
28	Naphthalene	80–81	140	B	2.3	78–80.5	<25	32.5–34	Fair
	2-Methylnaphthalene	32–34							
29	Naphthalene	80–81	100	B	2.3	<25–53	<25	<25	Poor
	2-Ethylnaphthalene	<25							
30	2-*tert*-Butylnaphthalene	<25	100	C	2.6	<25	<25–35	63–80	Poor
	Naphthalene	80–81							
31	Naphthalene	80–81	100	A	2.5	80–81	46.5–52	55–56	Fair
	2-Bromonaphthalene	56–57							
32	2-Bromonaphthalene[m]	56–57	100	A	(6.6)	55–57	—[t]	46–49	Complete
	2-Acetonaphthone	53.5–55							
33	Naphthalene	80–81	100	A	(1.8)	78–80	—[t]	47–50	Complete
	2-Acetonaphthone	53.5–55							
34[n]	Anthracene	211–212	100	B	13	210–212	75–176	74–78	Good
	9-Methylanthracene	79–80							
35[n]	9-Ethylanthracene	56–58	100	A	18	56–58	<25	76.5–79	Good
	9-Methylanthracene	79–80							
36	Anthracene	211–212	50	A	16	191–206	120–186	45–161	Poor
	9-Ethylanthracene	56–58							
37[o]	9-Isopropylanthracene	75–76	100	A	8.5	74–76	147–205	210–212	Fair
	Anthracene	211–212							
38[p]	9-Isopropylanthracene	75–76	50	A	5.2	71.5–74	(Trace)	54.5–57.5	Good
	9-Ethylanthracene	56–58							
39[n]	Benz[*a*]anthracene	158.5–160	25	A	29	144–156	100–123	110–118	Poor
	6-Methylbenz[*a*]anthracene	125–128							
40	4-Methylbenz[*a*]anthracene	194.5–195	9.5	A	60	117–160	120–160	107–160	None
	7-Methylbenz[*a*]anthracene	139–140							
41[n]	2-Methylbenz[*a*]anthracene	149–150.5	25	A	30	143–146	146–152	176–179	Fair
	10-Methylbenz[*a*]anthracene	180–181.5							
42[n]	12-Methylbenz[*a*]anthracene	136–138	25	A	72	132–135	—	186–192	Very good
	4-Methylbenz[*a*]anthracene	194.5–195							
43	1-(2-Naphthyl)cyclohexene (IV)	60–61	150	A	4	58.5–60.5	67–73	71–76	Poor
	1-(2-Naphthyl)cyclopentene (I)	85–86							

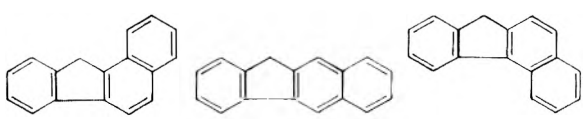
[a] Unless otherwise designated the components were added to the column as a solution in the minimum volume of reagent grade petroleum ether (30–60°) and eluted with the same solvent. Other solvents used are listed as % (by vol.) reagent grade benzene in petroleum ether. Where separation of components occurred, names given in the table for each particular run are listed in order of appearance of the compounds in the effluent—*i.e.*, in order of increasing adsorbability. [b] The column of alumina used was as follows: Size A, 1.9 × 30 cm. (av. 105 g.); size B, 1.9 × 40 cm. (av. 140 g.); size C, 1.6 × 80 cm. (av. 250 g.). [c] Determined on the residue from evaporation of the solvent. [d] First fraction which contained more than a trace of residue. [e] Usually taken as the middle fraction, the fraction of widest melting range, or the one which best illustrates the degree of separation of the components. [f] In most (but not all) cases the last fraction collected represented virtually complete removal of hydrocarbon substrate from the column. [g] As based on general observations of the melting ranges of the various fractions. [h] Components dissolved in 50% benzene–petroleum ether, but eluted with petroleum ether only. [i] The less strongly adsorbed component was completely eluted in the first fractions. Intermediate fractions contained little, if any, residue. Acetone was added to the petroleum ether developer to help elute the more strongly adsorbed component. [j] Only a trace was present. [k] Separation was readily observed on the column because of characteristic fluorescences. Naphthacene (yellow fluorescence) was more strongly adsorbed than chrysene or benz[*a*]anthracene (blue fluorescence). [l] That chrysene was not eluted so readily as benz[*a*]anthracene was confirmed by comparison of the melting ranges of the effluent fractions with a standard m.p. *vs.* composition curve for the mixed components. [m] Because of the proximity of the melting points of the components, the identities of the eluted fractions were established by m.m.p. with *bona fide* samples, by Beilstein tests (positive on first fractions, negative on later ones), and by the fact that 2-acetonaphthone fluoresces (light blue) when adsorbed on alumina while 2-bromonaphthalene does not fluoresce. [n] Run with 2% benzene. [o] Run with 4% benzene. [p] Run with 5% benzene. [q] Run with 50% benzene.

degree of separation seemed to be somewhat (though not markedly) dependent on the length of the column and the uniformity achieved in its packing. General results for all runs are summarized in Table I. Detailed information on the fractions obtained in two runs where successful separations of the components were attained under experimental conditions as nearly divergent from one another as any attempted in our studies are recorded in Tables III and IV in the experimental section.

As a check on the structural significance of the results we included a series of triads of adsorbates (taken two at a time) to ascertain if the experimentally determined adsorbabilities followed the Law of Inequalities—*i.e.* if (in adsorbability) A > B and B > C, then also A > C (where A, B, and C are three different substrates). The various cases in point are listed in Table II. The fact that no exceptions to this law have been observed in our studies is evidence in support of the belief that steady-state processes are occurring on the columns. Such is the situation even for runs 31–33 where the chemically different compounds naphthalene, 2-bromonaphthalene, and 2-acetonaphthone are compared. In a few test runs, results on relative adsorbabilities were found to be qualitatively the same with both petroleum ether alone and benzene–petroleum ether, though the mixed solvent sometimes gave a cleaner separation. On the basis of such results it will be assumed that the Law of Inequalities can be applied to all cases considered in this paper.

Runs 1–6 were made in an effort to check the Coplanarity Rule further. The first five involve isomeric biaryls and arylalkenes which differ from one another in angle of twist. The decreasing orders of adsorbability 2-phenylanthracene > 1-phenylanthracene > 9-phenylanthracene; 2,2′-binaphthyl[9] > 1,2′-binaphthyl > 1,1′-binaphthyl; 2-alkenylnaphthalene > 1-alkenylnaphthalene (where the alkenyl group is vinyl, 1-cyclopentenyl, or 1-cyclohexenyl[7]); and 2-phenylnaphthalene > 1-phenylnaphthalene[7], which follow increasing angles of twist in the molecules as well as the frequently noted more tenacious retention of *trans* (as compared to *cis*) isomers,[7] constitute the main basis for this rule. Moreover, the rule holds in run 14, where the nearly coplanar (to the naphthalene ring) cyclohexenyl double bond fosters greater adsorbability than does the non-coplanar (also to the naphthalene ring) cyclopentenyl double bond, which is of greater inherent conjugative effect.[10] In run 6[fluorene (coplanar) > biphenyl (twisted in solution)] the components are iso-π-electronic, though the excellent degree of separation achieved is perhaps ascribable partially to the presence of an alkylene bridge *per se* in the fluorene (*vide infra*) as well as to differences in coplanarity. A similar consideration applies to the observation[11] that a mixture of benzo[*a* and *b*]fluorenes[12] is adsorbed more tenaciously than 2-phenylnaphthalene. The case of benzo[*b* or *c*]fluorene > 2-benzylnaphthalene[13] is free of the alkylene complication but involves instead the difficulty that the former is completely conjugated (*vide infra*), while the latter is not.

Operation of the Unsaturation Rule is apparent in runs 7 [phenanthrene (7 double bonds) > 2-vinylnaphthalene (6 double bonds) > naphthalene (5 double bonds)], 8[pyrene (8 double bonds) > anthracene (7 double bonds)], and 9[naphthalene > 1,2,3,4-tetrahydronaphthalene], as well as in the



benzo[*a*]fluorene benzo[*b*]fluorene benzo[*c*]fluorene

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

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

(11) M. Orchin and L. Reggel, *J. Am. Chem. Soc.*, 70, 1245 (1948).

(12) I.U.P.A.C. 1957 Rules for nomenclature are used throughout this paper.

(13) M. Orchin, E. O. Woolfolk, and L. Reggel, *J. Am. Chem. Soc.*, 71, 1126 (1949).

TABLE II

TRIADS OF ADSORBATES WHICH CORROBORATE THE LAW OF INEQUALITIES FOR CHROMATOGRAPHIC ADSORBABILITY ON ALUMINA

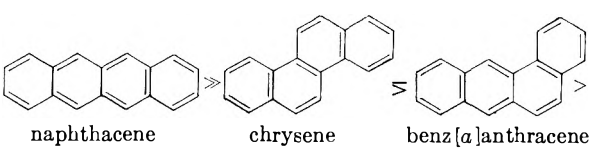
Adsorbate Triad			
Strongest adsorbability	Intermediate adsorbability	Weakest adsorbability	Reference[a]
Anthracene	Phenanthrene	Naphthalene	W. and S., 7
Chrysene	Pyrene[b]	Anthracene[b]	W. and S., 8
Pyrene[b]	Anthracene[b]	Phenanthrene	W. and S., 8
Naphthacene	Benzo[*a*]pyrene	Chrysene	W. and S., 16
Chrysene	Triphenylene	Pyrene	W. and S., 15, 17
Naphthacene	Chrysene	Benz[*a*]anthracene	16, 18, 19
Hexamethylbenzene	Pentamethylbenzene	Durene	22, 23, 24
2-Acetonaphthone	2-Bromonaphthalene	Naphthalene	31, 32, 33
9-Methylanthracene	9-Ethylanthracene	Anthracene	34, 35, 36
9-Ethylanthracene	Anthracene	9-Isopropylanthracene	36, 37, 38
II	V	III	4, 14, 43

[a] W. and S. refers to work of Winterstein and Schön, see ref. 5 in regular text. Numbers refer to particular runs as given in Table I. [b] Pyrene and anthracene separated readily in our experiment but were not separated by Winterstein and Schön.

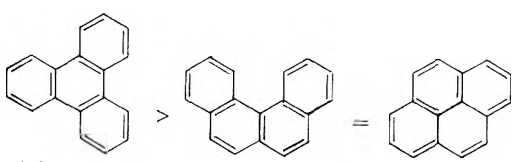
cases of 2-phenylnaphthalene > naphthalene[11]; 2-benzylnaphthalene > naphthalene,[13] and 6,12-dimethylbenz[*a*]anthracene > 6,12-dimethyl-1,2,3,-4-tetrahydrobenz[*a*]anthracene.[14] In our hands separation of the pyrene-anthracene mixture occurred readily though Winterstein and Schön did not succeed in their attempt at this.

Runs 10–12 represent examples where coplanarity and unsaturation effects should tend to counteract one another. Though cases involving more subtle differences in degree of unsaturation would be desirable, the general gross dominance of the Unsaturation Rule over the Coplanarity Rule is noteworthy. Though it is not clear that the conditions of the experiment justify comparison here, the observation[15] that dianthracene (formed *in situ* by chromatography of anthracene in the presence of light) > anthracene may also illustrate the point. Run 13, on the other hand, shows the additivity of effects in the good separation of 2-phenylnaphthalene from 1-(1-naphthyl)cyclopentene.

Interpretation of the relative adsorbabilities of condensed polynuclear arenes appears more difficult. In this regard the experimentally determined (runs 15–19) relationships among the six possible



naphthacene chrysene benz[*a*]anthracene



triphenylene benzo[*c*]phenanthrene pyrene

Scheme I

benzenoid tetracyclic compounds (Scheme I) are instructive. Thus the strong adsorption of naphthacene is consistent with the Acene Rule and the weak adsorption of pyrene (one less double bond than in the others) with the Unsaturation Rule. Though quantitative evaluation of these factors is not yet possible, it is proposed that the entire Scheme I may be rationalized in terms of three rules, *viz.* (a) the forementioned Unsaturation Rule, (b) an expanded Coplanarity Rule and (c) a Symmetry Rule. Briefly, the Symmetry Rule states that adsorbability increases with increasing symmetry number[16] (S.N.) of the molecule. For practical application of this rule one considers condensed molecules as two-dimensional only. If such rule were completely dominant, Scheme I ought to have the order triphenylene (S.N. 6) > naphthacene = pyrene (S.N. 4) > chrysene = benzo[*c*]phenanthrene (S.N. 2) > benz[*a*]anthracene (S.N. 1). The expanded Coplanarity Rule, then, takes cognizance of the fact that "intramolecular overcrowding"[17] will cause distortion of four of these tetracyclic compounds out of coplanar configurations.[18] For complete dominance of coplanarity effects the expected order of adsorbability would be naphthacene = pyrene (both coplanar) > benz[*a*]anthracene (bumping of "*phene hydrogens*" in the 1- and 12-positions) > chrysene (two sets of *phene* hydrogens) > triphenylene (three sets of *phene* hydrogens) > benzo[*c*]phenanthrene (over-

(14) L. F. Fieser and R. N. Jones, *J. Am. Chem. Soc.*, 60, 1940 (1938).

(15) W. J. Levy and N. Campbell, *J. Chem. Soc.*, 1442 (1939).

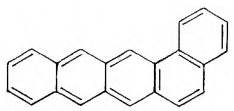
(16) Symmetry number as used here represents the number of equivalent orientations possible for flatwise adsorption of the substrate molecule onto a surface.

(17) A discussion of intramolecular overcrowding is given by J. C. Speakman in W. Klyne and P. B. D. de la Mare, *Progress in Stereochemistry*, Butterworths, London, Vol. 2, 1958, pp. 22–31.

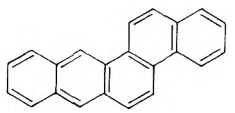
(18) For comparison of phenanthrene-type distortions with the more conventional type of molecular overcrowding noted in ref. 17 see C. A. Coulson, "Molecular Geometry and Steric Deformation," presented at the Kekule Symposium on Theoretical Organic Chemistry, London, Sept., 1958, in press.

crowding of carbons and hydrogens at the 1- and 12-positions). The observed order might reasonably follow from an order of precedence for these rules of (a) > (b) > (c). It is then apparent that the Acene Rule may be considered a corollary of these other three.

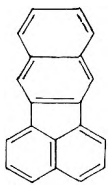
For more complicated arenes, cases accounted for by rule (a) have been considered elsewhere.[5] Rule (b) may be invoked to account for the order benzo[*a*]naphthacene > dibenzo[*a*,*h*]phenanthrene > dibenz[*a*,*c*]anthracene;[5] a combination of rules (a), (b), and (c), to account for the observations[11,13] that benzo[*a*]fluorene and benzo[*b*]fluorene (equivalent in terms of the three rules) are not separated but are more strongly adsorbed than the isomeric benzo[c]fluorene (*phene*-type hydrogen bumping); and rule (c), to account for the greater



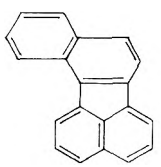
benzo[*a*]naphthacene



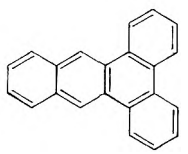
dibenzo[*a*,*h*]phenanthrene



benzo[*k*]fluoranthene



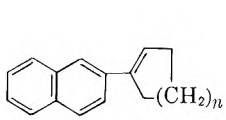
benzo[*j*]fluoranthene



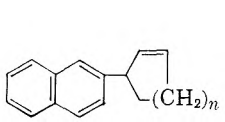
dibenz[*a*, c]anthracene

adsorbability[9] of benzo[*k*]fluoranthene over that of benzo[*j*]fluoranthene.[19] The order anthracene > phenanthrene[5] is accounted for by rules (b) and (c). A variety of other cases investigated by Winterstein and Schön[5] may be rationalized, but would not be predictable on the basis of these qualitative rules.

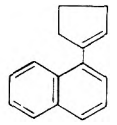
The greater adsorbability of conjugated (as compared to isomeric unconjugated) polyenes on alumina has been noted by previous investigators.[20] Runs 20 and 21 confirm the presumption that conjugation *per se* is also of pertinence in naphthylcycloalkenes. However, rule (a) is dominant over effects of conjugation in determining the order of adsorbability 9,10-dihydroanthracene (6 double bonds) > 1,2,3,4-tetrahydroanthracene (5 double bonds).[21] Tentatively, we propose a Conjugation Rule to the effect that of isomeric unsaturated hydrocarbons which differ from one another only in degree of conjugation, the most extensively conjugated isomer will be adsorbed most tenaciously on alumina.



I (n = 1)
IV (n = 2)



II (n = 1)
V (n = 2)



III

From runs 28–30 [2-methylnaphthalene > 2-ethylnaphthalene ≳ naphthalene > 2-*tert*.-butylnaphthalene] and runs 34–38 [9-methylanthracene > 9-ethylanthracene ≳ anthracene > 9-isopropylanthracene] it is noted that adsorbability of the 2-naphthyl and 9-anthryl moieties is affected by the presence of an alkyl substituent in the order Me > Et ≳ H > *i*-Pr, *tert*-Bu. The enhanced adsorbability of a methylarene (as compared to the parent arene) is also noted in the only benz[*a*]anthracene case so studied (run 39). This reversal in trend for the effect of an alkyl group on adsorbability as a function of increasing size of the group might result from the operation of two opposing factors, namely (1) donation of electronic charge to the aromatic ring and (2) steric hindrance to adsorption. One would expect any alkyl group to enhance adsorbability through operation (1). On the other hand, factor (2) should increase with the bulkiness of the substituent, especially if flatwise adsorption of the arene ring onto the alumina surface were preferred so that projection of a substituent in a direction perpendicular to the plane of the aryl moiety would interfere with the adsorption process. Conceivably, the reversal in trend might be a consequence merely of the increasing molecular weight of the substrate without simultaneous increase in the π-electronic system, rather than as a result of factor (2). That this latter alternative is not particularly pertinent, however, is indicated by the data from runs 22–25 where one finds the order of adsorbability hexamethylbenzene > pentamethylbenzene > durene > mesitylene.[22,23] The good separation (run 26) of acenaphthene (dimethylene group coplanar with the naphthalene ring) from naphthalene (less strongly adsorbed) as compared to the poor separation of 2-ethylnaphthalene from naphthalene (run 29) supports these views, as does also the stronger adsorption (run 27) of I (a virtually coplanar,[24] trimethylene derivative of 2-vinylnaphthalene) as compared to its parent, 2-vinylnaphthalene (also essentially coplanar).[24]

A check on the consequences of having a sterically hindered methyl group was attempted in runs 40 and 42 where one has the order 7-methylbenz-

(19) *Cf.* M. Orchin and L. Reggel, *J. Am. Chem. Soc.*, **73**, 436 (1951), for proofs of structures of these compounds.

(20) L. Zechmeister and L. Cholnoky, *Principles and Practice of Chromatography*, John Wiley, New York, 1941, p. 26.

(21) M. Orchin, *J. Am. Chem. Soc.*, **66**, 535 (1944).

(22) One might also note that these results are inconsistent with edgewise adsorption of the benzene ring, *cf.* ref. 31.

(23) Evidence that hexamethylbenzene and durene are coplanar in the crystalline state is surveyed by E. Harnik, F. H. Herbstein, G. M. J. Schmidt, and F. L. Hirshfeld, *J. Chem. Soc.*, 3288 (1954).

(24) L. H. Klemm, H. Ziffer, J. W. Sprague, and W. Hodes, *J. Org. Chem.*, **20**, 190 (1955).

[*a*]anthracene (uncrowded methyl group) = 4-methylbenz[*a*]anthracene (likewise uncrowded methyl group) > 12-methylbenz[*a*]anthracene (overcrowding of the methyl group and the 1-hydrogen atom,[25] essentially complete separation from the 4-isomer). However, overcrowding in the 12-isomer may well cause both out-of-plane bending of the C_{Ar}—C_{Me} bond and twisting of the aromatic system (in opposite directions).[17] The fair separation (run 41) of the 2- and 10-isomers (both uncrowded) indicates that electronic factors may also be of some significance in considerations of adsorbability in the series. A more definitive case would seem to be the observation of Wieland and Probst[26] that 9-methylfluorene (uncrowded, but sidewise-projecting methyl group) is adsorbed less tenaciously than fluorene.

From the foregoing observations we draw the following tentative alkyl-alkylene rule: Substitution of an alkyl or alkylene group on a parent arene increases adsorbability of the compound on alumina, provided that such substitution does not bring about increased steric hindrance to flatwise adsorption of the arene moiety. Where this substitution increases steric hindrance sufficiently, adsorbability will be lessened.

It has been suggested by Basu[27] that chromatographic adsorption of non-polar organic compounds involves auxiliary valence types or molecular complex formation. Our results on adsorbability seem readily interpretable in terms of such a model, whereby the hydrocarbon substrate functions as an electron donor (D) of relatively limited planar extent which is adsorbed preferentially flatwise (where this is sterically possible) onto broader areas of the electron acceptor (A), alumina,[28] by π-type complex formation. If such a model is appropriate and if steady state conditions do exist in the chromatographic column, our adsorbabilities should be directly correlatable with equilibrium data for stabilities (as measured in inert solvents) of *bona fide* molecular compounds of the same substrates with planar acceptors *provided that* either (1) the other acceptors are of sufficiently extensive areas so as to cover the entire substrate molecule or (2) they are geometrically so disposed as to "sense" all out-of-plane projections and the entire π-electronic system of the substrate molecule.

Let us consider some cases which ought to satisfy either condition (1) or (2). Measurements by Anderson and Hammick[29] on the picrates of the methylbenzenes in chloroform solution[30] showed the order of stability hexamethylbenzene > durene > mesitylene > xylenes > toluene > benzene, and, on the picrates of the monoalkylbenzenes, the order in fostering stability by a substituent of Me (K = 0.51) > Et (0.45) > H (0.43) > *i*-Pr (0.36) > *tert*-Bu (0.31). For tetracyanoethylene complexes measured in methylene chloride solution Merrifield and Phillips[31] found the stability constant increased by a factor of 1.9–3.1 for each additional methyl group substituted on the benzene nucleus. The order Me > Et > H in fostering stability was found for the series hexamethylbenzene (K = 263) > hexaethylbenzene (5) > benzene (2). Also of interest are their findings that fluorene > biphenyl; naphthalene > benzene; and pyrene > naphthalene.[32] A methyl group on naphthalene has been found to enhance TNF complexation in glacial acetic acid.[30,33] These results are in remarkably good agreement with our data on adsorbabilities of alkylarenes (runs 23, 25, 28–30, 34–39).[34] On the basis of the proposed geometries of overlap,[35] the order of stability of TNF complexes[33] I > 2-vinylnaphthalene > naphthalene is likewise correlatable with adsorbabilities (runs 7, 27).[36]

Though the benz[*a*]anthracene molecule is too large to ensure complete overlap of its π-electronic system by TNF one notes that the relative adsorbabilities found in runs 39–41, involving only sterically uncrowded methyl substituents (in the 2-, 4-, 6-, 7-, and 10-positions) are consistent[37] with the data of Takemura, Cameron, and Newman[38] on the dissociation constants of TNF com-

(25) A diagram indicating the magnitude of this effect is given by M. Orchin, *J. Org. Chem.*, 16, 1165 (1951).

(26) H. Wieland and O. Probst, *Ann.*, 530, 274 (1937).

(27) S. Basu, *Chemistry and Industry*, 764 (1956).

(28) The attraction of the alumina may be ascribed to polarization by the Al^{3+} ions. For suggestions on the action of γ-alumina as a Lewis acid see D. A. Dowden in W. E. Garner, *Chemisorption*, Butterworths, London, 1957, p. 15.

(29) H. D. Anderson and D. Hammick, *J. Chem. Soc.*, 1089 (1950).

(30) See also data of T. S. Moore, F. Shepherd, and E. Goodall [*J. Chem. Soc.*, 1447 (1931)] for stabilities of picrates as based on water-chloroform partition studies.

(31) R. E. Merrifield and W. D. Phillips, *J. Am. Chem. Soc.*, 80, 2778 (1958). Their comments on the relation of structures of the TCNE complexes to stabilities would seem to fit our adsorption complexes equally well (except, perhaps, for absolute distances between the adsorbate and the alumina surface layer).

(32) Though we did not measure benzene *vs.* naphthalene directly, common laboratory experience indicates that the latter is more strongly adsorbed. *Cf.* run 8 and ref. 5 for the pyrene-naphthalene relationship.

(33) L. H. Klemm, J. W. Sprague, and H. Ziffer, *J. Org. Chem.*, 20, 200 (1955).

(34) Some discrepancies occur between orders of adsorbability and stabilities of complexes formed between alkylarenes and small inorganic molecules, where stereochemical interactions may be less definite [*cf.* L. J. Andrews, *Chem. Revs.*, 54, 713 (1954), and especially L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, 74, 4500 (1952)].

(35) L. H. Klemm and J. W. Sprague, *J. Org. Chem.*, 19, 1464 (1954).

(36) It is interesting to note that the order of adsorbability 2-acetonaphthone > 2-bromonaphthalene > naphthalene (runs 31–33) is opposite to that found for the stabilities of their TNF complexes (see ref. 33).

(37) This assumes that the ratio of stability constants of 1.5 for 6-Me/10-Me is too small to ensure separation by adsorption.

(38) K. H. Takemura, M. D. Cameron, and M. S. Newman, *J. Am. Chem. Soc.*, 75, 3280 (1953).

plexes of these compounds in chloroform. In run 42, however, where the sterically crowded 12-methyl derivative is run against the sterically uncrowded 4-isomer, the relative adsorbabilities found are opposite to the stabilities of the TNF complexes. The position occupied by the TNF moiety in its complex with the 12-isomer may be automatically adjusted so as to avoid the steric hindrance of the sidewise-projecting methyl group, whereas such adjustment cannot be made by the alumina surface.

In runs conducted by frontal analysis using TNF-impregnated silicic acid in the manner described by Klemm, Reed, and Lind[7] it was found that the conjugated hydrocarbons I and IV were retained on the column more tenaciously than their unconjugated isomers II and V, respectively. The consistency of these results with the data from alumina results because the TNF molecule is too small to allow simultaneous maximum overlap of both the naphthyl and alkenyl π-electronic systems (as alumina might conceivably do) in II and V (and, hence, may be presumed to overlap only the naphthyl nucleus) but just large enough for such simultaneous overlap in I and IV.[35] Also the relationships 2-alkenylnaphthalene > isomeric 1-alkenylnaphthalene and 2-phenylnaphthalene > 1-phenylnaphthalene may be ascribed to a closer approach to coplanarity in the 2-isomer for the alumina adsorption process and to better overlap in the 2-isomer for polynitroarene complexation in solution[33] or on silicic acid.[7]

Stabilities in *crystalline* molecular compounds have been correlated directly with melting point by Orchin.[39] Such stability refers to the equilibrium process

$$A{\cdot}D_n\ (\text{solid}) \rightleftharpoons A{\cdot}D_n\ (\text{liq}) \qquad \text{(process 1)}$$

while stabilities of molecular complexes in solution refer to a *different* equilibrium, *viz.*

$$A{\cdot}D_{(\text{soln})} \rightleftharpoons A_{(\text{soln})} + D_{(\text{soln})} \qquad \text{(process 2)}$$

where crystalline geometries and intermolecular forces (other than in the unit complex A·D) are not involved.[40] The lack of correlation between melting point and adsorbability on impregnated silicic acid has been noted previously,[7] where it has been suggested that adsorption is identifiable with molecular compound formation of a type essentially like that which occurs in solution rather than like that which occurs in a crystalline solid. Pursuing this same general theme, one also notes that if crystallites (Z_n) of adsorbate (Z) form on the alumina column and are pertinent to the final overall separation process, then one would be concerned primarily[41] with the steady-state phenomena

$$Z_n\ (\text{solid}) \rightleftharpoons Z_n\ (\text{liq}) \rightleftharpoons Z_n\ (\text{soln}) \rightleftharpoons Z(\text{soln}) \qquad \text{(process 3)}$$

If, on the other hand, adsorbate molecules are held monomolecularly and widely dispersed on the alumina surface, one would have the steady state

$$Z_{(\text{adsorbed})} \rightleftharpoons Z_{(\text{soln})} \qquad \text{(process 4)}$$

If process 3 is an appropriate representation of chromatography on alumina, then adsorbability ought to vary directly with melting point and/or inversely with solubility. If process 4 is appropriate, however, adsorbability should be independent (at least within wide limits)[42] of both of these adsorbate properties. A check of the data in Table I shows that, in 40% of the binary mixtures run, stronger adsorption occurred for the lower melting component. Moreover, though only gross differences in relative solubilities have been noted in our experiments, in some cases (runs 3, 8, 12, 24, 28, 34, and 36) the more soluble component is more tenaciously adsorbed and in other cases (runs 10, 15, 16, 17, 19, and 37) it is less tenaciously adsorbed. On the basis of these considerations and the preceding correlations of adsorbability with stabilities of *bona fide* molecular compounds as measured in solution, we propose that separations on our alumina columns involve as the most pertinent process[43] a relatively rapidly reversible steady-state condition (process 4) occurring between molecules of hydrocarbon adsorbed monomolecularly on "active spots" of the alumina surface in a π-type (outer- or charge-transfer) complex and molecules of hydrocarbon dissolved in the eluting solvent.

Additional studies to test further the generalizations and proposals made in this paper are planned for the future.

EXPERIMENTAL

Syntheses and purification of substrates. Unless specifically noted otherwise, every substrate used in adsorbability studies was (a) obtained from Distillation Products Industries (white label grade), (b) chromatographed separately using alumina with petroleum ether (30–60°), benzene, or a mixture of the two solvents, and (c) recrystallized once or twice from ethanol.

Triphenylene.[44] A mixture of 10 g. of dodecahydrotriphenylene[45] (m.p. 230–232°) and 1 g. of 30% palladium-on-charcoal (American Platinum Works) was heated in a 40 × 300-mm. Pyrex test tube fitted with a cork bearing a bent glass tube (to prevent loss of triphenylene through sublimation and entrainment by evolved hydrogen) for one hr. in a

(39) *Cf.* ref. in footnote 25.

(40) Discrepancies between stabilities of molecular compounds as measured by criteria of m.p. and equilibrium constant have been noted previously; see, for example, refs. 35 and 38.

(41) For the relatively few molecules adsorbed directly to the alumina surface in this case, process 4 would apply.

(42) It is readily apparent that extremes of solubility may prevent process 4 from operating because of lack of adsorption or lack of dissolution.

(43) Though the systematic investigation of this point has not yet been made, there are indications that even in cases where the adsorbate components are observed to crystallize out of solution in the uppermost region of the column, use of a sufficiently long column ensures that the order of appearance of components in the effluent remains unchanged.

(44) Method developed by Dr. Herman Ziffer.

(45) C. Mannich, *Ber.*, 40, 153 (1907).

Wood's metal bath maintained at 240°. Over a period of 6 hr. the bath temperature was increased gradually to 310° where it was held for 11 hr. longer. The cooled benzene extract (after treatment with Nuchar) of the mixture deposited needles, m.p. 198–199° (first crop) and 196–199° (second crop), total av. yield 8.2 g. (86%). Percentage yields were lower for larger batches.

9-Ethylanthracene. To the Grignard reagent from 20.3 g. (0.13 mole) of ethyl iodide, 3 g. of magnesium, and 70 ml. of anhydrous ether was slowly added a solution of 10 g. (0.051 mole) of anthrone[46] in 100 ml. of anhydrous benzene. The mixture was refluxed for 9 hr. and then poured onto ice and concentrated hydrochloric acid. Distillation of the dried organic layer gave 9.2 g. (87%) of liquid, b.p. 149–156°/1 mm. which solidified on cooling. This was recrystallized and chromatographed. The first fraction (3.6 g., m.p. 56–58°) was selected for further use; reported[47] m.p. 59°.

9-Isopropylanthracene. In the foregoing manner there was obtained from 10 g. of anthrone and 22 g. of isopropyl iodide 8 g. (71%) of liquid, b.p. 153–160°/1.3 mm. The first fraction (3.4 g.) from chromatography was recrystallized from methanol, m.p. 75–76°; reported[48] m.p. 76°.

1-Phenylanthracene. 1-Phenylanthraquinone[49] was reduced according to published directions[50] except that the zinc was activated[51] and the period of reflux was 58 hr. After chromatography and recrystallization, the product formed white needles, m.p. 113–114.5°; reported[50] yellow needles, m.p. 123°.

2-Phenylanthracene.[52] The black product resulting from refluxing (air condenser) 10 g. of 2-methyl-4′-phenylbenzophenone[53] for 7.5 hr. (whereupon evolution of water had ceased) was sublimed in portions of 1–3 g. at *ca.* 150°/0.5–1.0 mm. for periods up to 12 hr. Combined sublimates (4.1 g.) were recrystallized (Norit) from methyl ethyl ketone, yield 2.1 g. (22%) of pale yellow leaflets, m.p. 211.5–212.5° [reported[54] m.p. 207–207.5°], $\lambda_{max}^{isooctane}$ 229 mμ (log ε 4.41), 257 (4.80), 276 (4.90), 318 (3.24)—shoulder, 330 (3.52), 346 (3.75), 364 (3.87), 384 (3.73),[55] used without recrystallization.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.32; H, 5.56.

1,2′-Binaphthyl was prepared according to the method of Hooker and Fieser,[56] except that dehydrogenation of the intermediate was effected by heating with 1 g. of 30% palladium-on-charcoal at 280–290° for 3.5 hr. and finally at 350° momentarily. The product was chromatographed first with TNF-impregnated silicic acid[7]—Florisil (1:2 by vol.) and then with alumina, m.p. 74.5–76° (without recrystallization). 1,1′-Binaphthyl was prepared and purified likewise; yield 28%, m.p. 155–158° from the first chromatographic column; final m.p. 157–158° (without recrystallization). This sample did not exhibit the melting peculiarities described by Orchin and Friedel.[57] 2-Ethylnaphthalene,[58] prepared by Clemmensen reduction of 2-acetonaphthone, was distilled twice (b.p. 79–80°/0.8 mm.) and used directly. 2-*tert*-Butylnaphthalene[58,59] (b.p. 96–99°/1.5 mm.) was converted to its picrate (m.p. 99–101°) which was dissociated on alumina. The sample used was obtained by evaporation (*sans* heating) of the first fraction of effluent.

For preliminary purification benzo[*c*]phenanthrene[60] was converted to its picrate which was dissociated on alumina. Pyrene (Matheson practical grade) was recrystallized from ethanol, treated with maleic anhydride to remove reactive impurities,[61] and chromatographed. Chrysene was treated with maleic anhydride and recrystallized from benzene as white platelets. Benz[*a*]anthracene was converted to its picrate, which was recrystallized three times from glacial acetic acid and then dissociated on alumina. Chromatography twice gave white platelets (not recrystallized). Naphthacene (H. and M. Chemical Co., practical grade) was chromatographed using benzene and a column protected from light by means of an aluminum foil wrapping and was used without recrystallization. 9-Phenylanthracene[62] (Aldrich Chemical Co.) was chromatographed on 1:1 (by vol.) alumina-Celite using hexane as solvent and then recrystallized twice from absolute ethanol and once from acetonitrile. 9-Methylanthracene was obtained from Aldrich Chemical Co.; durene, from Humble Oil and Research Co. 2-Bromonaphthalene was available from previous research.[33] 2-Acetonaphthone was purified merely by recrystallization from petroleum ether (30–60°); 2-methylnaphthalene, from methanol. Acenaphthene was given a preliminary treatment with decolorizing carbon in ethanol. The liquids 1,2,3,4-tetrahydronaphthalene and mesitylene were used directly after careful fractional distillation, b.p.'s 59–59.5°/1.8 mm. and 156–157°/1 atm., respectively. Naphthalene (Baker's analytical reagent) and samples (kindly supplied by Prof. M. S. Newman) of the methylbenz[*a*]anthracenes were used as obtained. Anthracene,[7] phenanthrene,[7] phenylnaphthalenes,[7] and alkenylnaphthalenes[33,63,64] were used directly in the purified forms described previously.

Chromatography on alumina. In general, a Pyrex chromatographic tube, fitted at the bottom end (*via* a nonlubricated ground-glass joint) with a fritted glass disc and constricted end, was filled with reagent grade petroleum ether (30–60°). Alcoa activated alumina (grade F-20 γ-alumina, used directly from the can) was gradually introduced while the tube was tapped vigorously with heavy rubber tubing until a column of adsorbent 30–80 cm. high (105–250 g.) resulted. A layer of purified sand, 1 cm. thick, was placed atop the alumina to protect the latter from disturbance by the solvent. The solvent was allowed to drain until its level reached the top of the sand. Thereupon, a mixture containing equal weights (10–300 mg.) of each component, dissolved in a minimum volume of either reagent grade[65] petroleum ether (30–60°) alone or admixed with reagent grade benzene (up to 50% by vol.), was added to the top of the column and the chromatogram was de-

(46) K. H. Meyer, *Org. Syntheses*, Coll. Vol. I, 60 (1941).
(47) F. Krollpfeiffer and F. Branscheid, *Ber.*, 56, 1617 (1923).
(48) E. B. Barnett and M. A. Matthews, *Ber.*, 59, 1429 (1926).
(49) E. Bergmann, L. Haskelberg, and F. Bergmann, *J. Org. Chem.*, 7, 303 (1942).
(50) C. Weizmann, E. Bergmann, and L. Haskelberg, *J. Chem. Soc.*, 391 (1939).
(51) E. L. Martin, *J. Am. Chem. Soc.*, 58, 1441 (1936).
(52) Synthesized by Dr. Roger H. Mann.
(53) W. E. Bachmann and F. H. Moser, *J. Am. Chem. Soc.*, 54, 1124 (1932).
(54) J. W. Cook, *J. Chem. Soc.*, 1087 (1930).
(55) *Cf.* Y. Hirshberg, *Trans. Faraday Soc.*, 44, 285 (1948).
(56) S. C. Hooker and L. F. Fieser, *J. Am. Chem. Soc.*, 58, 1216 (1936).
(57) M. Orchin and R. A. Friedel, *J. Am. Chem. Soc.*, 68, 573 (1946).
(58) Prepared by Dr. Jack T. Spence.
(59) N. G. Bromby, A. T. Peters, and F. M. Rowe, *J. Chem. Soc.*, 144 (1943).
(60) M. S. Newman, H. V. Anderson, and K. H. Takemura, *J. Am. Chem. Soc.*, 75, 347 (1953).
(61) E. Clar, *Ber.*, 65, 1425 (1932).
(62) Purified by Dr. C. Douglas Lind.
(63) L. H. Klemm and W. Hodes, *J. Am. Chem. Soc.*, 73, 5181 (1951).
(64) L. H. Klemm, B. T. Ho, C. D. Lind, B. T. MacGowan, and E. Y. K. Mak, *J. Org. Chem.*, 24, 949 (1959).
(65) Of several brands tried only Mallinckrodt reagent grade (30–60°) petroleum ether was found to leave a sufficiently small amount of residue upon evaporation of a 1- to 2-l. sample as to be suitable for use as an eluent for the methylbenzanthracenes and other slightly soluble hydrocarbons.

TABLE III

FRACTIONS COLLECTED IN RUN 6

Total Wt. of Effluent Fraction[a] (g.)	Wt. of Residue (mg.)	M.p. of Residue (°C.)
150	None	—
64	50	70–71
85	50	65.5–69
62	None	—
92	5	104–110
87	50	114–115
115	20	114–116
107	20	113.5–115

[a] Fractions are listed in order of appearance.

TABLE IV

FRACTIONS COLLECTED IN RUN 42

Total Wt. of Effluent Fraction[a] (g.)	Wt. of Residue (mg.)	M.p. of Residue (°C.)
132	3	132–135
127	4	134–136
524	13	136–138
254	2	132.5–136
289	1	133.5–136
301	1	128–135
324	1	120–129
155	None[b]	—
315	1	180–188
272	2	188–192
211	2	190–192
949	4	183.5–190.5
218	3	185–192
307	3	186–190.5
210	2	186–192
242	3	181–188
ca. 1200[c]	5	181–188

[a] Fractions are listed in order of appearance. The first fractions, which yielded no residue, are not listed. [b] Separation of the two components was facilitated by the fact that two distinct, light blue fluorescent zones could be seen throughout the development process. [c] Eluted with 3% benzene–petroleum ether.

veloped and eluted at room temperature by gravity flow using, in general, the same solvent. The solvent and the size of the sample were determined by solubility and availability of the components. The rate of flow through the column was 150–300 ml./hr. for columns 30–40 cm. long and 75–150 ml./hr. for those 80 cm. long. Fractions of effluent were collected somewhat arbitrarily, weighed, evaporated rapidly almost to dryness in a stream of nitrogen on a steam bath and then slowly on a tared watchglass in air at room temperature. Any resultant residue was weighed and (if crystalline) was powdered, mixed thoroughly, and used for m.p. determination. Details of the individual runs are given in Table I and typical data for fractions collected in two runs where successful separations were obtained are given in Tables III and IV.

In test runs, samples of the unconjugated cycloalkenylnaphthalenes II and V were passed through alumina individually and the effluents were checked for the possible presence of the conjugated isomers I and IV, respectively. No evidence of doublebond migration under the conditions of our experiments was found.

Chromatography on TNF-impregnated silicic acid. This was conducted in the manner previously described[7] using adsorbent 4% by weight in TNF and spectral analysis of the effluent at 226 and 298 mμ for the mixture I-II and at 227 and 296 mμ for the mixture IV-V. In each case the conjugated isomer was more tenaciously adsorbed (retention ratios I/II = 2.4; IV/V = 2.0–2.5) and the concentration of the unconjugated isomer reached a transient maximum in the effluent which was slightly greater than that in the influent. With the mixture IV-V an orange zone preceded a red zone down the column until the former was eluted and the latter had expanded to occupy the entire column.[66] With the mixture I-II the column became red-orange. In a test run using only V in the influent the column became orange and no spectral evidence was found for the presence of IV in the effluent.

EUGENE, ORE.

(66) This spectacular phenomenon is readily interpreted in terms of a preceding zone containing essentially only V (forms an orange TNF complex) and a following expanding zone containing both V and IV (forms an orange red TNF complex, *cf.* ref. 35).

[CONTRIBUTION NO. 2012 FROM THE KODAK RESEARCH LABORATORIES]

The Synthesis of Polyazaindenes and Related Compounds

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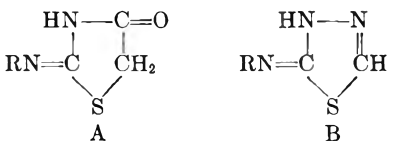
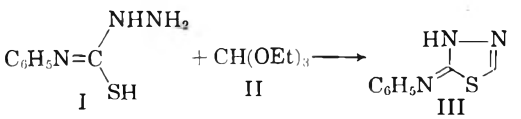
The reactions of the 2-hydrazino derivatives of pyridine, quinoline, benzothiazole, benzoxazole, benzoselenazole, and benzimidazole with orthoesters, aliphatic acids, aromatic esters, nitrous acid, phenylisothiocyanate, and phenylisocyanate which, in most cases, form ring-closed products, were investigated. The reaction of phenylthiosemicarbazide and orthoesters was also studied. Some heterocyclic compounds substituted in the 2-position with chlorine were treated with arylhydrazides in phenol to give ring-closed products. The ultraviolet spectra of the materials are discussed.

In continuation of the study of ring systems related to the iminothiazolidine A,[1] attention was turned to the action of orthoesters on 4-phenylthiosemicarbazide with the intention of obtaining compounds of the type B.



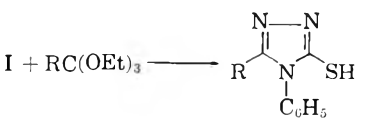
A B

The reaction of equimolecular portions of phenylthiosemicarbazide (I) with triethyl orthoformate (II) in boiling xylene proceeded as expected to give 2-phenylimino-1,3,4-thiadiazole (III), which had been obtained previously by ring closure of I with formic acid.[2] However, triethyl orthoacetate (IV)



I II III

and triethyl orthopropionate (V) rather surprisingly reacted with I to give 3-mercapto-5-methyl-4-phenyl-1,2,4-triazole (VI) and 5-ethyl-3-mercapto-4-phenyl-1,2,4-triazole (VII), respectively, in good yield.



VI. R = CH_3
VII. R = C_2H_5

Thus, in these latter two cases, ring closure occurred through the anilino group rather than through the sulfur atom. A somewhat analogous case was found by Marckwald and Bott.[3] Benzoylphenylthiosemicarbazide and acetyl chloride gave 2-anilino-5-phenyl-1,3,4-thiadiazole but substitution of benzoyl chloride for acetyl chloride produced 4,5-diphenyl-3-mercapto-1,2,4-triazole.

These mercapto compounds are easily soluble in dilute sodium hydroxide. Methyl *p*-toluenesulfonate forms a salt with VI from which the free base, 5-methyl-2-methylmercapto-1-phenyl-1,3,4-thiadiazole (VIa), may be obtained. Sodium chloroacetate reacts with VII to give 5-methyl-2-carboxymethylmercapto-1-phenyl-1,3,4-thiadiazole (VIIa).

Lawson and Morley[4] have shown conclusively that 2-mercaptoimidazoles exist almost exclusively as the thione tautomers and that the absorption at 260 mμ in 2-mercaptoimidazoles is due mainly to contributions from the thione form. They have also shown that the absorption of the *S*-methyl derivative of 2-mercaptoimidazoles occurs at slightly lower wave lengths and with a much reduced intensity.

Spectroscopic examination of VIa, VII, and VIIa shows an interesting parallel in the light-absorption of these compounds to those of Lawson and Morley, as shown in Table I.

TABLE I

COMPARISON OF THE LIGHT-ABSORPTION OF 2-MERCAPTOIMIDAZOLES AND OF 2-MERCAPTO-1,3,4-THIADIAZOLES

	λ_{max}(mμ)	ε	Solvent
2-Mercapto-4(5)-methylimidazole	263	14,700	EtOH
4(5)-Methyl-2-methylmercaptoimidazole	250	3,400	EtOH
VII	258	11,000	MeOH
VIa	245	2,620	MeOH
VIIa	245	3,075	MeOH

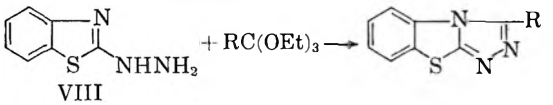
These results indicate that VII exists predominantly in the thione form and that alkylation occurs on the sulfur atom.

The ultraviolet absorption spectrum of III (λ_{max} 243 and 285 mμ) (ε = 5,800 and 16,200) is very different from that of VII and serves as a basis for distinguishing these isomers.

The behavior of 2-hydrazinobenzothiazole (VIII), a substance which is formally analogous to I, with II, IV, and V was next examined. Ring closure through the sulfur group is not possible in VIII, and the reaction proceeds readily, as expected, to give 8-thia-1,2,3a-triazacyclopent[a]indene (IXa), its 3-methyl (IXb), and 3-ethyl (IXc) derivatives,

(1) J. A. VanAllan, *J. Org. Chem.*, 21, 24 (1956).
(2) G. Pulvermaker, *Ber.*, 27, 617 (1894).
(3) W. Marckwald and A. Bott, *Ber.*, 29, 2914 (1896).
(4) A. Lawson and H. V. Morley, *J. Chem. Soc.*, 1103 (1956).

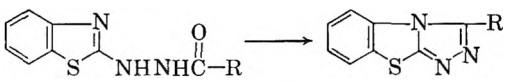
respectively, in good yield. The cyclization of VIII to IXa may also be effected with formic acid or with $CH_3COCH(OEt)_2$. Refluxing VIII with acetic



VIII

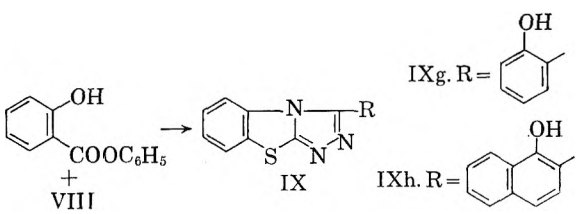
IXa. R = H
IXb. R = CH_3
IXc. R = C_2H_5

acid, propionic acid, or other higher aliphatic acids in attempts to obtain IXb and IXc resulted only in the formation of the corresponding acyl derivatives of the hydrazine. It was then found that the acyl derivatives of the hydrazines could be cyclized by refluxing them in phenol.[5] This reaction affords a convenient route to the higher alkyl derivatives of IXa, for which the necessary orthoesters are not readily available. Several 3-alkyl derivatives were prepared in this manner. In one example, a dibasic

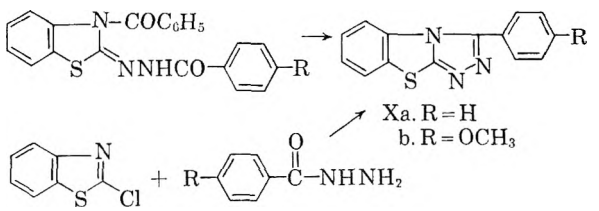


IXd. R = C_3H_7
IXe. R = i-C_3H_7
IXf. R = n-C_5H_{11}

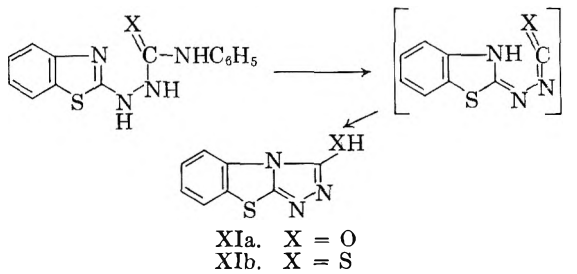
acid was reacted with VIII. As an excess of the acid could not be employed as the solvent, phenol was used, thus yielding the ring-closed material directly. Phenyl salicylate reacts readily with VIII in trichlorobenzene to give 3-(2-hydroxyphenyl) - 8 - thia - 1,2,3a - triazacyclopent[a]indene (IXg).



In a similar manner, phenyl 1-hydroxy-2-naphthoate gives the corresponding 1-hydroxy-2-naphthyl derivative, IXh. Phenyl benzoate failed to form a hydrazide with VIII. Equimolecular proportions of benzoyl chloride and VIII in the presence of pyridine gave a poor yield of 2,x-dibenzoylhydrazinobenzothiazole. Two molecular equivalents of benzoyl chloride to one of VIII under the same conditions gave a quantitative yield of the dibenzoyl compound which was cyclized in refluxing phenol to Xa. Alternatively, 2-chlorobenzothiazole and benzhydrazide react smoothly in boiling phenol to give Xa, and 4-methoxybenzhydrazide gave the methoxy derivative, Xb.



When heated either with or without a solvent, 1-(2-benzothiazolyl)-4-phenylsemicarbazide readily undergoes ring closure, with the loss of anilin to give 3-hydroxy-8-thia-1,2,3a-triazacyclopent[a]indene (XIa). In a similar fashion, 1-(2-benzothiazolyl)-4-phenylthiosemicarbazide under the same conditions gives 3-mercapto-8-thia-1,2,3a-triazacyclopent[a]indene (XIb). Both of these latter



XIa. X = O
XIb. X = S

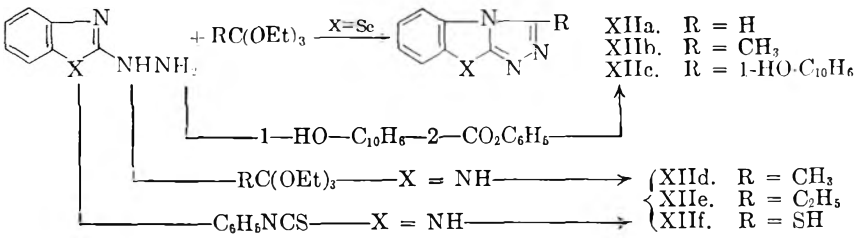
substances are soluble in dilute alkali and can be precipitated therefrom with acetic acid. Although XIa and XIb have been represented here in the enol and thiol forms, the absence of a hydroxy band in the infrared spectrum of XIa indicated that the oxygen in this substance is double-bonded and, by analogy, XIb may have a double-bonded sulfur rather than a mercapto group in position 3.

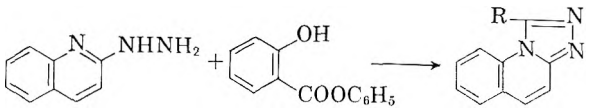
The cyclization proceeds equally well if the sulfur atom of VIII is replaced by selenium or nitrogen. For example, 2-benzoselenazolylhydrazine reacts with triethylorthoformate to give 8-selena-1,2,3a-triazacyclopent[a]indene (XIIa), and 2-benzimidazolylhydrazine with triethyl orthoacetate gives 3 - methyl - 1,2,3a,8 - tetrazacyclopent[a]indene (XIId). Other derivatives were prepared as noted in the diagram.

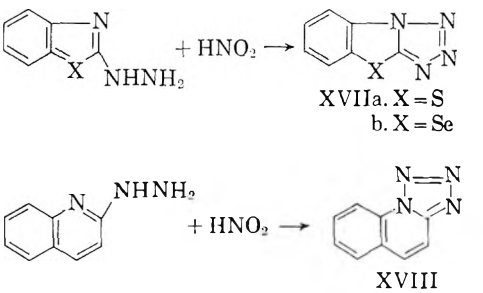
2-Quinolylhydrazine, which may be considered analogous to VIII in that the sulfur atom has been replaced by the ·CH=CH· group, was next examined with respect to its behavior with orthoesters, phenyl salicylate, and phenyl isocyanate. In each case, a product entirely analogous to those just described was obtained. The reaction of 2-quinolylhydrazine with phenyl salicylate to give 1 - (2 - hydroxyphenyl) - 2,3,9b - triazabenz[e]-indene (XIIIa) will serve to illustrate the course of the reaction. 2-Quinolylbenzhydrazide is readily cyclized to 1-phenyl-2,3,9b-triazabenz[e]indene by refluxing in phenol.[6]

(5) Refluxing the acylhydrazines in pyridine and pyridine hydrochloride, xylene and p-toluenesulfonic acid, or various other solvents, and an acid catalyst failed to bring about ring closure.

(6) The reaction of 2-quinolylhydrazine with formic acid, nitrous acid, and phenyl isothiocyanate was investigated by W. Marckwald and E. Meyer, *Ber.*, **33**, 1892 (1900), and the expected azabenz-[e]indenes were obtained in each case.

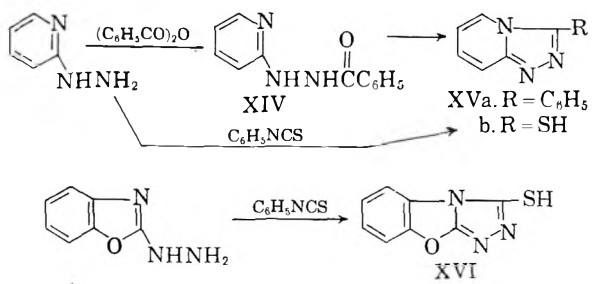






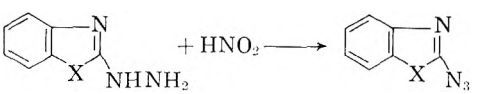
In a similar fashion, 2-pyridylhydrazine was converted to 2-(2-pyridyl)benzhydrazide (XIV) with benzoic anhydride in alcohol. 3-Phenyl-1,2,3a-diazaindene (XVa) was obtained in excellent yield by refluxing XIV in phenol for several hours.

Phenyl isothiocyanate reacts with 2-pyridylhydrazine and 2-benzoxazolylhydrazine to give 3-mercapto-1,2,3a-triazaindene (XVb), which has been synthesized by different methods,[7,8] and 3-mercapto - 8 - oxo - 1,2,3a - triazacyclopent[a]indene (XVI), respectively. Knott and Williams[9] have disclosed the preparation of XVb and XVI by the treatment of the heterocyclic hydrazine with carbon disulfide.



2 - Benzothiazolylhydrazine, 2 - benzoselenazolylhydrazine, and 2-quinolylhydrazine, on treatment with nitrous acid, give 8-thia-1,2,3,3a-tetrazacyclopent[a]indene (XVIIa), 8-selena-1,2,3,-3a-tetrazocyclopent[a]indene (XVIIb), and 1,2,3,-9b-tetrazabenz[e]indene (XVIII), respectively. The reaction of 2-chloroquinoline with sodium azide in aqueous ethanol also gives XVIII. These latter three substances were made to determine the effect of replacing the three carbon atoms of IXa and of XIIa and the one carbon atom of XIIIc with nitrogen on the ultraviolet absorption spectra of these compounds, which will be discussed in the next section. These tetraza compounds are exceptional in that they do not form quaternary salts, while those compounds containing the triaza system readily form crystalline metho-*p*-toluenesulfonates which may serve as convenient derivatives. The greater symmetry and consequent greater diffusion of the charge in the tetraza series is probably responsible for the nonformation of quaternary salts in the tetraza series.

The behavior of 2-hydrazinobenzimidazole, 1-(β-hydroxyethyl)-2-hydrazinobenzimidazole and 2-hydrazinobenzoxazole is unusual in that nitrous acid converts them to 2-azidobenzimidazole (XIXa), 1 - β - hydroxyethyl - 2 - azidobenzimidazole (XIXb), and 2-azidobenzoxazole (XIXa), respectively. The presence of the azido group is confirmed by a strong band at 4.64 μ, which is characteristic of the azido group. These latter



XIXa. X = NH
XIXb. X = NCH2CH2OH
XIXc. X = O

materials are extremely sensitive to light and turn from white to black after a few minutes' exposure to a sunlamp.

The cyclizations of the various hydrazides described take place at very different rates, depending on whether ring closure takes place at a heterocyclic atom which is located in a five- or a six-membered ring. For example, 2-quinolylbenzhydrazide is readily cyclized by several hours' heating in phenol or by heating above its melting

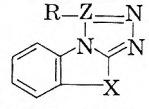
(7) W. H. Mills and H. Schindler, *J. Chem. Soc.*, 123, 312 (1923).

(8) D. S. Tarbell, C. W. Todd, M. C. Paulson, E. G. Lindstrom, and V. P. Wystrach, *J. Am. Chem. Soc.*, 70, 1381 (1948).

(9) E. B. Knott and L. A. Williams, U. S. Patent 2,861,-076 (1958).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF THE CYCLOPENT[e]INDENES[a]



$\lambda m\mu(\epsilon \times 10^{-3})$. X = S, Z = C

R = H	R = CH_3	R = C_2H_5	R = n-C_3H_7	R = n-C_5H_{11}	R = i-C_3H_7	R = OH	R = SH	R = $OCCH_3$ (O=)	R = C_6H_5	4—$CH_3OC_6H_4$
212(24.4)	213(22.0)	213(23.4)	213(23.2)	214(30.0)	214(21.5)	218(30.0)	212(31.5)	214(21.0)	214(21.2)	214(22.0)
220(22.0)	220(38.6)	221(21.7)	270(24.3)	220(24.3)	221(23.0)	232(12.3)	...	232(14.0)	246(15.0)	255(15.7)
225(23.8)	225(37.0)	223(21.5)	226(21.8)	225(22.9)	225(23.5)	254(5.8)	254(5.5)	238(12.8)	294(6.3)	294(8.8)
~244(10.6)	~244(10.4)	~244(10.5)	~243(10.3)	~243(10.5)	~244(10.5)	...	...	255(6.2)		
282(2.7)	282(4.6)	282(2.7)	282(2.9)	282(2.9)	286(3.6)	286(3.5)	274(7.6)	288(3.7)		
289(2.8)	289(4.8)	290(2.8)	290(3.0)	290(3.0)	291(3.4)	292(3.3)	311(11.5)	294(3.5)		

X = Se, Z = C		X = NH, Z = C		X = S, Z = N	X = Se, Z = N	X = O, Z = C
R = H	R = CH_3	R = CH_3	R = C_2H_5	R = H	R = H	R = SH
214(18.8)	214(23.4)	214(60.0)	214(61.0)		228(23.3)	
229(20.0)	229(17.8)			222(21.0)		
~244(12.0)	~244(11.0)	~232(19.5)	~232(20.0)	~240(10.0)	~240(15.0)	
283(2.6)	283(2.0)	288(4.9)	288(5.5)	282(6.7)	286(3.5)	250(9.1)
292(2.8)	292(2.1)	293(5.0)	294(5.6)	292(6.8)	295(3.9)	290(7.9)

[a] The absorption spectra were measured using methanol as a solvent.

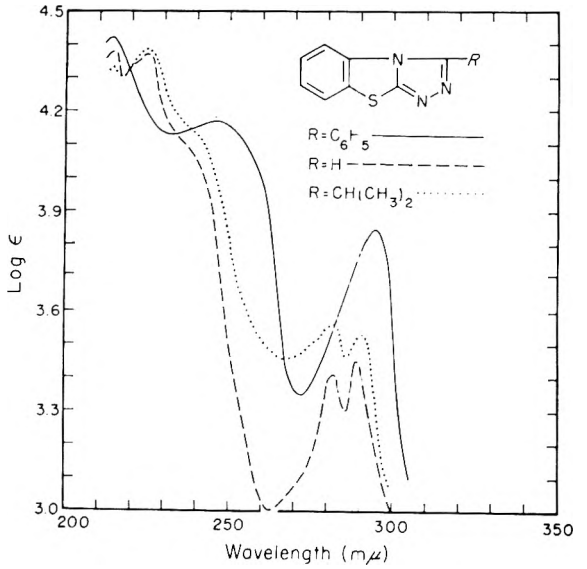


Fig. 1. Ultraviolet absorption spectra of cyclopent[a]indenes in methanol

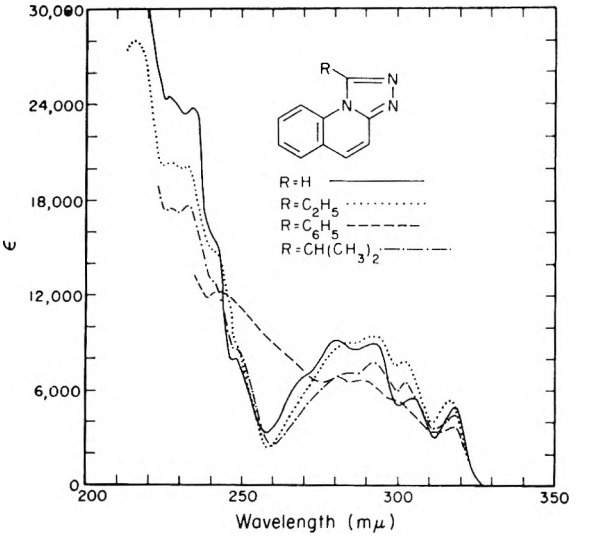


Fig. 2. Ultraviolet absorption spectra of the 2,3,9b-triazabenz[g]indenes in methanol

point, while benzothiazolylbenzhydrazide is not ring-closed unless it is refluxed in phenol for about 24 hr. This also applies to the other hydrazides which were cyclized.

DISCUSSION OF THE ULTRAVIOLET ABSORPTION SPECTRA

The ultraviolet absorption spectra of the alkyl cyclopent[a]indenes IXa → IXf are practically identical, indicating that there is no steric interference of the 3-alkyl group with the hydrogen atom in the 4-position. The shape of the absorption spectrum is reminiscent of benzimidazole,[10] which has peaks at 244(5,500), 272(5,100), and 279(5,400) mμ. The 244-mμ peak of benzimidazole occurs only as a shoulder in the alkyl cyclopent[a]indenes, while the 272-mμ and 279-mμ bands of benzimidazole have been shifted to longer wave lengths by about 10 mμ, but the absorbency remains about the same. The spectra of the aryl cyclopent[a]indenes Xa and Xb show a single peak in the 214-mμ region, a definite peak at 246 mμ for Xa and at 255 mμ for Xb, and both have a single peak at 294 mμ. The longer wave-length bands show increased absorbency over the alkyl derivative (Table II and Fig. 1). The selenium analogues, XIIa and XIIb, show a bathochromic shift of about 5 mμ in the 225-mμ region of their spectra over that of their corresponding sulfur derivative, while the nitrogen analogues, XIId and XIIe, are exceptional in the high absorbency of the 214 mμ band ($\epsilon \approx$ 60,000) and the disappearance of the 229-mμ band. The spectra of the tetrazaindenes, XVIIa and XVIIb, are quite similar to those of XIIa. The spectra of the hydroxy compound, XIa, and those of the mercapto derivative, XIb, show a bathochromic shift and a hyperchromic effect in keeping with their respective auxochromic properties, the sulfur atom, as is known, being the more powerful auxochrome.

The spectra of the 2,3,9b-triazabenz[e]indenes are similar to those of the cyclopent[a]indenes. There is, however, a bathochromic shift of the entire spectrum and an increase of fine structure. The progressive lowering of the absorbency of the shorter wave-length bands as the substituent in the 1-position, R, as hydrogen, ethyl, and isopropyl is indicative of steric hindrance. The spectrum of 1-phenyl-2,3,9b-triazabenz[e]indene (XIIIg) is typical of a compound in which there is considerable steric interference, *i.e.*, a broadening of the maxima and decreased absorbency. The planarity of the phenyl group relative to the rest of the molecule is destroyed by its interference with the hydrogen in the 9-position (Fig. 2 and Table III). The spectra of the triazabenz[e]indenes are plotted by using molecular extinction coefficients, as this scale emphasizes the lowering of the absorbency due to steric hindrance.

In those cases where a number of compounds were prepared by the same method, a generalized procedure is given and the materials synthesized by this procedure are indicated by the appropriate letter in Tables IV, V, VI, VII, and VIII. The physical properties and analytical data for the compounds described in this paper are collected in these latter tables. Thus, 2-phenyl-1,3,4-thiadiazole (III), 5-methyl-(VI) and 5-ethyl-2-mercapto-1-phenyl-1,3,4-triazole (VII) were prepared according to the following procedure.

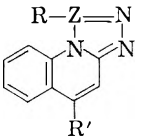
EXPERIMENTAL

Procedure A. A mixture of 0.1 mole of 4-phenylthiosemicarbazide and 0.11 mole of the orthoester in 60 ml. of xylene was heated to reflux. The alcohol which was formed was

(10) E. Steck, F. Nachod, G. Ewing, and N. Gorman, *J. Am. Chem. Soc.*, **70**, 3408 (1948).

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF THE 2,3,9b-TRIAZABENZ[e]INDENES



Z = C

λmμ

(ε × 10^{-3})

R = H	R = CH_3	R = H; R′ = CH_3	R = C_2H_5	R = $CH(CH_3)_2$	R = C_6H_5	R = OH	R = SH
216 (32.5)		220 (23.1)	216 (28)			214 (14.5)	216 (34)
226 (24.6)		230 (21.8)	226 (20.4)	226 (17.7)			
234 (24)		235 (22.4)	232 (20.1)	232 (17.8)		230 (21.9)	225 (26)
240∼(15.7)		242 (14.6)	240∼(15)	240∼(13)	242 (12.5)	236 (21.8)	240 (8.8)
248 (8.2)	248∼(8.9)	252 (9.5)	248∼(9.6)	249∼(8.5)	252 (9.5)	247 (20.4)	
						255 (19.0)	270∼(15)
280 (9.2)	283∼(8.9)	280 (8.0)	285 (8.8)	285 (7.4)	281 (6.9)	282 (2.8)	278 (22.3)
292 (9.2)	292 (9.5)	292 (8.2)	292 (9.5)	292 (7.9)	292 (6.8)	292 (3.5)	
305 (5.7)	302 (7.9)	304 (6.0)	302 (7.7)	302 (6.6)	303∼(5.5)	303 (4.1)	310 (7.2)
318 (5.2)	316 (5.7)	318 (5.6)	316 (5.7)	318 (4.8)	318 (4.1)	330 (6.0)	320 (7.6)

mμ (ε × 10)$^{-3}$

R = SCH_2COOH	R = 4—$CH_3OC_6H_4$	Z = N
		209 (15.5)
215 (14.6)		
		236 (26.2)
		264 (8)
254 (6.5)		273 (10.8)
263 (6.7)		283 (7.9)
278 (3.4)		
297 (3.4)	288 (23.5)	
308 (3.9)	309 (17.3)	305 (2.8)
323 (3.8)	322 (13)	316 (3.3)

R = C_6H_5	R = SH
240 (11.5)	242 (12.5)
281 (9.4)	285 (10.2)
	340 (2.9)

R′ = hydrogen except where otherwise indicated.

TABLE IV

1,3,4-THIADIAZOLES AND 1,2,4-TRIAZOLES

	M.P., °C.	Empirical Formula	Calcd. C	Calcd. H	Found C	Found H	Solvent	Method of Prepn.	Yield, %
III	173							2	76
VI	220	$C_9H_9N_3S$	56.5	4.6	56.5	4.7	Xylene	A	68
	180[a]	$C_{17}H_{18}ON_3S$	54.2	4.8	54.1	5.1	Ethanol		92
VIa	120	$C_{10}H_{11}N_3S$	58.7	5.4	58.5	5.2	Toluene		79
VII	180	$C_{10}H_{11}N_3S$	58.5	5.4	58.4	5.4	Butanol	A	50
VIIa	189	$C_{12}H_{13}O_2N_3S$	54.9	5.0	54.5	5.1	Ethanol		91

[a] *p*-Toluenesulfonate salt.

removed continuously. When the theoretical amount of alcohol had been collected, the reaction was considered to be complete. The clear, faintly yellow residue was cooled. The precipitate which separated was collected by filtration, and recrystallized. The physical constants and analytical data are collected in the tables.

The conditions for the reaction of orthoesters with heterocyclic hydrazines are set forth in Procedure B.

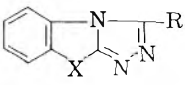
Procedure B. A mixture of 0.1 mole of the heterocyclic hydrazine and 0.11 mole of the orthoester in 60 ml. of xylene was refluxed for 3 to 4 hr. in a flask surmounted with an efficient fractionating column. The alcohol which was formed was continuously removed. When the theoretical amount of alcohol (0.3 mole) had been collected, the reaction was considered to be complete.

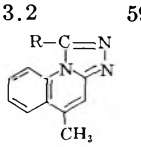
Procedure C gives the conditions for the condensation of *o*-hydroxyphenyl esters with the heterocyclic hydrazines.

Procedure C. A mixture of 0.1-molar quantities of the *o*-hydroxyphenyl ester and of the heterocyclic hydrazines in 50 ml. of 1,2,4-trichlorobenzene was refluxed. The water

TABLE V

CYCLOPENT[a]INDENES

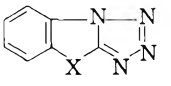


Notes	X = S R	M.P., °C.	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Solvent	Method of Prepn.	Yield, %
					X = S							
	H	178	$C_8H_5N_3S$	54.8	2.8	24.3	54.8	2.7	24.3	H_2O or BuOH	B	76
a, b, c	CH_3	156	$C_9H_7N_3S$	57.1	3.7		57.1	3.7		H_2O	B and E	82, 70
	C_2H_5	126	$C_{10}H_9N_3S$	59.4	4.4		59.6	4.7		BuOH	B	77
d, e	n-C_3H_7	129	$C_{11}H_{11}N_3S$	60.8	5.1	19.4	60.7	4.9	19.1	CH_3CN	E	55
f	i-C_3H_7	b.p. 195–8/1 mm.	$C_{11}H_{11}N_3S$	60.8	5.1	19.4	60.2	4.8	18.8		E	40
g, h	n-C_5H_{11}	95	$C_{13}H_{15}N_3S$	63.6	6.0	17.2	63.6	6.0	17.3	CH_3CN	E	50
	C_6H_5	153	$C_{14}H_9N_3S$	67.0	3.6	12.8	66.9	3.7	13.1	EtOH	G	40
	p-$CH_3OC_6H_4$	145	$C_{15}H_{11}ON_3S$	64.2	3.9	14.9	63.9	4.1	15.4	EtOH	G	30
	OH	238	$C_5H_5ON_3S$	50.1	2.6		50.0	2.5		BuOH	D	63
i	CH_3CO_2	196	$C_{10}H_7O_2N_3S$	51.6	3.0		51.5	2.7		BuOH		88
	SH	250	$C_5H_5N_3S_2$	46.3	2.4	20.3	46.6	2.6	20.8	EtOH	D	63
	SCH_3	129	$C_9H_7N_3S$	49.0	3.2	19.0	49.5	4.0	19.7	EtOH		78
	2—HOC_6H_4	284	$C_{14}H_9ON_3S$	62.8	3.4		62.6	3.6		Trichloro-benzene	C	81
	1-HO-$C_{10}H_6$	259	$C_{18}H_{11}ON_3S$	68.0	3.5		68.3	3.0		BuOH	C	68
	SCH_2COOH	269	$C_{10}H_7O_2N_3S_2$	45.2	2.6	15.8	45.6	3.0	15.8	H_2O + DMF	H	70
	—$(CH_2)_4$—	>300	$C_{20}H_{16}N_6S_2$	59.5	4.0	20.8	58.7	4.4	20.6	DMF		65
					X = Se							
	H	165	$C_8H_5N_3Se$	43.1	2.3	18.9	43.7	2.3	19.3	EtOH	B	80
	CH_3	159	$C_9H_7N_3Se$	45.8	3.0	17.8	45.4	2.8	17.7	EtOH	B	70
	1—$HOC_{10}H_6$—	284	$C_{18}H_{11}ON_3Se$	59.2	3.0		58.9	3.0		$(Me)_2SO$ / EtOH ⟶	C	
	SCH_2COOH	250	$C_{10}H_7N_3SeSO_2$	38.5	2.3	13.5	39.1	2.3	13.7	H_2O + DMF	H	50
					X = NH							
	CH_3	231	$C_9H_8N_4$	62.8	4.7		63.2	5.1		BuOH	B	84
j		218	$C_{19}H_{19}O_3N_3S$	61.8	5.1		61.9	5.4		BuOH		87
	C_2H_5	260	$C_{10}H_9N_4$	64.9	4.9		64.2	5.6		BuOH	B	79
k		220	$C_{17}H_{18}O_3SN_4$	56.9	5.0		56.8	5.2		EtOH		91
l	SH	275 dec.	$C_8H_6N_4S$	50.5	3.2		50.4	3.0			D	59
					X = (CH=CH)							
	H	175	$C_{10}H_6N_2$	71.5	3.6		71.3	4.0		i-BuOH	5	
	CH_3	176	$C_{11}H_9N_2$	72.0	4.9		72.4	5.2		i-BuOH	B	78
	C_2H_5	123	$C_{12}H_{11}N_2$	73.1	5.6		73.5	5.7		Toluene	B	84
	$CH(CH_3)_2$	83–4	$C_{12}H_{13}N_2$	72.4	6.5		72.5	6.4		Ligroin	E	58
	OH	248	$C_{10}H_7ON_2$	65.0	3.8		65.0	3.7		BuOH	D	65
	SH	276									ref. (5)	
	C_6H_5	89	$C_{16}H_{11}N_2$	79.0	4.5		79.1	5.0		Benzene Ligroin		76
	2—HOC_6H_4	>290	$C_{16}H_{11}ON_2$	73.5	4.2		73.5	4.5		$(CH_3)_2SO$	C	87
	2—$HOC_{10}H_6$	289	$C_{20}H_{13}ON_2$	77.1	4.2		77.3	4.0		Trichlorobenzene	C	77
					X = O							
	SH	263	$C_5H_6ON_2$	60.2	3.2		59.9	3.5		EtOH	D	89
												
	H	222–3	$C_{11}H_9N_3$	72.2	4.9	22.9	71.9	5.0	23.0	H_2O	D	80
	SH	300									ref. 5	
	SCH_2COOH	230	$C_{13}H_{11}O_2N_3S$	57.2	4.0	15.4	57.6	4.1	15.2	H_2O-DMF		85

[a] Methyl p-toluenesulfonate salt, m.p. 170°(alc.). *Anal.* Calcd. for $C_{17}H_{17}O_3N_3S$: C, 54.5; H, 4.5. Found: C, 54.2; H, 5.0. [b] Also obtained by substituting $CH_3C{=}OCH(OEt)_2$ for triethyl orthoacetate. [c] The intermediate acetylhydrazinobenzothiazole melted at 214–215°. [d] Butyrylhydrazinobenzothiazole, m.p. 273–274°. [e] B. p. 198–202°/1 mm. [f] Isobutyrylhydrazinobenzothiazole, m.p. 230–231°. [g] Hexanoylhydrazinobenzothiazole, m.p. 240–241°. [h] B.p. 220–225°/1 mm. [i] Obtained by acetylation of the hydroxy compound with acetic anhydride containing sulfuric acid as a catalyst. [j] Methyl p-toluenesulfonate salt of the methyl derivative, m.p. 231°. [k] Methyl p-toluenesulfonate salt. [l] Purified by solution in dilute sodium hydroxide and reprecipitation with acetic acid.

TABLE VI

1,2,3,3a-TETRAZAINDENES AND AZIDES

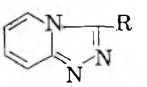


Notes	M.P., °C	Empirical Formula	Calcd. C	H	N	S	Found C	H	N	S	Solvent	Method	Yield, %
						X = S							
[a]	110–1	$C_7H_4N_4S$	47.7	2.3	31.9	18.1	47.9	2.4	31.9	17.7	EtOH	F	98
						X = Se							
[a]	170 dec.	$C_7H_4H_4Se$	37.7	1.8	25.1		38.3	2.0	25.0		BuOH	F	96
						X = N, R = H							
[b–d]	192 dec.	$C_7H_5N_5$	52.8	3.2	44.0		52.9	3.4	44.0		EtOH—H_2O	F	66
						X = N, R = CH_2CH_2OH							
	165 dec.	$C_9H_9N_5O$	53.2	4.4	34.5		53.3	4.6	33.8		H_2O	F	36
						X = O, R = H							
	67	$C_7H_4N_4O$	52.4	2.5			52.6	2.4			EtOH	F	72

[a] The IR curve showed no adsorption in the 4.6-μ region. [b] Strong band at 4.62 μ. [c] Adsorbed in the UV at 235 mμ (9,300) and 288 mμ (15,000). [d] Hydrazinobenzimidazole also gave results different from the other hydrazines when it reacted with formic acid. The product, m.p. 174°, analyzed as the formate salt of the hydrazine.

TABLE VII

1,2,3a-TRIAZAINDENES

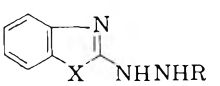


Notes	R	M.P., °C	Empirical Formula	Calcd. C	H	Found C	H	Solvent	Method	Yield, %
[a]	C_6H_5	175[c]	$C_{12}H_9N_3$	73.8	4.6	74.1	4.6	BuOH		89
	1—$HOC_{10}H_6$	239	$C_{16}H_{11}ON_3$	73.5	4.4	73.7	4.5	Trichlorobenzene	C	86
	SH	215	$C_6H_5SN_3$	47.0	3.3	47.4	3.5	BuOH	D	81
[b]		189	$C_6H_5ON_3$	63.1	5.3	63.0	5.4	BuOH	D	84

[a] 2-(2-Pyridyl)benzhydrazide, m.p. 202°, was refluxed in phenol as described in Procedure E. [b] Ring closure did not take place. This material is 1-phenyl-4-(2-pyridylsemicarbazide). [c] M.p. given as 176° in *J. Chem. Soc.*, 727 (1957).

TABLE VIII

AROYLHYDRAZIDES



Notes	R	M.P., °C	Empirical Formula	Calcd. C	H	Found C	H	Solvent
			X = S					
[a]	4—$CH_3OC_6H_4CO$	184	$C_{15}H_{13}O_2N_3S$	60.1	4.3	60.0	4.3	BuOH
[b]		257–8	$C_{22}H_{18}O_4N_3S$	58.5	4.0	58.4	4.2	EtOH
	$C_6H_5CH=CHCO$	258	$C_{16}H_{13}ON_3S$	65.2	4.3	65.6	4.9	
			X = (CH=CH)					
[d]	C_6H_5CO	204						
[c]		264 dec.	$C_{24}H_{23}O_4N_3$	64.2	5.1	64.2	5.0	H_2O
			X = O					
	C_6H_5NHCO	225	$C_{14}H_{12}O_2N_4$	62.6	4.4	62.8	4.5	BuOH

[a] Calcd.: N, 14.2. Found: 13.9. [b] Methyl *p*-toluenesulfouate salt of the 184° compound. [c] Methyl *p*-toluenesulfonate salt of 204° compound. [d] R. G. Fargher and R. Furness, *J. Chem Soc.*, **107**, 688 (1915).

which was formed distilled over first at 98–101°. The temperature at the stillhead then rose sharply and phenol distilled over at 180–190°. The reaction was considered complete when the stillhead temperature was 203°. Reaction was usually complete in about 2 hr. The product which had crystallized was collected by filtration and washed with alcohol and dried.

The hydroxy and mercapto derivatives were produced as follows.

Procedure D. A mixture of 0.1 mole of the isocyanate or isothiocyanate and heterocyclic hydrazine in 60 ml. of trichlorobenzene was refluxed for about 2.5 hr. After cooling to room temperature, the crystals which had separated were collected by filtration, washed well with benzene, and extracted twice with 400-ml. portions of warm 5% sodium hydroxide.

The extracts were combined and were acidified with acetic acid. The precipitate was collected by filtration, and crystallized from a suitable solvent.

Procedure E.[11] The procedure for cyclization with phenol is as follows. The heterocyclic hydrazine and a large excess of the appropriate aliphatic acid were refluxed 2 hr., cooled, and the acyl hydrazine collected by filtration. The acyl hydrazine was refluxed 2–20 hr. with 2.5 times its weight of phenol and the phenol was then removed by steam distillation. The residue was either recrystallized or first distilled *in vacuo* and then recrystallized.

Procedure F. Nitrous acid ring closure. The heterocyclic hydrazine was dissolved in 15 times its weight of 50% aqueous acetic acid, the solution cooled to 10–15°, and the calculated amount of sodium nitrite in a small amount of water was added. The tetraza compound usually separated at once, but the reaction mixture was allowed to stand in the cold for an hour before the product was collected.

Procedure G. The thiazaindenes substituted in the 3-position by an aromatic group were prepared in the following manner. A mixture of 0.1 mole each of 2-chlorobenzothiazole, arylhydrazide, and sodium phenoxide in 40–50 ml. of phenol was refluxed for 20 hr. The solvent was steam-distilled and the residue recrystallized from the appropriate solvent. Several runs made without sodium phenoxide resulted in slightly lower yields of the product.

Procedure H gives the conditions for the reaction of the mercapto compounds with sodium chloroacetate.

Procedure H. A mixture of 1 part each of mercapto compound and sodium chloroacetate in 10 parts of water was heated 15 min. on the steam bath, 1 part of sodium carbonate was added, and the heating was continued for 1 hr. After any insoluble material present had been filtered off, the filtrate was acidified with acetic acid and the product was collected and recrystallized.

2-Chlorobenzoselenazole. To 41 g. (0.19 mole) of 2-mercaptobenzoselenazole[12] was added 30 g. (0.22 mole) of sulfur monochloride in small portions, with stirring. When the exothermic reaction had subsided, external heat was applied until the frothing ceased; the mixture was then refluxed for 30 min. and allowed to stand at room temperature overnight. The dark tar was distilled to yield 36 g. of product, b.p. 135°/10 mm.

2-Hydrazinobenzoselenazole. A mixture of 36 g. (0.167 mole) of 2-chlorobenzoselenazole, 18.5 g. of hydrazine hydrate, and 10 ml. of water was heated on the steam bath for 1 hr. A solid began to separate almost at once and, after the reaction mixture was chilled, it was collected. Recrystallization from ethanol gave 25 g. of product, m.p. 226–227°.

Anal. Calcd. for $C_7H_7N_3Se$: C, 39.6; H, 3.3; N, 19.8. Found: C, 39.7; H, 3.0; N, 20.3.

1,2-Bis(8-thia-1,2,3a-triazacyclopent[a]inden-3-yl)ethane. A mixture of 33 g. (0.2 mole) of hydrazinobenzothiazole and 15 g. (0.1 mole) of adipic acid in 100 ml. of phenol was refluxed 4 hr. and the phenol removed by steam distillation. The solid residue was recrystallized, the yield and physical properties being indicated in Table V.

The methyl p-toluenesulfonate salts were prepared by heating equal weights of the compound to be quaternized and methyl *p*-toluenesulfonate for 5 hr. on the steam bath. The crystalline product was washed with acetone and crystallized from a suitable solvent.

2,x-Dibenzoylhydrazinobenzothiazole. A mixture of hydrazinobenzothiazole (8.2 g.; 0.05 mole) and 14 ml. of benzoyl chloride in 50 ml. of pyridine was allowed to stand for 2 hr. The mixture was poured into water and acidified with acetic acid. On standing overnight, the oily precipitate solidified. The product was collected by filtration and recrystallized from toluene to give 17 g. of product, m.p. 215°, yield 91%.

Anal. Calcd. for $C_{21}H_{16}O_2N_3S$: C, 67.2; H, 4.3; N, 11.2; S, 8.6. Found: C, 67.2; H, 4.1; N, 11.0; S, 8.8.

1,2,3,9a-Tetrazabenz[e]indene (XVIII). *Sodium azide method.* A mixture of 16.4 g. of 2-chloroquiuoline and 8.0 g. of sodium azide in 60 ml. of 15% aqueous ethanol was refluxed for 6 hr. The solution was filtered while still hot. On chilling, 8.0 g. of XVIII, m.p. 153–154°, separated. A mixed melting point with an authentic sample of XVIII showed no depression of melting point.

Acknowledgment. We are indebted to D. Stewart and Thelma Davis, of the Chemistry Department, and E. R. Richardson, of the Physics Department, for the determination of the ultraviolet and infrared spectra.

ROCHESTER 4, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD RESEARCH INSTITUTE]

Some Nitrogen-Containing Ferrocene Derivatives

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The preparation of several derivatives of ferrocenylamine and a number of *N*-substituted ferrocenecarboxamides is described.

A number of *N*-substituted ferrocenecarboxamides and ferrocenylamine derivatives were prepared for evaluation as high-temperature antioxidants. It had been found[1] that *N*-phenylferrocenecarboxamide inhibited oxidative gelation of a dimethylsilicone fluid, and it was of interest to investigate other ferrocenecarboxamides. Furthermore, many aromatic amines are known to be effective antioxidants, and it seemed possible that if the ferrocene system possessed oxidation-inhibiting-properties, ferrocenylamine and its derivatives might show enhanced antioxidant activity.

Two syntheses of ferrocenylamine have been published. One involves lithiation of ferrocene and treatment of ferrocenyllithium with benzyloxyamine.[2] The other method proceeds through the azide of ferrocenecarboxylic acid, subsequent rearrangement to the isocyanate (isolated from benzyl alcohol as the benzylurethan), and reductive cleavage to the amine.[3] Neither method appeared attractive because of poor over-all yields. Consequently, the following possibilities were examined briefly: nitration of ferrocene using (a) fuming nitric acid in glacial acetic acid[4] at $-10°$, (b) nitric acid and urea;[5] nitrosation using (a) ferrocene and sodium nitrite in acetic acid, (b) chloromercuriferrocene[6] in chloroform with butyl nitrite and hydrochloric acid,[7] and with gaseous nitrosyl chloride,[8,9] (c) ferrocenyllithium with nitrosyl chloride[8,9] in ether. In each case, oxidation to the blue ferricinium salt took place, and only ferrocene was recovered on reduction.

Minor changes in the published procedures for ferrocenylamine afforded some improvement in yield. The reaction between ferrocenyllithium and benzyloxyamine in our hands gave less than a 1% yield over-all from ferrocene. By substitution of methoxyamine for benzyloxyamine, the over-all yield of ferrocenylamine was increased to 8%, or 28% based on the amount of ferrocene recovered in the lithiation step. Preparation of ferrocenylamine from ferrocenecarboxylic acid by the Curtius rearrangement was also improved by use of milder conditions in the preparation of ferrocenecarboxylic acid chloride and in the hydrogenolysis of ferrocenylamine benzylurethan. The over-all yield of ferrocenylamine by this method was 18% from ferrocenecarboxylic acid, or 7% from ferrocene.

Ferrocenylamine was converted into *N*-ferrocenyl-*p*-toluenesulfonamide in 74% yield by treatment with a slight excess of *p*-toluenesulfonyl chloride in pyridine. 1,3-Diferrocenylurea was obtained in 24% yield by treating ferrocenylamine in pyridine solution with a $^1/_2$-molar equivalent of phosgene dissolved in benzene. Reaction of ferrocenylamine in pyridine solution with ferrocenecarboxylic acid chloride in benzene afforded 22% of *N*-ferrocenylferrocencarboxamide.

It was found that amides of ferrocenecarboxylic acid were best prepared from ferrocenecarboxylic acid chloride by reaction with a molar equivalent of amine in pyridine or an excess of amine in refluxing toluene. Using these methods, amides were prepared from 2-aminothiazole, morpholine, ethanolamine, phenothiazine, and *N*-phenyl-*N*-1-naphthylamine, as well as from ferrocenylamine. In the preparation of 10-(ferrocenylcarbonyl)phenothiazine a second product with the same composition was also obtained. Presence of N—H absorption in the infrared, and carbonyl absorption comparable to that of benzoylferrocene, suggested that carbonacylation may have occurred to form an isomeric ferrocenylcarbonylphenothiazine. An attempt to prepare *N*-2-thiazolylferrocenecarboxamide directly from ferrocenecarboxylic acid and 2-aminothiazole by the phosphazo reaction[10] resulted in the formation of only 8% of the amide and the recovery of 60% of unreacted acid.

The main product from attempts to condense ferrocenecarboxylic acid and 2-aminothiazole by treatment with dicyclohexylcarbodiimide in chloroform solution was 1-ferrocenylcarbonyl-1,3-dicyclo-

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(2) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and L. S. Shilovtseva, *Doklady Akad. Nauk S.S.S.R.*, 102, 535 (1955).
(3) F. S. Arimoto and A. C. Haven, Jr., *J. Am. Chem. Soc.*, 77, 6295 (1955).
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hexylurea, the adduct between the acid and the carbodiimide. Ferrocenecarboxylic anhydride (20%) and a small amount of ferrocenecarboxylic acid were also obtained, but none of the amide. The anhydride was identified by comparison with a sample of authentic ferrocenecarboxylic anhydride, prepared in 56% yield by treating ferrocenecarboxylic acid chloride with water in pyridine solution.[11] Attempted condensation of ferrocenecarboxylic acid and 2-aminothiazole with dicyclohexylcarbodiimide in acetonitrile solution afforded 1-ferrocenylcarbonyl-1,3-dicyclohexylurea in 86% yield.

EXPERIMENTAL[12]

Ferrocenecarboxylic acid. Although ferrocenecarboxylic acid is available by several synthetic routes,[13] it was most easily obtained by lithiation of ferrocene in a tetrahydrofuran-ether mixture and carbonation of the lithium salt.[14] The yield was 37%, or 47% based on recovered ferrocene. A 32% yield of the insoluble 1,1'-ferrocenedicarboxylic acid was also obtained.

Ferrocenecarboxylic acid chloride. To a stirred solution of 0.23 g. (0.0011 mole) of phosphorus pentachloride in 2.5 ml. of dry benzene, 0.23 g. (0.0010 mole) of ferrocenecarboxylic acid was added, and stirring at room temperature was continued for 2 hr. with exclusion of atmospheric moisture. The mixture was then decanted and concentrated at 25–30° to remove benzene and phosphorus oxychloride. The acid chloride, obtained as a residual dark oil, was dissolved in benzene or other suitable solvent, and the solution was decanted and used directly for acylation.

Ferrocenylamine from ferrocenecarboxylic acid azide. The procedure of Arimoto and Haven[3] was used with minor modifications. Ferrocenecarboxylic acid chloride, prepared as described above, was converted to the acid azide. The yield of azide based on ferrocenecarboxylic acid used was 38%. Ferrocenylamine benzylurethan was obtained in 65% yield upon rearrangement of the azide in benzyl alcohol; it was purified by chromatography on alumina in benzene followed by recrystallization from a mixture of ether and petroleum ether. Reductive cleavage of the urethan (m.p. 113–114°) was accomplished at low pressures. A 5% palladium-on-carbon catalyst (0.20 g.) was added to a solution of 2.70 g. (0.00806 mole) of ferrocenylamine benzylurethan in 80 ml. of absolute ethanol. The mixture was shaken under hydrogen at 50 p.s.i. for 2 hr. at 25° and then at 45° for 2 hr. The solution was filtered, the filtrate was taken to dryness under reduced pressure, and the solid residue was dissolved in 25 ml. of ether. The ether solution was extracted with three 5-ml. portions of 1*N* hydrochloric acid. The aqueous extracts were filtered and then made basic with potassium hydroxide. The precipitate which formed was separated by filtration and dried *in vacuo*, giving 1.28 g. (84%) of crude ferrocenylamine, m.p. 127–137°. Recrystallization from ligroin afforded 1.15 g., m.p. 145–153°. Infrared absorption maxima at 2.95 μ, 6.20 μ, and 6.68 μ corresponded to those reported.[3]

Ferrocenylamine from ferrocenyllithium. A solution of 13.0 g. (0.070 mole) of ferrocene in 200 ml. of anhydrous tetrahydrofuran was cooled to −30° under a nitrogen atmosphere, and a solution of 0.21 mole of butyllithium in 160 ml. of ether was added dropwise during 25 min. The mixture was stirred for 2 hr. at 0° and 4 hr. at 25°. A solution of 10.3 g. (0.22 mole) of methoxyamine in 75 ml. of anhydrous ether was added dropwise during 30 min. while the reaction mixture was stirred at −20°. The mixture was allowed to warm gradually to room temperature and stirred for 4 hr. Then 10% hydrochloric acid was added slowly with stirring until a *p*H of 2 was attained in the aqueous layer. The ether layer was separated, dried over magnesium sulfate, and evaporated to give 9.5 g. of ferrocene (73% recovery) after recrystallization from benzene. The aqueous layer was made strongly basic with potassium hydroxide solution, and the precipitate which formed was extracted into ether. The ether extracts were in turn extracted with 2*N* hydrochloric acid, and the acidic solution was made basic as before and again extracted with ether. The final ether extracts were dried over magnesium sulfate and evaporated to a brown solid residue. Recrystallization of this material from an ether–petroleum ether mixture afforded 1.06 g. of ferrocenylamine (8%, or 28% based on the amount of ferrocene recovered), m.p. 140–145°. The infrared spectrum was identical to that reported above. Sublimation at 70° (2 mm.) separated a few mg. of nonvolatile material having essentially the same infrared spectrum; this may have been diaminoferrocene, but was not characterized. The sublimed ferrocenylamine had m.p. 147–152° (lit.[3,2] m.p. 151–155°, 153–155°).

N-Ferrocenyl-p-toluenesulfonamide. A solution of 0.080 g. (0.00040 mole) of ferrocenylamine in 0.8 ml. of pyridine was treated with 0.095 g. (0.00050 mole) of *p*-toluenesulfonyl chloride and the mixture was heated for 1 hr. on the steam bath. On addition of water (5 ml.) to the cooled solution, a dark oil separated which solidified after a few minutes standing. This dark solid was separated by filtration and crystallized from a mixture of benzene and ligroin to give 0.105 g. (74%) of *N*-ferrocenyl-*p*-toluenesulfonamide, m.p. 168–174°. After two recrystallizations from a benzene-ligroin mixture, 0.085 g. of material was obtained, m.p. 177–179°. The infrared spectrum showed a strong —SO_2— absorption at 8.58–8.65 μ and N—H absorption at 3.05 μ.

Anal. Calcd. for $C_{17}H_{17}FeNO_2S$: C, 57.48; H, 4.82; Fe, 15.72. Found: C, 57.76; H, 4.89; Fe, 15.65.

1,3-Diferrocenylurea. A solution of 0.240 g. (0.0012 mole) of ferrocenylamine in 1.5 ml. of pyridine was cooled to 5°, and a benzene solution (0.95 ml.) containing 0.059 g. (0.00060 mole) of phosgene was added dropwise with stirring. After addition was complete, the mixture was allowed to stand for 60 hr. at room temperature. Water (5 ml.) was added and the mixture was extracted with three 5-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate, filtered, and concentrated to a solid residue. Crystallization of this material from a benzene-chloroform mixture afforded 0.061 g. (24%) of crude 1,3-diferrocenylurea, which was recrystallized from methanol. 1,3-Diferrocenylurea did not melt below 250°. The

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(12) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Under these conditions, ferrocene exhibits a liquid crystal region from about 140° to 173°, where true melting is observed by sudden decrease in viscosity and loss of birefrigence. This phenomenon seems not to have been reported, probably because the rapid sublimation of ferrocene near the melting point makes its observation by this method difficult. Infrared spectra were determined on KBr disks with a Perkin-Elmer spectrophotometer, model 21, and on a Beckman spectrophotometer, model IR4. All the compounds prepared in this study were monosubstituted ferrocene derivatives; most showed infrared bands at 3.22–3.27 μ due to aromatic C—H bands, at 9.00–9.08 μ and 9.97–10.03 μ characteristic of monosubstitution, and weak maxima or shoulders at 7.07–7.10 μ. The few exceptions are mentioned along with the bands listed as characteristic for each compound.

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(14) D. W. Mayo, P. D. Shaw, and M. Rausch, *Chem. and Ind.*, 1388 (1957).

infrared spectrum showed prominent amide absorption maxima at 6.04 μ and 6.35 μ and N—H absorption at 3.05 μ.

Anal. Calcd. for $C_{21}H_{20}Fe_2N_2O$: C, 58.91; H, 4.71. Found: C, 58.57; H, 5.03.

N-Ferrocenylferrocenecarboxamide. Ferrocenecarboxylic acid chloride obtained from 0.092 g. (0.00040 mole) of the free acid was dissolved in 0.5 ml. of benzene and added slowly to a solution of 0.080 g. (0.00040 mole) of ferrocenylamine in 0.5 ml. of pyridine. A brown precipitate formed immediately. The mixture was allowed to stand overnight and then heated on a steam bath for 45 min. The precipitate was separated by filtration and dissolved in chloroform. A small amount of chloroform-insoluble material was removed by filtration. Upon extraction of the chloroform solution with 2% sodium bicarbonate solution and acidification of the extracts, 0.023 g. (25%) of unreacted ferrocenecarboxylic acid was recovered. The extracted chloroform solution was dried and concentrated to a solid residue which was recrystallized from benzene, then from methanol, giving 0.035 g. (22%) of *N*-ferrocenylferrocenecarboxamide. This compound did not melt below 300°. The infrared spectrum showed amide absorption bands at 6.10 μ and 6.40 μ, and an N—H band at 3.03 μ. *N*-Ferrocenylferrocenecarboxamide ignited on combustion for microanalysis; the low values obtained for carbon may be explained by this fact.

Anal. Calcd. for $C_{21}H_{19}Fe_2NO$: C, 61.03; H, 4.65; N, 3.39. Found: C, 60.35, 60.16; H, 4.89, 4.88; N, 3.64.

N-2-Thiazolylferrocenecarboxamide. Ferrocenecarboxylic acid chloride prepared from 0.092 g. (0.00040 mole) of the acid was dissolved in 0.5 ml. of benzene and added to a solution of 0.040 g. (0.00040 mole) of 2-aminothiazole in 0.5 ml. of pyridine. After the mixture was allowed to stand at room temperature for 40 hr., 5 ml. of 2*N* hydrochloric acid and 5 ml. of benzene were added. The benzene layer was separated, the aqueous layer was extracted twice with 5-ml. portions of benzene, and the benzene solutions were combined. Extraction of the benzene solution with 2% sodium carbonate solution permitted the recovery of 0.010 g. of ferrocenecarboxylic acid. The extracted benzene solution was dried over magnesium sulfate, filtered and concentrated to a solid residue. The solid was recrystallized from ligroin, and 0.046 g. (37%) of *N*-2-thiazolylferrocenecarboxamide, m.p. 183–188°, was obtained. After further recrystallization from aqueous methanol, the product melted at 190.5–192.0°. The infrared spectrum showed amide bands at 6.05 μ and 6.53 μ; N—H absorption was observed at 2.92 μ. The characteristic C—H band[12] near 3.25 μ was obscured by broad absorption in this region.

Anal. Calcd. for $C_{14}H_{12}FeN_2OS$: C, 53.86; H, 3.88; Fe, 17.9. Found: C, 54.10; H, 4.08; Fe, 17.5.

4-(Ferrocenylcarbonyl)morpholine was obtained by the above procedure using ferrocenecarboxylic acid chloride prepared from 0.69 g. (0.0030 mole) of acid and 0.30 g. (0.0035 mole) of morpholine in 2.0 ml. of pyridine. Extraction with benzene and recrystallization from ligroin gave 0.35 g. (39%) of amide, m.p. 127.5–130°. The infrared spectrum showed strong amide absorption at 6.20 μ. The band at 10.0 μ characteristic of monosubstituted ferrocene[12] was partially obscured in this compound by a maximum at 9.93 μ.

Anal. Calcd. for $C_{15}H_{17}FeNO_2$: C, 60.22; H, 5.73. Found: C, 60.36; H, 5.79.

N-[2-(Ferrocenylcarboxy)ethyl]ferrocenecarboxamide was obtained by the same procedure (for *N*-2-thiazolylferrocenecarboxamide) using ferrocenecarboxylic acid chloride prepared from 0.92 g. (0.0040 mole) of acid and 0.098 g. (0.0016 mole) of ethanolamine in 2.5 ml. of pyridine. The product precipitated on acidification of the reaction mixture. Extraction of the mixture with benzene recovered 14% of ferrocenecarboxylic acid. The solid product was extracted with chloroform and 0.18 g. (10%) of amide, m.p. 202–204°, was obtained after recrystallization from methanol. The infrared spectrum showed amide bands at 6.13 μ and 6.53 μ and ester carbonyl absorption at 5.86 μ.

Anal. Calcd. for $C_{21}H_{23}Fe_2NO_3$: C, 59.42; H, 4.78. Found: C, 59.13; H, 5.00.

N-Phenyl-N-1-naphthylferrocenecarboxamide. Ferrocenecarboxylic acid chloride, prepared from 0.92 g. (0.0040 mole) of the acid, was dissolved in 15 ml. of toluene and treated with 1.75 g. (0.0080 mole) of *N*-phenyl-1-naphthylamine. The mixture was heated under reflux for 4 hr., then concentrated to remove the solvent. The residue was triturated with ether to remove unreacted amine. After several recrystallizations of the ether-insoluble material from benzene, 0.35 g. (20%) of *N*-phenyl-*N*-1-naphthylferrocenecarboxamide was obtained, m.p. 237–240°. The infrared spectrum showed amide carbonyl absorption at 6.13 μ.

Anal. Calcd. for $C_{27}H_{21}FeNO$: C, 75.18; H, 4.91. Found: C, 75.42; H, 4.88.

10-(Ferrocenylcarbonyl)phenothiazine. A toluene solution (15 ml.) of ferrocenecarboxylic acid chloride prepared from 0.99 g. (0.0043 mole) of acid was treated with 1.71 g. (0.0086 mole) of phenothiazine as described for *N*-phenyl-*N*-1-naphthylferrocenecarboxamide. The residue, after removal of toluene, was dissolved in benzene and separated into 3 components by chromatography on 20 g. of alumina. Elution with benzene afforded 0.80 g. of unreacted phenothiazine, followed in a second fraction by 0.55 g. of 10-(ferrocenylcarbonyl)phenothiazine (30%), m.p. 163–165° after recrystallization from methanol. The infrared spectrum showed amide carbonyl absorption at 6.12 μ.

Anal. Calcd. for $C_{23}H_{17}FeNOS$: C, 67.17; H, 4.16; S, 7.81. Found: C, 67.33; H, 4.27; S, 7.65.

Elution of the chromatogram with 10% ether in benzene afforded an isomeric product, which was recrystallized from ether, m.p. 203–204°. That acylation of an aromatic ring in phenothiazine may have occurred to give a ferrocenyl ketone was suggested by the infrared spectrum. Presence of a band at 3.01 μ identical with the N—H band in phenothiazine indicated absence of reaction on the nitrogen. Absorption at 6.27 μ and 6.38 μ due to aromatic unsaturation in phenothiazine was also present, as well as the characteristic ferrocene bands[12] at 3.25 μ, 7.08 μ, 9.05 μ, and 10.00 μ. A strong band at 6.17 μ compared favorably with the ketone carbonyl absorption of benzoylferrocene at 6.13 μ.[15]

Anal. Calcd. for $C_{23}H_{17}FeNOS$: C, 67.17; H, 4.16; S, 7.81. Found: C, 66.91; H, 4.39; S, 7.34; 7.42.

Ferrocenecarboxylic anhydride. Ferrocenecarboxylic acid chloride, obtained from 0.23 g. (0.0010 mole) of the free acid, was dissolved in 7.5 ml. of dry benzene. The solution was cooled to 5–10°, and 1.0 ml. of pyridine was added dropwise, followed by the addition of 0.10 ml. of water to the cold solution.[11] The solution was agitated for 30 min., allowed to stand overnight, and filtered. The filtrate was washed with *N* hydrochloric acid to remove pyridine until the aqueous wash solutions were strongly acidic (*p*H 2). The benzene solution was washed with four 6-ml. portions of 1% aqueous sodium carbonate to remove ferrocenecarboxylic acid. After acidification of the basic solutions and extraction with ether, 0.055 g. of ferrocenecarboxylic acid (24%) was recovered from the ether extracts. The extracted benzene solution was washed with water and dried over magnesium sulfate. Filtration and evaporation of the solution afforded a dark reddish oil which crystallized on standing. After recrystallization from ligroin, 0.123 g. (56%) of ferrocenecarboxylic anhydride was obtained, m.p. 140–142°, m.p. 143–145° after further recrystallization. The infrared spectrum showed strong carbonyl absorption bands at 5.67 and 5.84 μ. The monosubstituted ferrocene band[12] near 10.0 μ was obscured by a maximum at 9.90 μ. A strong and distinct band at 8.06 μ was assigned tentatively to the C—O—C grouping, although the band was displaced from the expected range.

Anal. Calcd. for $C_{22}H_{18}Fe_2O_3$: C, 59.77; H, 4.10. Found: C, 60.06; H, 4.34.

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(15) N. Weliky and E. S. Gould, *J. Am. Chem. Soc.*, 79, 2742 (1957).

1-Ferrocenylcarbonyl-1,3-dicyclohexylurea. A solution of 0.046 g. (0.00020 mole) of ferrocenecarboxylic acid in 5 ml. of acetonitrile was treated with 0.020 g. (0.00042 mole) of 2-aminothiazole, followed by 0.043 g. (0.00042 mole) of dicyclohexylcarbodiimide. An orange-brown crystalline solid began to crystallize from the solution after standing 1 hr. at room temperature. After 20 hr., 1 drop of glacial acetic acid was added (to destroy any unreacted carbodiimide) and the mixture was filtered. Unreacted 2-aminothiazole (0.20 g.) was recovered from acidic extracts of the filtrate. The filtrate was concentrated to an orange-brown solid which was combined with the precipitate collected on the filter. The combined product was recrystallized from aqueous methanol and from ligroin to give 0.075 g. (86%) of 1-ferrocenylcarbonyl-1,3-dicyclohexylurea, m.p. 171–172°.

Anal. Calcd. for $C_{24}H_{32}FeN_2O_2$: C, 66.05; H, 7.39; N, 6.42. Found: C, 66.32; H, 7.59; N, 6.50.

The infrared spectrum showed N—H absorption at 3.05 μ and carbonyl absorption at 6.20 μ, but a strong band at 5.89 μ could not be assigned with certainty.[16]

Acknowledgment. This work was carried out under USAF Contract No. AF 33(616)-5276, and was administered through the Materials Laboratory, Wright Air Development Center with Mr. George Baum acting as project engineer.

MENLO PARK, CALIF.

(16) The identity of the compound was verified by comparison with the spectrum of an authentic sample[17] of 1-benzoyl-1,3-dicyclohexylurea, which also showed a strong band at 5.88 μ and N—H absorption at 3.02 μ, although the carbonyl peak was at 6.07 μ. Both compounds showed aromatic CH absorption at 3.25 μ, CH_2 bands at 3.42 μ and 3.50 μ, and unassigned maxima at 6.48–6.53 μ, 6.88 μ, 8.11 μ, and 11.21 μ. 1-Ferrocenylcarbonyl-1,3-dicyclohexylurea showed an additional peak at 2.93 μ which was not assigned.

(17) F. Zetzsche and A. Fredrich, *Ber.*, 72B, 1735 (1939).

[CONTRIBUTION NO. 113 FROM THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

Desulfuration Experiments with 1,3-Oxathiolan-5-ones

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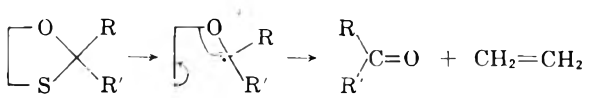
By condensation of mercaptodiphenylacetic acid with several aldehydes and ketones, 1,3-oxathiolan-5-ones were prepared, and by desulfuration with Raney nickel the original carbonyl compound was regenerated. When an electron attracting group is present in alpha position to the oxathiolanone ring, diphenylacetic ester is formed. Diphenylketene or the corresponding biradical is regarded as the probable intermediate in the desulfuration mechanism.

It has been shown[1] that on desulfuration of oxathiolanes formed by condensation of β-mercaptoethanol with steroidal ketones the original carbonyl compound is regenerated and the β-mercaptoethanol moiety is converted to ethylene or ethylene derivatives by the following mechanism:



On the other hand no ethyl ether was obtained.

Later Djerassi *et al.*[2,3] studied this reaction in more detail by carrying out the condensation of β-mercaptoethanol derivatives with several additional ketones. Following desulfuration they isolated the moieties corresponding to the original carbonyl compound and to the β-mercaptoethanol derivative. In polar solvents these authors found an introduction of oxygen in the β-mercaptoethanol moiety[2,3] whereas in benzene as the solvent the corresponding ethylenes or ethanes are obtained due to fission and rearrangement of the intermediate 1,4-biradical.[1] On the other hand, Jaeger and Smith[4] have described a saturation of the 1,4-biradical yielding the ethyl ether when there is an electron attracting group in the alpha position to the oxathiolane ring.

The above mentioned results stimulated us to study the influence of a carbonyl group in the oxathiolane ring on the course of the desulfuration reaction.

Diphenyl substituted oxathiolanones can be prepared conveniently by condensation of mercaptodiphenylacetic acid (I) with carbonyl compounds.[5] Several 1.3-oxathiolan-5-ones have been prepared in this manner by Bistrzycki and Brenken.[6] Using *p*-toluenesulfonic acid as the condensing agent, we have prepared the previously reported 2,4,4 triphenyloxathiolan-5-one (IIa).[6] 9-Anthraldehyde[7] yielded 2(9-anthryl), 4,4-diphenyl-1,3-oxathiolan-5-one (IIb). This yellow substance has the interesting property that when exposed to sunlight the crystals become bluish green and change back to yellow immediately when returned to dim light. This phenomenon can be repeated several times but the intensity of the color change gradually decreases until the substance remains

(1) J. Romo, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, 73, 4961 (1951).

(2) C. Djerassi, M. Gorman, and J. A. Henry, *J. Am. Chem. Soc.*, 77, 4647 (1955).

(3) C. Djerassi, M. Shamma and T. Y. Kan, *J. Am. Chem. Soc.*, 80, 4723 (1958).

(4) R. A. Jaeger and H. Smith, *J. Chem. Soc.*, 160 (1955).

(5) H. Becker and A. Bistrzycki, *Ber.*, 47, 3149 (1914).

(6) A. Bistrzycki and B. Brenken, *Helv. Chim. Acta*, 3, 447 (1920).

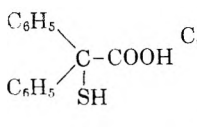
(7) L. F. Fieser, J. L. Hartwell and J. E. Jones, *Org. Syntheses*, 11, 20 (1940).

TABLE I

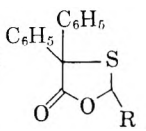
Oxathiolanone (G.)	Solvent, Ml.	Reaction Time (Hr.)	Products of Desulfuration and Yields (in Mg.)
IIa (3)	Ethanol (150)	5	Diphenylacetic acid (40) Ethyl diphenyl acetate (255)
IIa (.580)	Acetone (50)	4	Diphenylacetic acid (67) benzaldehyde[a] (10)
IIa (1.5)	Benzene (100)	5	Diphenylacetic acid (35) benzaldehyde[a] (180)
IVa (2)	Ethanol (70)	4	Diphenylacetic acid (40) Ethyl diphenyl acetate (518) Diphenylethanol (60)
IVa (2)	Acetone (100)	4	Diphenylacetic acid (180) cyclohexanone[a] (600)
IVa (3)	Benzene (100)	5	Diphenylacetic acid (3) Diphenylethanol (255) cyclohexanone[a] (390)
IVa (1)	Benzene (150) Aniline (5)	5	Diphenylacetanilide (385) cyclohexanone[a] (65)
IVb (3.525)	Ethanol (170)	5	Cyclohexanediol-diphenylacetate (1.195)
V (2)	Ethanol (250)	10	Diphenylacetic acid (320) oxindol (65)
VI (1.85)	Ethanol (300)	8	Ethyl diphenyl-acetate (50) androstan-17β-ol-acetate (65) androstan-3β,17β-diol, 17-mono-acetate (535)

[a] Isolated and weighed as the dinitrophenyl hydrazone.

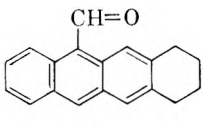
yellow in direct sunlight. The color change is observed only in the solid state but not in solutions exposed either to sun light or ultraviolet light. The substance is not thermochromic or piezochromic. The anthryl substituted 2-(2,3-tetramethylene-9-anthryl), 4,4-diphenyl, 1,3-oxathiolan-5-one (IIc) prepared by condensing 2,3-tetramethyleneanthracene-9-aldehyde (III) with mercaptodiphenylacetic acid (I) does not show this color change. The aldehyde (III) was obtained applying the method of Fieser, Hartwell, and Jones[7] to 2,3-tetramethyleneanthracene.



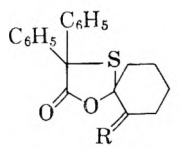
I



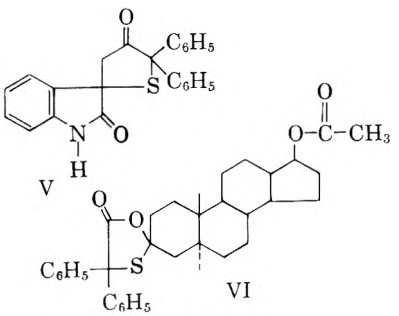
IIa. R = Phenyl
b. R = 9-Anthryl
c. R = 2,3, Tetramethylene-9-anthryl



III

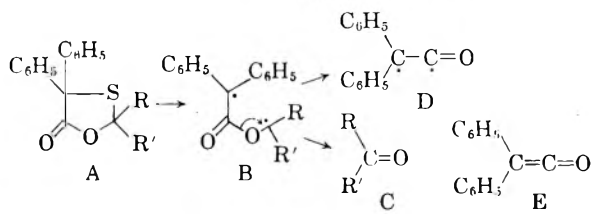


IVa. R = H_2
b. R = O



V

VI



A B C D E

(8) The Raney nickel was prepared according to the method of Mozingo [R. Mozingo, *Org. Syntheses*, 21, 15 (1941)] and used four months after its preparation.

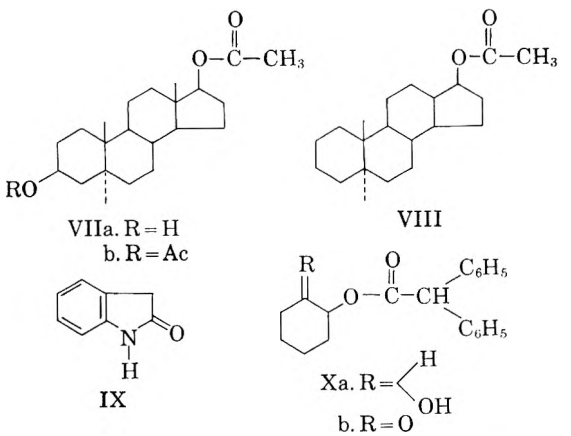
The 1,3 - oxathiolan - 5 - ones of cyclohexanone (IVa), cyclohexanedione (IVb), isatin (V), and dihydrotestosterone acetate (VI) have also been prepared.

Desulfurations[8]: The desulfuration of mercaptodiphenylacetic acid (I) in ethanol has been found to yield diphenylacetic acid. The results of the desulfurations of the 1,3-oxathiolan-5-ones are given in Table I.

The results of the present investigation indicate that the desulfurations proceed by formation of a 1,4-biradical (B)[9] which rearranges to a 1,2-biradical (D) and the original carbonyl compound (C). Eventually the biradical (D) may further rearrange to diphenylketene (E). The products obtained in the desulfurations of oxathiolanones (IIa), (IVa), (V) and (VI) can be formed by way of the biradical (D) or diphenyl ketene (E). The solvent does not appear to have a decisive influence on the reaction mechanism. It is possible that the active species (D) or (E) in the presence of a suitable solvent like ethanol, form ethyl diphenylacetate or with water, diphenylacetic acid, whose formation can be ascribed to the presence of water in the Raney nickel which is extremely difficult to remove completely. Furthermore D or E can be saturated by the hydrogen adsorbed on the Raney nickel, affording diphenylethanol. When benzene was used in the desulfuration, the Raney nickel was supended in the solvent, prior to the addition of the oxathiolanone, and benzene distilled off, until no moisture was detected in the distillate. In spite of these precautions small amounts of diphenylacetic acid were obtained; however in the latter case diphenylethanol is the main product because benzene is inert towards D or E and only the

(9) For the free radical mechanism in the desulfuration see W. A. Bonner, *J. Am. Chem. Soc.*, 74, 1034 (1952) and H. Hauptmann, B. Wladislaw, L. L. Nazario, and W. F. Walter, *Ann*, 576, 45 (1952).

hydrogen adsorbed in the nickel reacts, forming diphenylethanol. When aniline is present in the reaction mixture it adds to the biradical (D) or to diphenylketene (E) producing diphenylacetanilide. That there is no previous attack of aniline on the oxathiolanone (IVa) was demonstrated by refluxing a benzene solution with aniline, whereupon the unchanged oxathiolanone (IVa) was recovered. On desulfuration of the above mentioned oxathiolanones in acetone or benzene, the original carbonyl compound was isolated. In ethanol on the other hand the carbonyl group is known to be further reduced[3,10] to the corresponding alcohol, and this is also the case in the desulfuration of oxathiolanone (VI) which afforded androstane 3β,17β diol, 17-monoacetate (VIIa). In the desulfurations of oxathiolanones (IIa) and (IVa) the corresponding alcohols could not be isolated.



Of interest is the isolation of androstane 17β-ol (VIII) together with the main product (VIIa). It is very unlikely that this 3-desoxy derivative (VIII) had been produced by saturation of a double bond formed by dehydration of the 3-hydroxyl grouping of VIIa. In the desulfuration of the oxathiolanone (V), there is also an elimination of the keto group since oxindol (IX) instead of isatin, was obtained. The desulfuration of the oxathiolanone (IVb) yielded cyclohexanediol-diphenylacetate (Xa). The biradical (B) was therefore reduced by hydrogen and it seems that the carbonyl in the alpha position stabilizes the biradical, permitting the attack of the hydrogen adsorbed on the catalyst. In the course of the desulfuration of (IVb) the carbonyl function is reduced to a hydroxyl group (see ref. 4). The resulting ester (Xa) then was oxidized with chromium trioxide, yielded the ketone (Xb) identical with a specimen prepared by esterification of 2-hydroxy-cyclohexanone with diphenylacetyl chloride.

(10) G. Rosenkranz, St. Kaufmann and J. Romo, *J. Am. Chem. Soc.*, 71, 3689 (1949).

EXPERIMENTAL[11]

Mercaptodiphenylacetic acid (I). This compound was prepared according to H. Becker and A. Bistrzycki,[5] m.p. 152–153° (prisms from acetone-hexane).

2,2,4-Triphenyl-1,3-oxathiolan-5-one (IIa). Mercaptodiphenylacetic acid (7 g.), benzaldehyde (3 g.) and *p*-toluenesulfonic acid (0.5 g.) were refluxed in benzene (125 ml.) for 5 hr. The solution was then washed with sodium carbonate solution, to remove unreacted mercaptodiphenylacetic acid and then with water. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization of the residue from ether-hexane produced small prisms (8.05 g.) m.p. 94–95° [reported[6] m.p. 94–96°].

In the infrared it showed a band at 5.7 μ; characteristic of 5-membered lactone (the following oxathiolanones also showed this band).

4,4-Diphenyl-2-(9-anthryl)-1,3-oxathiolan-5-one (IIb). A mixture of 1 g. of anthraldehyde,[7] 1.5 g. of mercaptodiphenylacetic acid and 0.1 g. of *p*-toluenesulfonic acid were refluxed in 40 ml. of benzene. The isolation of the oxathiolanone (IIb) was carried out as in the previous case. Crystallization from ether-methanol yielded yellow prisms (2.1 g.) m.p. 157–159°.

Anal. Calcd. for $C_{29}H_{20}O_2S$: C, 80.53; H, 4.66; S, 7.39. Found: C, 80.81; H, 4.51; S, 7.38.

2,3-Tetramethyleneanthracene-9-aldehyde (III). Following the procedure for the preparation of 9-anthraldehyde,[7] a mixture of 2,3-tetramethyleneanthracene[12] (2.5 g.) *N*-methylformanilide (3 g.) phosphorus oxychloride (3 g.) in chlorobenzene (5 ml.) was heated on the steam bath for 80 min., after external cooling with ice; a solution of 14 g. of sodium acetate in 25 ml. of water was added with mechanical stirring. The volatile components of the mixture were then steam distilled, the solid residue was collected, dried at room temperature and crystallized from acetone-hexane, m.p. 125–128° (2.05 g.). Further crystallizations from acetone-hexane raised the m.p. to 130–132°.

Anal. Calcd. for $C_{19}H_{16}O$: C, 87.16; H, 6.44. Found: C, 87.46; H, 6.40.

4,4-Diphenyl-2-(2,3-tetramethylene-9-anthryl)-1,3-oxathiolan-5-one (IIc) was prepared by the same method as IIb. Crystallization from chloroform-hexane afforded prisms (1.2 g.) m.p. 159–160°.

Anal. Calcd. for $C_{33}H_{26}O_2S$: C, 81.46; H, 5.28; S, 6.57. Found: C, 81.77; H, 5.17; S, 6.28.

Spiro(4,4-diphenyl-1,3-oxathiolan-5-one-2,1'-cyclohexane) (IVa), m.p. 80–82° (prisms from ether-hexane, yield: 68% based in the ketone).

Anal. Calcd. for $C_{20}H_{20}O_2S$: C, 74.02; H, 6.21; S, 9.88. Found: C, 74.06; H, 6.69; S, 9.63.

Spiro(4,4-diphenyl-1,3-oxathiolan-5-one-2,1'-cycloheptane), m.p. 112–113° (prisms from ether-hexane, yield: 21%).

Anal. Calcd. for $C_{21}H_{22}O_2S$: C, 74.50; H, 6.55; S, 9.47. Found: C, 73.96; H, 6.60; S, 9.53.

Spiro(4,4-diphenyl-1,3-oxathiolan-5-one-2,1'-cyclohexan-2'-one) (IVb), m.p. 108–110° (prisms from acetone-hexane, yield: 37%).

Anal. Calcd. for $C_{20}H_{18}O_3S$: C, 70.99; H, 5.36; S, 9.46. Found: C, 70.93; H, 5.52; S, 9.60.

Spiro(4,4-diphenyl-1,3-oxathiolan-5-one-2,3'-oxindol (V). In the preparation of this compound the mixture was refluxed for 8 hr. since isatin is only slightly soluble in benzene. The product (V) showed m.p. 210–211° (white needles from ether-hexane, yield 35%).

(11) The melting points are uncorrected; rotations were determined in chloroform, the infrared spectra were measured on a Perkin-Elmer double beam spectrophotometer in chloroform solution. The microanalyses were performed by Dr. Franz Pascher, Bonn, Germany.

(12) J. von Braun, O. Bayer and L. F. Fieser, *Ann.*, 459, 287 (1927).

Anal. Calcd. for $C_{22}H_{15}O_3NS$: C, 70.76; H, 4.04; N, 3.74; S, 8.58. Found: C, 70.61; H, 4.12; N, 3.30; S, 8.74.

Spiro(4,4-diphenyl-1,3-oxathiolan-5-one-2,3'-17β-acetoxyandrostane) (VI). Only one stereoisomer was obtained; m.p. 179–181°, $[\alpha]_D^{20}$ +7.5° (in $CHCl_3$) (small prisms from acetone-methanol, yield: 73%).

Anal. Calcd. for $C_{35}H_{42}O_4S$: C, 75.24; H, 7.58; S, 5.72. Found: C, 75.01; H, 7.67; S, 5.73.

The results of the various desulfurations are described in Table I. In all cases the amount of Raney nickel used was six times the weight of oxathiolanone. The operations are illustrated by the following examples.

Desulfuration of mercaptodiphenylacetic acid (I). The acid (I) (4 g.) was dissolved in ethanol (50 ml.) and Raney nickel (24 g.) added. The mixture was refluxed for 90 min., the nickel filtered off, washed with ethanol, and the solution concentrated whereupon diphenylacetic acid (3.1 g.) crystallized. It showed m.p. 142–144° (no depression with an authentic specimen).

Desulfuration of oxathiolanone (IVa). (a) *In ethanol.* The oxathiolanone (IVa) (2 g.) was dissolved in ethanol, and Raney nickel (12 g.) was added. The suspension was refluxed for 4 hr., the nickel filtered off, washed with ethanol, and the ethanolic solution evaporated to dryness. The oily residue was taken up in ether and extracted by 8 ml. of a 5% sodium carbonate solution. After acidification with dilute hydrochloric acid and extraction with ether, the diphenylacetic acid (40 mg.) was crystallized from ether-hexane, m.p. 145–147°. The neutral ethereal extract was evaporated to dryness and the oily residue (760 mg.) chromatographed on 15 g. of alumina (washed with ethyl acetate). The crystalline fractions obtained by elution with hexane, were combined and recrystallized from methanol, yielding ethyl diphenylacetate (518 mg.) m.p. 56–58° (no depression of m.p. when mixed with an authentic specimen). The crystalline fractions obtained by elution with benzene, were combined and recrystallized from ether-hexane, yielding diphenylethanol m.p. 53–55° (60 mg.) (undepressed when mixed with an authentic specimen).

The *phenylurethane* derivative of diphenyl ethanol showed m.p. 135–317°.[13]

Anal. Calcd. for $C_{21}H_{19}O_2N$: N, 4.41. Found: N, 4.40.

(b) *In acetone.* The procedure was identical as above except that the Raney nickel was washed 3 times with 80 ml. of acetone to free it from ethanol. The ethereal solution (*vide supra*), after elimination of diphenylacetic acid was evaporated and the oily residue shaken with 15 ml. of a saturated solution of sodium bisulfite. The crystalline adduct of cyclohexanone was collected and after washing with ether, weighed 565 mg. The cyclohexanone was regenerated with acid and extracted with ether. The ethereal solution was evaporated and the cyclohexanone converted to the 2,4-dinitrophenyl hydrazone, m.p. 158–160° (600 mg.).

(c) *In benzene.* The Raney nickel was washed 3 times with 80 ml. of benzene, then suspended in benzene, and the solvent distilled until the distillate was free of water. The cyclohexanone was purified through its sodium bisulfite adduct. When this desulfuration was carried out in the presence of aniline, the ethereal extract was washed first with dilute hydrochloric acid. The diphenylacetanilide had the correct m.p. of 181–182°.

Desulfuration of oxathiolanone (IV). The cyclohexane 1,2-diol-diphenylacetate (Xa) crystallized several times from acetone-hexane, showed m.p. 97–100°.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.15. Found: C, 77.55; H, 7.17.

2-Hydroxycyclohexanone diphenylacetate (Xb). The ester (Xa) (100 mg.) was dissolved in acetic acid (5 ml.), a solution of chromium trioxide (50 mg.) in water (0.5 ml.) and acetic acid (0.5 ml.) was added and the mixture left at 15° for 30 min. It was then diluted with water, extracted with ether, the ethereal extract washed with water, dilute sodium hydroxide, and again with water. Thereafter the solvent was evaporated and the residue crystallized first from methanol, and then from acetone-hexane, m.p. 106–107°.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.82; H, 6.52.

2-Hydroxycyclohexanone (80 mg.) was esterified with diphenyl acetyl chloride (400 mg.) by heating in anhydrous pyridine (1 ml.) for 45 min. on the steam bath. Crystallization from ether-hexane afforded the ester (Xb) (140 mg.) m.p. 95–97° this product showed no depression in m.p. with the product described above and the infrared spectra of the two samples were identical.

Desulfuration of oxathiolanone (V). The oxindol (IX) obtained in the desulfuration showed m.p. 123–125°. A small amount (50 mg.) of a product m.p. 159–160° was also obtained and not further characterized.

Desulfuration of oxathiolanone (VI). The oily residue from the desulfuration (820 mg.) was chromatographed on alumina (30 g.). Two compounds were eluted by hexane. The first fractions furnished ethyl diphenylacetate m.p. 53–55° and the later fractions afforded androstan 17β-ol-acetate m.p. 71–74°, $[\alpha]_D^{20}$ +6° in $CHCl_3$ (needles from methanol) [identified by mixed m.p. and infrared comparisons[10]]. The combined crystalline fractions eluted with benzene yielded on crystallization from methanol, prisms of androstane 3β,17β-diol-17-acetate (VIIa) m.p. 150–151°, $[\alpha]$ +5° in $CHCl_3$, λmax. 2.9 and 5.75 μ.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.12; H, 10.13.

The diacetate (VIIb) (acetic anhydride and pyridine) showed m.p. 128–129° [identified by mixed m.p. and infrared comparison with an authentic specimen[14,15]].

Acknowledgment. We are indebted to Dr. George Rosenkranz of Syntex, S. A., for a generous gift of dihydrotestosterone acetate.

MÉXICO 20, D. F.

(13) Ramart, *Amagat Comt. Rend.*, **179**, 901.

(14) L. Ruzicka, M. W. Goldberg and H. R. Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935).

(15) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

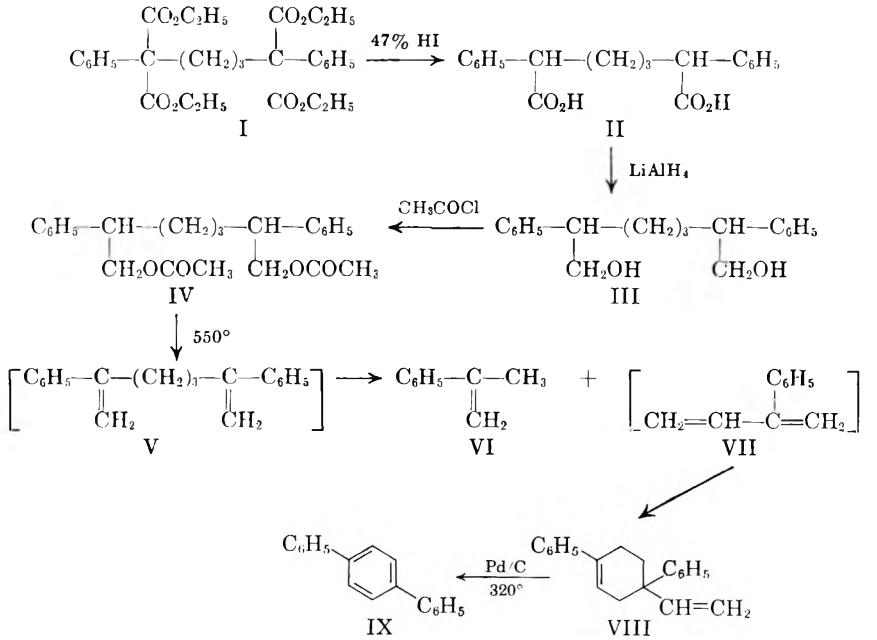
Pyrolytic Cleavage of 2,6-Diphenyl-1,7-diacetoxyheptane and 2,6-Diphenylheptadiene[1]

C. S. MARVEL AND E. J. GALL

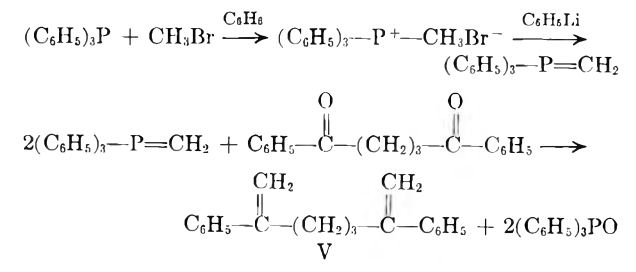
Received April 9, 1959

Pyrolysis of 2,6-diphenyl-1,7-diacetoxyheptane gives a high yield of α-methylstyrene and 2-phenyl-1,3-butadiene. Pyrolysis of 2,6-diphenyl-1,6-heptadiene under the same conditions gives the same cleavage products.

The diolefin, 2,6-diphenylheptadiene-1,6 (V) was desired in connection with the study of the formation of cyclic units during polymerization, which is being carried on in this laboratory.[2,3] The simplest synthesis seemed to be the pyrolysis of 2,6-diphenyl-1,7-diacetoxyheptane (IV). This ester was synthesized by the reactions shown below. On pyrolysis of the diacetate the expected diene (V) was not obtained. Instead, the products isolated in good yield were α-methylstyrene (VI) and the dimer of 2-phenyl-1,3-butadiene (VII). The latter was characterized by conversion to *p*-terphenyl (IX) as reported by Alder and Haydn.[4]



When the diene (V), prepared from 1,3-dibenzoylpropane (X) by means of the Wittig reaction,[5]



reported by Bailey and Lieske[6] on the cleavage of α-olefins substituted at the 2 and 4 positions at temperatures as low as 500°.

(1) This work was carried out under the sponsorship of Contracts AF 33(616)-3772 and -5486 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio. This paper may be reproduced for any purpose of the United States Government.

(2) C. S. Marvel and R. D. Vest, *J. Am. Chem. Soc.*, **79**, 5771 (1957); **81**, 984 (1959).

(3) C. S. Marvel and J. K. Stille, *J. Am. Chem. Soc.*, **80**, 1740 (1958).

(4) K. Alder and J. Haydn, *Ann.*, **570**, 201 (1950).

(5) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954); N. Field, private communication.

(6) W. J. Bailey and C. N. Lieske, Abstr. Am. Chem. Soc. Meeting, Chicago, Ill., September 7-12, 1958, 83 pp.

EXPERIMENTAL

(All m.p.'s are uncorrected.)

Tetraethyl 1,5-diphenyl-1,1,5,5-pentanetetracarboxylate (I). A two-liter, three-necked, round-bottomed flask was fitted with a reflux condenser with calcium chloride drying tube attached, a mechanical stirrer with a strong variable motor, and nitrogen inlet tube. The system was dried by heating with a free flame while passing dry nitrogen through it, and then flushing with nitrogen for about 2 hr. Anhydrous *t*-butanol (750 ml.), previously dried by refluxing over sodium and distilling, was introduced into the flask, followed by the careful addition, in portions, of freshly-cut potassium metal (49 g., 1.25 moles). The mixture was heated under gentle reflux for about 2 hr., was allowed to cool, and redistilled diethyl phenylmalonate (295 g., 1.25 moles) was added in a steady stream with stirring. When the addition was about a third complete, a voluminous white solid precipitated, rendering stirring difficult. The mixture was diluted with 250 ml. of anhydrous *t*-butanol, and the rate of stirring was increased. After all the malonate had been added, the mixture was rapidly stirred and heated under reflux for about 30 min. Freshly distilled 1,3-dibromopropane (101 g., 0.5 mole) was then added dropwise over a period of 45 min. The resulting mixture was stirred and heated under reflux overnight.

After allowing the mixture to cool, most of the excess *t*-butanol was removed by distillation, and, with stirring, 500 ml. of a 2% aqueous sulfuric acid solution was added, causing the salt to dissolve and producing two layers. The organic layer was diluted with diethyl ether, was separated, and was washed well with water. The aqueous layer was extracted with three 250-ml. portions of diethyl ether, the ether extracts were combined with the organic layer, and the ethereal solution was dried over anhydrous magnesium sulfate. The solvent was removed from the dried solution by distillation, and the resulting viscous, red liquid was distilled through a small heated Vigreux column under reduced pressure. There was obtained 196.6 g. (76.5% of theory, based on 1,3-dibromopropane) of orange-colored liquid, b.p. 210–220°/0.2–0.3 mm., n_D^{20} 1.5190. A small sample was redistilled, b.p. 164°/0.07 mm., n_D^{20} 1.5178.

Anal. Calcd. for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08. Found:[7] C, 68.04; H, 7.39.

When this condensation of malonic ester with 1,3-dibromopropane was carried out under the usual conditions with sodium ethoxide, the yields were less than 40%.

α,α'-Diphenylpimelic acid (II). In a three-liter, three-necked, round-bottomed flask, fitted with a mechanical stirrer (Hershberg) and modified Dean-Stark trap, was placed 350 g. (0.683 mole) of tetraethyl 1,5-diphenyl-1,1,5,5-pentanetetracarboxylate. Hydriodic acid (47%; 1120 g.; 4.1 moles of acid) was added, and the mixture was stirred and heated under reflux until no more ethyl iodide was collected (almost 5 days). During this time 204.1 g. (1.3 moles) of ethyl iodide was collected. The mixture was allowed to cool, and enough 25% aqueous sodium hydroxide was added to render the mixture basic to litmus. The red-colored basic solution was extracted with two 500-ml. portions of diethyl ether, and was acidified with cold, concentrated sulfuric acid. Ethyl acetate was added to dissolve the red oil obtained, and the aqueous layer was separated. The organic solution was washed well with aqueous sodium thiosulfate to remove the red color, and was dried over anhydrous magnesium sulfate. The dried solution was concentrated to about 750 ml. and petroleum ether (b.p. 30–60°) was added until the hot solution became cloudy. Enough ethyl acetate was added to render the solution clear, and, upon cooling, there was obtained 54.3 g. of a white solid, m.p. 150–155°. Concentration of the mother liquor resulted in the isolation of 103 g. or more of crude di-acid. A third crop of crystals was obtained by evaporating the remaining solution to dryness and crystallizing the resultant oil from benzene–low-boiling petroleum ether. The yellow-colored solid obtained weighed 64.9 g. and had m.p. 150–160°. Total yield of crude acid was 222.2 g. A small sample was purified further by recrystallization from benzene–low-boiling petroleum ether three times to yield a white, crystalline solid, m.p. 136–138°. Infrared analysis[8] was in agreement with the structure of the di-acid.

Anal. Calcd. for $C_{19}H_{20}O_4$: C; 73.06; H, 6:45. Found: C, 73.90; H, 6.72.

Because of difficulties in crystallization, this crude acid was not purified further.

2,6-Diphenylheptandiol-1,7 (III). In a two-liter, three-necked, round-bottomed flask fitted with reflux condenser, mechanical stirrer, and dropping funnel was placed a slurry of finely-powdered lithium aluminum hydride (7.6 g., 0.2 mole) in 700 ml. of dry diethyl ether. α,α'-Diphenylpimelic acid (16.0 g.; 0.051 mole), dissolved in 300 ml. of dry diethyl ether, was added dropwise by means of the dropping funnel with stirring at such a rate so as to maintain gentle reflux. When the addition was complete, stirring and heating were continued overnight.

After allowing the mixture to cool, 50 ml. of water was cautiously added with stirring while the flask was cooled in an ice water bath; this was followed by the addition of 150 ml. of 10% aqueous sulfuric acid, again while the flask was cooled in an ice water bath. When it was certain that the excess lithium aluminum hydride had been decomposed, the mixture was transferred to a separatory funnel, and the aqueous layer was separated. The organic layer was washed with 150 ml. of 10% aqueous sodium carbonate and then with 150 ml. of water. The aqueous layer was extracted with diethyl ether, and the extract was washed, first with 10% aqueous sodium carbonate and then with water. The combined ether solutions were dried overnight over anhydrous magnesium sulfate.

The solvent was removed from the dried solution by distillation under reduced pressure, yielding 14.5 g. (98% yield) of a clear viscous oil, which crystallized upon cooling. This waxy solid was purified by recrystallization from methanol. An accurate melting point could not be obtained on the resulting waxy solid. Analytical data, however, were in agreement with the structure of 2,6-diphenylheptandiol-1,7.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.20; H, 8.51. Found: C, 79.95; H, 8.71.

2,6-Diphenyl-1,7-diacetoxyheptane (IV). In a 300-ml., three-necked, round-bottomed flask, fitted with reflux condenser with calcium chloride drying tube attached, stirrer, and dropping funnel, was placed a solution of 2,6-diphenylheptandiol-1,7 (19.3 g.; 0.067 mole) in 100 ml. of anhydrous ether. With stirring, acetyl chloride (20.4 g.; 0.26 mole) was added dropwise at room temperature. When the addition was complete (15 min.), the mixture was stirred and heated under gentle reflux overnight.

The solvent and excess acetyl chloride were removed by distillation under reduced pressure, and the viscous liquid obtained was distilled under vacuum. There was obtained 22.9 g. (93% yield) of a clear, viscous liquid, b.p. 172–176°/0.08 mm., n_D^{20} 1.5273.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.05; H, 7.67.

Pyrolysis of 2,6-diphenyl-1,7-diacetoxyheptane. The various pyrolyses were carried out in the following way: The liquid diacetate was dropped at the rate of about 50 drops/min. through a vertical, 20 × 250 cm. Vycor glass combustion tube packed with 1/16 inch glass helices. The tube was con-

(7) The microanalyses were performed by Mr. Jozsef Nemeth, Mrs. F. Ju, Miss Claire Higham, and Miss Jane Liu, University of Illinois.

(8) The infrared spectra were determined by Mr. P. E. McMahon and Miss Mary DeMott, University of Illinios.

tinuously swept out with dry, oxygen-free nitrogen, and was heated externally at temperatures varying between 540 and 560° with a 12-inch Hoskins electric furnace.

A typical pyrolysis was as follows: At the rate given above, 145 g. (0.394 mole) of 2,6-diphenyl-1,7-diacetoxyheptane was dropped through the column, heated to 555–560°. The pyrolysate was collected in a receiver immersed in a Dry Ice–acetone bath. At the completion of the pyrolysis, the pyrolyzate was diluted with diethyl ether, and was washed well with 10% aqueous sodium carbonate and then with water. After drying over anhydrous sodium sulfate, the solvent was removed from the solution by distillation under reduced pressure, and the red-colored liquid residue was distilled through an 8-inch Vigreux column under reduced pressure. The water-white liquid (30.8 g.) boiling between 60 and 75°/17 mm. was collected. The residue from this distillation was allowed to cool and was subjected to pyrolysis once again at 555–565°. After the usual work-up and distillation, there was obtained 21.8 g. more of colorless liquid, b.p. 60–80°/19–20 mm.

In the manner described above 344 g. (0.934 mole) of diacetate was pyrolyzed to give 125.1 g. of colorless liquid, b.p. 60–80°/17–20 mm. After two distillations of this liquid (inhibited with 1,3,5-trinitrobenzene) in a dry nitrogen atmosphere there was obtained 43.7 g. of colorless liquid, b.p. 70°/26 mm., n_D^{25} 1.5360. The infrared and nuclear magnetic resonance spectra[9] of this liquid were identical with those of an authentic sample of α-methylstyrene. A vapor-phase chromatogram obtained from a 1:1 mixture of this distillate with pure α-methylstyrene showed only one peak. In addition to this pure fraction, there was obtained a slightly lower-boiling fraction (14.4 g.), b.p. 65–68°/26 mm., n_D^{25} 1.5350, which was shown by vapor phase chromatography to be largely α-methylstyrene contaminated with a small amount of lower-boiling liquid.

1,4-Diphenyl-4-vinylcyclohexene (2-phenylbutadiene dimer) (VIII). The pot residues from the distillations which gave α-methylstyrene as described above were combined and heated at 160° in an oil bath for 1 hr. The mixture was then distilled under vacuum to give 21.7 g. of a yellow oil, b.p. 140–175°/1.0–1.5 mm. This oil was dissolved in enough boiling methanol to render it completely soluble, and, after cooling overnight, there was obtained from this solution 14.1 g. of a white crystalline solid, m.p. 59.5–61.0°. (Alder[4] reports the melting point of 2-phenylbutadiene dimer as 60°.) A small sample of this solid was recrystallized twice from methanol to give colorless needles, m.p. 63.5–64.0°. Infrared analysis was in agreement with the structure of 1,4-diphenyl-4-vinylcyclohexene (the structure of the dimer as reported by Alder[4]).

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.35; H, 8.00.

Dehydrogenation of 2-phenylbutadiene dimer. The pure dimer (3.0 g.) was mixed thoroughly with 2.0 g. of 10% palladium on charcoal catalyst in a 50-ml., round-bottomed flask. The mixture was heated by means of a Wood's metal bath to 320° for 16 hr. in a dry nitrogen atmosphere. After cooling, the mixture was extracted several times with hot ethyl acetate. From this solution was isolated 0.61 g. of shiny leaflets, m.p. 211–212.5°. (Lit.[10] m.p. of *p*-terphenyl, 209°.)

2,6-Diphenylheptadiene-1,6 (V). 1,3-Dibenzoylpropane was prepared without difficulty from glutaryl chloride and benzene in 86% yield by following a procedure analogous to that for the preparation of 1,4-dibenzoylbutane.[11]

Methyl triphenylphosphonium bromide was typically prepared in the following manner: Triphenylphosphine (65.6 g.; 0.25 mole) dissolved in benzene (150 ml.) was combined with methyl bromide (40 g.; 0.42 mole) in a one-liter centrifuge bottle cooled in a Dry Ice–acetone bath. The bottle was stoppered while cold by wiring a rubber stopper in the opening, and the mixture was allowed to stand at room temperature for 2 days. At the end of this time the bottle was cooled in an ice bath, and was carefully opened. The white crystalline salt was isolated by filtration on a Büchner funnel, and was washed well with benzene. The amount of dried salt obtained was 87.5 g. (98%); m.p. 229–230°. (Wittig[5] reports m.p. 227–229°.)

The phosphonium salt (121 g.; 0.338 mole) was dispersed in 500 ml. of anhydrous ethylene glycol dimethyl ether contained in a two-liter, three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, reflux condenser, and nitrogen inlet tube. The system was swept with dry nitrogen while a solution of 0.37 mole of phenyllithium in diethyl ether was added over a period of approximately 45 min. Practically all of the solid dissolved, giving a red-colored solution. A solution of 40 g. (0.158 mole) of 1,3-dibenzoylpropane in 200 ml. of dry ethylene glycol dimethyl ether was then added dropwise to the stirred mixture over a period of about 1 hr., and the mixture was stirred and heated under gentle reflux for 19 hr. The solvents were then evaporated to near dryness, and about 700 ml. of dry diethyl ether was added. The dark red oil which formed was thoroughly shaken with the solvent, and the ethereal solution was decanted into a three-liter separatory funnel. After washing well with water, the ether solution was dried over anhydrous sodium sulfate overnight, and the solvent was then removed under vacuum, leaving 43.0 g. of dark red oil. This oil, inhibited with a small amount of 4-*t*-butylpyrocatechol, was distilled under vacuum by means of a small Vigreux column to give 18.3 g. (46.7%) of water-white liquid, b.p. 113–117°/0.02–0.04 mm. Hg, n_D^{25} 1.5795. The infrared spectrum of a chloroform solution showed absorption peaks at 890 cm.$^{-1}$ ($CR_1R_2{=}CH_2$), 1490 and 1595 cm.$^{-1}$ (C_6H_5), 1570 cm.$^{-1}$ (conjugated C_6H_5—), and 1625 cm.$^{-1}$ (C_6H_5— conjugated —C=C—).

Anal. Calcd. for $C_{19}H_{20}$: C, 91.88; H, 8.12. Found: C, 91.71; H, 8.32.

We are indebted to Dr. N. Field for permission to use his method for the synthesis of this hydrocarbon.

Pyrolysis of 2,6-diphenylheptadiene-1,6. By means of the apparatus and in an analogous manner to that described above for the pyrolysis of 2,6-diphenyl-1,7-diacetoxyheptane, 10.0 g. (0.04 mole) of 2,6-diphenylheptadiene-1,6 was pyrolyzed at 540–550°. At the completion of the pyrolysis, the column was washed with diethyl ether, and the washings were combined with the pyrolyzate. After the solvent was removed under vacuum, the red-colored liquid residue (8 g.), inhibited with a small amount of hydroquinone, was distilled under reduced pressure by means of a 10-inch spinning-band column. There were collected three fractions: I, 0.66 g., b.p. 45–50°/12 mm., n_D^{25} 1.5324; II, 2.19 g., b.p. 49–50°/11 mm., n_D^{25} 1.5369; III, 0.31 g., b.p. 54–58°/11 mm., n_D^{25} 1.5438. The infrared spectra of fractions I and II in carbon tetrachloride were identical with the spectrum of an authentic sample of α-methylstyrene in the same solvent. The spectrum of III was that to be expected of 2-phenyl-1,3-butadiene, slightly contaminated with α-methylstyrene. This spectrum showed the following important absorption maxima: 895 cm.$^{-1}$ ($CR_1R_2{=}CH_2$), 915 cm.$^{-1}$ (CH_2 out-of-plane deformation of the —CH=CH_2 grouping), 990 cm.$^{-1}$ (CH out-of-plane deformation of the —CH=CH_2 grouping), 1497 and 1595 cm.$^{-1}$ (C_6H_5—), 1630 (C_6H_5— conjugated —C=C—), in addition to a weak absorption at 1375 cm.$^{-1}$ (C—CH_3).

The residue from the above distillation was heated under reflux at 150–160° for about 2 hr. It was then distilled under vacuum to yield 1.6 g. of an orange oil, b.p. 130–140°/0.02

(9) The nuclear magnetic resonance spectrum was determined by Mr. B. A. Shoulders, University of Illinois.

(10) J. V. Braun, *Ber.*, 60, 1180 (1927).

(11) *Org. Syntheses*, Coll. Vol. II, 169, (1943).

mm. It was not possible to crystallize this oil from methanol, even after attempted purification of an *n*-pentane solution on an activated alumina column. The infrared spectrum of this oil dissolved in chloroform, however, was consistent with that to be expected of the impure dimer of 2-phenyl-1,3-butadiene. A broad absorption maximum in the region of 900 cm.$^{-1}$ ($CR_1R_2{=}CH_2$) seems to indicate that dimerization was not complete.

URBANA, ILL.

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH DIVISION, DIRECTORATE OF RESEARCH, USA CHEMICAL WARFARE LABORATORIES]

Synthesis of Some Hydroxamic Acids. Reactivity with Isopropyl Methylphosphonofluoridate (GB)

G. F. ENDRES[1] AND JOSEPH EPSTEIN[2]

Received April 13, 1959

Eight hydroxamic acids, of which five are new compounds, were synthesized and tested for reactivity with the nerve gas GB, isopropyl methylphosphonofluoridate. The compounds were designed to sterically increase the reactivity of hydroxamic acids with GB. The reactivity however, was found to be not appreciably different from that predicted from well-established relationships of *p*Ka and reaction rate with other hydroxamic acids.

Several papers[3-5] have appeared since the publication of Hackley *et al.*[6] reporting on various aspects of the reaction between hydroxamic acids and the nerve gas GB (isopropyl methylphosphonofluoridate). In connection with our program to find nonprotein substances which react more rapidly with GB in aqueous solution at neutral *p*H than the compounds studied in the previous publications, we have synthesized and tested several hydroxamic acids. Table I contains data on the dissociation constants, rate constants for their reaction with GB and the moles of hydrogen ion released per mole of GB at infinite time for hexanehydroxamic acid, gluconohydroxamic acid, three long-chain hydroxamic acids derived from sebacic acid and three carboxyhydroxamic acids. The results of our kinetic studies indicate that none of the compounds is significantly more or less active than would be predicted from the relationship of the reactivity with the basic strength of the hydroxamic acid anion reported in previous publications[4,5] (*e.g.* see Fig. 1) and hence offer no clues as to the means of increasing the reactivity between hydroxamic acids and GB.

The hydroxamic acids reported herein represent an unsuccessful attempt to increase the reactivity of these materials by steric effects. Some success has been achieved by pursuing this line of approach with the hydroxylated benzenes,[7,8] and ortho substituted hydroxybenzyl amines.[9]

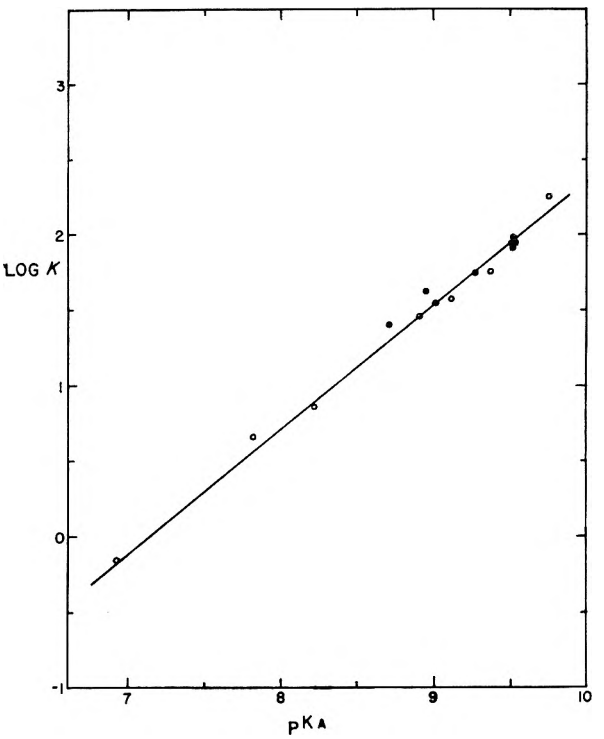


Fig. 1. Relationship between log k (second order rate constant 1 mole^{-1} sec.$^{-1}$) and *p*Ka of various hydroxamic acids. ● Data of present publication. ○, Data of Swidler *et al.* (see ref. no. 7 of ref. 4)

In the design of the hydroxamic acids sterically capable of polyfunctional attack, it was assumed that (*a*) the reaction is mediated through a simultaneous nucleophilic and electrophilic attack of the hydroxamic acid anion on the phosphorus and

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(3) R. Swidler and G. M. Steinberg, *J. Am. Chem. Soc.*, **78**, 3594 (1956).
(4) M. A. Stolberg and W. A. Mosher, *J. Am. Chem. Soc.*, **79**, 2618 (1957).
(5) A. L. Green, G. L. Sainsbury, B. Saville and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).
(6) B. E. Hackley, Jr., R. Plapinger, M. A. Stolberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955).
(7) B. J. Jandorf, T. Wagner-Jauregg, J. J. O'Neill and M. Stolberg, *J. Am. Chem. Soc.*, **74**, 1521 (1952).
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(9) To be published.

TABLE I

DISSOCIATION CONSTANTS, RATE CONSTANTS OF GB REACTION[a] AND MOLES OF ACID PRODUCED PER MOLE OF GB REACTING FOR EIGHT HYDROXAMIC ACIDS

Compd. No.	Hydroxamic Acid	*p*Ka	No. of Runs	Pseudo First Order Rate Constant k_{obs} (min.$^{-1}$)	Bimolecular[b] Rate Constant k (L. mole^{-1} sec.$^{-1}$)	Moles [H^+] Released per Mole GB
I	$CH_3(CH_2)_4CONHOH$	9.48	4	0.0658 ± 0.0003	84.3	2.2 ± 0.2
II	$H_2NCO(CH_2)_8CONHOH$	9.49	2	0.067 ± 0.003	87.7	2.26 ± 0.00
III	$CH_3NHCO(CH_2)_8CONHOH$	9.47	2	0.073 ± 0.002	91.6	2.35 ± 0.08
IV	$HO(CH_2)_9CONHOH$	9.26	4	0.0735 ± 0.002	57.1	2.2 ± 0.2
V	$HOCH_2(CHOH)_4CONHOH$	8.94[c]	1	0.113	43.1	2.3
VI	HOOCCONHOH	8.69[d]	1	0.113	25.2	2.7
VII	$HOOC(CH_2)_2CONHOH$[e]	9.50[d]	2	0.0378	83.2[g]	1.48 ± 0.08
VIII	HOOCCH=CHCONHOH[f]	9.15[d]	1	0.0259	21.7[g]	1.7

[a] Rates determined at 30.0°, *p*H of reaction mixture = 7.6, [Hydroxamic Acid] = $1 \times 10^{-3}M$; [GB] = $1 \times 10^{-4}M$. [b] Calculated from equation $k = k_{obs}/[\text{Hydroxamic Acid Ion}] = k_{obs}\frac{[H^+ + K_A]}{[K_A]} \cdot \frac{1}{[HA]}$. [c] Ref. 13. [d] *p*Ka of the hydroxamic acid function. [e] Purity 69.7% by titration. [f] Purity 72.5% by titration. [g] Corrected for purity.

phosphoryl oxygen atoms[3,4,10] and (*b*) the attack is upon the side of the GB molecule opposite to the phosphorus-fluorine bond.

Compounds II, III, and IV, which contain a second electrophilic group at the opposite end of the molecule, are sterically able to attack the fluorine as well as the phosphorus (and perhaps the phosphoryl oxygen atoms[10]) by wrapping themselves around the GB molecule. Compound V contains a number of groups capable of hydrogen bonding at different distances from the hydroxamic acid function. Compounds VI, VII, and VIII contain negatively charged sites (carboxylate ions) at different distances from the hydroxamic acid anion. It is believed that the enzyme cholinesterase contains two negatively charged groups, one of which attacks the carbonyl function in esters, the other confers on the enzyme greater binding power for the substrate. The extreme reactivity with GB at the site containing the two negatively charged groups[11,12] suggested that compounds VI, VII, and VIII might be effective.

EXPERIMENTAL

I. *Kinetic studies and dissociation constant measurements.* The *p*Ka's of the carboxyhydroxamic acids (Compounds VI, VII, and VIII) were determined by titration of $0.025M$ ($0.05N$) solutions with $0.5N$ NaOH. The solutions were $0.1M$ in KNO_3 and their initial volume was 25.0 ml. Oxalomonohydroxamic acid (VI) appeared to be 100% pure by titration; succino and maleic hydroxamic acids (VII and VIII) were 69.7% and 72.5% pure, respectively.

For the other hydroxamic acids listed in Table I, the *p*Ka's were determined by the buffer method.[3] Solutions were made up $0.1M$ in potassium nitrate and approximately $0.01M$ (stoichiometric) in hydroxamic acid, exactly half-neutralized with $0.01N$ sodium hydroxide. Equilibrium water was used, and the *p*H's were read as quickly as possible. The value given for gluconohydroxamic acid is a literature value determined by titration.[13] In our hands, this compound was hydrolyzed too rapidly in alkaline solution for a determination by the buffer method.

The rate measurements were carried out using a Beckman automatic titrimeter, the solutions contained in a jacketed beaker of 250 ml. capacity through which water at 30.0° was circulated. The *p*H was maintained at 7.6, checked by an auxiliary *p*H meter and electrodes. All solutions were $0.1M$ in potassium nitrate, $1.00 \times 10^{-3}M$ in hydroxamic acid and approximately $1 \times 10^{-4}M$ in GB (known accurately).

The uptake of $0.01N$ sodium hydroxide was corrected for absorption of carbon dioxide (*ca.* 0.01 ml./min.) and the data treated according to the method of Guggenheim.[14] First order constants were calculated from the slopes of the straight lines obtained by plotting $\log(V' - V)$ against time. The bimolecular rate constant, k, was calculated from the equation

$$k_{obs} = k\left[\frac{K_A}{H^+ + K_A}\right] \cdot [KA]$$

where K_A is the acid dissociation constant of the hydroxamic acid, $[H^+]$ is the hydrogen ion concentration of the reaction and [HA] is the concentration of the hydroxamic acid. For a discussion on the kinetics of the reaction between GB and hydroxamic acid and the validity of these calculations see ref. (3).

The volume of base taken up at infinite time, used to determine the moles of hydrogen ion released per mole GB, was calculated from the intercept of the Guggenheim plot.

II. *Preparation of the hydroxamic acids.* (New compounds are marked with an asterisk.) A. *Sebacic acid derivatives.* Compounds of the structure $X(CH_2)_8CONHOH$, where X = H_2NCO—CH_3NHCO— and $HOCH_2$—, were synthesized by the action of hydroxylamine on the ethyl esters of the corresponding carboxylic acids, and attempts were made to prepare the compound where X = $H_2NCONHCO$— in the same manner. These four esters were prepared from sebacic acid as follows:

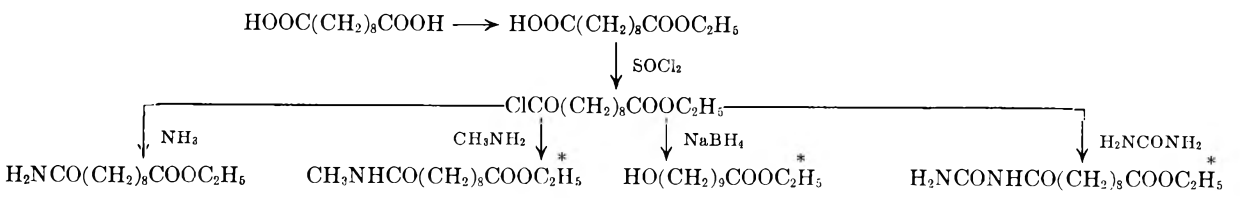
(10) The recent work of Green *et al.*, ref. 5, casts doubt upon the bifunctional mechanism of attack by the hydroxamic acid anion. The choice of hydroxamic acids used herein, however, is not dependent upon the mono- or bifunctionality of the hydroxamic acid anion attack.

(11) I. B. Wilson, *The Physical Chemistry of Enzymes*, A General Discussion of The Faraday Society, 1955, p. 120.

(12) B. J. Jandorf, H. O. Michel, N. K. Schaffer, R. Egan, and W. H. Summerson, *The Physical Chemistry of Enzymes*, A General Discussion of The Faraday Society, 1955, p. 135.

(13) F. Mathis, *Compt. rend.*, **231**, 357 (1950).

(14) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).



Ethyl hydrogen sebacate was prepared by the esterification of sebacic acid with ethanol in the presence of concentrated hydrochloric acid, diethyl sebacate, and di-*n*-butyl ether, following the directions of *Organic Syntheses*.[15]

9-Carboethoxypelargonyl chloride. Ethyl hydrogen sebacate (16.8 g., 0.0730 mole) was treated with thionyl chloride (8 ml., 0.11 mole) in a 50 ml. round bottom flask fitted with reflux condenser and drying tube. After about 1.5 hr. at room temperature, the flask was immersed in a water bath, the temperature of which was slowly raised to 40°, where it was maintained until the total reaction time was about 3 hr. After standing overnight at room temperature, the excess thionyl chloride was stripped off, at the water pump, and the product distilled at reduced pressure (oil pump). B.p. 137°/2.5 mm.–139°/2.7 mm., yield 17.4 g. (96%).

Ethyl sebacamate was prepared by a procedure similar to that given for the methyl ester in *Organic Syntheses*.[16] 21.6 g. (0.087 mole) of 9-carboethoxypelargonyl chloride was added slowly from a dropping funnel to 220 ml. of conc. aqueous ammonia cooled in an ice bath. The reaction mixture was mechanically stirred, and the temperature was not allowed to rise above 8°. The product separated immediately as a white solid, and was filtered off and washed with ice cold water. After drying in a vacuum desiccator, it weighed 19.8 g. (99.6% yield) and melted at 68–69°. Literature m.p. 68.5–69°.[17]

*Ethyl N-methylsebacamate.** 11.0 g. (0.044 mole) of 9-carboethoxypelargonyl chloride was added slowly from a dropping funnel to a mechanically stirred aqueous solution of 0.4 mole of methylamine, the temperature being kept below 8° with an ice bath. (The methylamine solution had been prepared by adding, slowly with cooling, 41 ml. of 10*N* sodium hydroxide solution to 30 g. of methylamine hydrochloride dissolved in 49 ml. of water.) The white precipitated product was filtered off, washed with ice cold water, and dried in the vacuum desiccator. The yield of crude product (m.p. 53–55°) was 10.7 g. (99.6%). Two recrystallizations from benzene–petroleum ether (32–63°) mixture gave a product melting at 55.5–56° (bundles of tiny silvery needles).

Anal. Calcd. for $C_{13}H_{25}NO_3$: C, 64.2; H, 10.4; N, 5.8. Found: C, 64.3; H, 10.0; N, 5.5.

*Ethyl 10-hydroxycaprate** was synthesized by the reduction of 9-carboethoxypelargonyl chloride by sodium borohydride in dioxane suspension after the general procedure of Chaiken and Brown.[18] This synthesis provides a further illustration of the selectivity of sodium borohydride as a reducing agent.

The apparatus consisted of a 300 ml. three-neck round-bottom flask with a reflux condenser and drying tube, mechanical stirrer with vapor-tight seal, and dropping funnel. To 7.6 g. (0.2 mole) of sodium borohydride stirred in 68 ml. dioxane (purified and dried over sodium ribbon) was added dropwise 9.9 g. (0.040 mole) of the ester chloride. The dropping funnel was washed with 5 ml. dioxane, and this was added to the reaction mixture, which was stirred for 0.5 hr. at room temperature, and then for 2 hr. on a steam bath. After being allowed to cool, the mixture was chilled in ice and treated dropwise with 25 ml. water. A vigorous reaction, accompanied by foaming, took place. The mixture was then warmed to room temperature over about 0.5 hr., stirred for 1.5 hr. longer, and filtered under suction. The residue was washed with 25 ml. dioxane, which was combined with the filtrate. This was treated with 125 ml. water, which induced phase separation, and extracted with three portions of ether (30, 15, and 15 ml.). After the ether was evaporated on the steam bath, dioxane was stripped off and the product distilled under reduced pressure through a 9-cm. Vigreux column. The yield of colorless oil boiling at 153–154.5°/4 mm. was 3.1 g. (36%). The compound solidifies on standing in the refrigerator. Redistillation through the same column afforded an analytical sample, $n_D^{24.3}$ 1.4465.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.6; H, 11.2. Found: C, 66.5; H, 11.3.

The product can be saponified to an acid of m.p. 71–73°. The literature m.p. of 10-hydroxycapric acid is 75–76° (corr.).[19]

*9-Carboethoxypelargonyl urea.** This compound was prepared according to the general procedure for monoacylureas given by Stoughton.[20] In a 100-ml. three-neck flask equipped with reflux condenser, sealed mechanical stirrer and dropping funnel, 4.8 g. (0.08 mole) of urea and two small drops of conc. sulfuric acid were dissolved in 12 ml. of benzene. While the solution was being stirred and refluxed on the steam bath, 17.4 g. (0.070 mole) of 9-carboethoxypelargonyl chloride was added dropwise over a period of 15 min. After heating on the steam bath for 0.5 hr. longer, the reaction mixture was a thick slurry. After 1 hr., 13 ml. of benzene was added, and after 3 hr. total reaction time the mixture was cooled to room temperature, 25 ml. petroleum ether (32–63°) was added and the insoluble product was filtered off. The reaction flask was rinsed with petroleum ether. The white solid was then transferred to a beaker, and treated with an excess of 5% aqueous sodium bicarbonate. It was collected once more on a filter, packed into a cake, and washed with distilled water. After being dried in the vacuum desiccator, the product weighed 13.7 g. (72% yield) and melted at 150–152°. An analytical sample recrystallized twice from 95% ethanol melted at 149.5–150.5°.

Anal. Calcd. for $C_{13}H_{24}N_2O_4$: C, 57.3; H, 8.9; N, 10.3. Found: C, 57.8; H, 9.2; N, 10.6.

The esters ethyl sebacamate, ethyl *N*-methylsebacamate, and ethyl 10-hydroxycaprate were converted to the corresponding hydroxamic acids by the method of Hurd and Botteron.[21] 9-Carboethoxypelargonyl urea yielded a mixture of products by this procedure, from which the pure hydroxamic acid could not be separated. The general procedure may be illustrated by the synthesis of *9-carboxamidopelargonohydroxamic acid* (*N*-hydroxysebacamide).* 1.10 g. (0.048 g. atom) of sodium metal was dissolved in 24 ml. absolute ethanol in a round-bottom flask fitted with reflux condenser and drying tube. An ethanolic solution of hydroxylamine was made up by dissolving 1.74 g. (*ca.* 0.024 mole) hydroxylamine hydrochloride (Coleman and Bell, Reagent, minimum assay 96%) in 36 ml. absolute ethanol, and treating this solution dropwise with about one half of the sodium

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(16) W. S Bishop, *Org. Syntheses*, Coll. Vol. III, 613 (1955)

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(18) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

(19) W. H Lycan and R. Adams, *J. Am. Chem. Soc.*, **51**, 628 (1929).

(20) R. W. Stoughton, *J. Org. Chem.*, **2**, 514 (1938).

(21) C. D. Hurd and D. G. Botteron, *J. Org. Chem.*, 11 207 (1946).

ethoxide solution. The flask was cooled in ice during the neutralization, which was carried on until a drop of the mixture was alkaline to phenolphthalein. The precipitated sodium chloride was then filtered off using suction, and the filter washed with a small amount of absolute ethanol. The hydroxylamine solution was added to a solution of 5.0 g. (0.022 mole) ethyl sebacamate in 10 ml. of absolute ethanol, followed by the remainder of the sodium ethoxide solution. Reaction commenced at once with a rise in temperature, and the solution was cooled in ice for about 0.5 hr., at the end of which time a white precipitate had separated. After standing at room temperature for 1.5 hr. longer, the mixture was again cooled in ice and the sodium salt of the hydroxamic acid was filtered off. The flask and precipitate were washed with a small amount of ice cold absolute ethanol. After drying in the vacuum desiccator, the salt weighed 3.8 g. (73% yield). 3.3 g. of this material was dissolved in about 40 ml. distilled water and acidified by addition of glacial acetic acid. The solution was cooled in ice, and the precipitated free acid filtered off and washed with ice cold water. The dried product weighed 2.5 g. (83% yield from the salt; 61% of the ester) and melted at 120–123.5°.

The yield of the sodium salt could be increased to 92.5% by treating ethyl sebacamate with hydroxylamine in solution in the absence of sodium ethoxide for 2 hr. in an ice bath, adding the sodium ethoxide solution and permitting to stand at room temperature for 1 hr. longer, and finally adding an equal volume of absolute ether to render the salt less soluble. The yield of free acid from the salt was not altered when the *p*H was lowered to 7.1 with the aid of a *p*H meter.

A sample of the hydroxamic acid suitable for analysis and kinetic studies was obtained by two recrystallizations from water. If the water solutions are only moderately concentrated so that crystallization takes place after some cooling, a white crystalline material is obtained which melts at 127–127.5° and gives an intense red-violet coloration with ferric chloride in solution.

Anal. Calcd. for $C_{10}H_{20}N_2O_3$: C, 55.5; H, 9.3; N, 13.0. Found: C, 55.7; H, 9.3; N, 13.2.

If the acid is crystallized from hot concentrated aqueous solution, a material melting at 140.5–141.5° may be obtained which is evidently a different crystalline modification of the hydroxamic acid. This material gives the same test with ferric chloride, and may be converted to the lower-melting form by recrystallization from dilute aqueous solution, or solutions in absolute ethanol, ethanol-ether or ethanol-benzene. Sodium in dilute aqueous alkali and neutralization with acetic acid also leads to the lower-melting form.

Anal. Found: C, 55.5; H, 9.3; N, 13.0.

*9-(N-Methylcarboxamido)pelargonohydroxamic acid.** (*N*-Hydroxy-*N'*-methylsebacamide) was prepared from ethyl *N*-methylsebacamate by a procedure similar to that used for the amide above, with the exception that the hydroxylamine solution was made up by treating a suspension of the hydrochloride in ethanol rather than a solution with sodium ethoxide. This is an alternative procedure described by Hurd and Botteron.[21] From 9.3 g. (0.038 mole) of the ester was obtained 7.3 g. of a sodium salt, which on acidification with acetic acid produced 5.0 g. of an impure product melting at 93–103°. Recrystallization from absolute ethanol and then from water produced 2.8 g. (32% yield from the ester) of material melting at 123–124.5° and giving a red-violet color with ferric chloride. Further recrystallization from ethanol gave an analytical sample of melting point 125–126.5°.

Anal. Calcd. for $C_{11}H_{22}N_2O_3$: C, 57.4; H, 9.6; N, 12.2. Found: C, 58.1, 57.8; H, 9.8, 9.8; N, 12.0.

The low purity of the precipitated acid and low yield of product are believed due to incomplete liberation of hydroxylamine from its hydrochloride in suspension. Hydroxylamine would then be present in less than an equivalent amount to the ester in the reaction mixture, permitting the ester to be partially saponified by hydroxide ion, a contaminant of the sodium ethoxide solution. This would produce *N*-methylsebacamic acid, the probable impurity.

*10-Hydroxycaprohydroxamic acid** was prepared by the same procedure as the *N*-methylcarboxamido compound, and in this instance also considerable difficulty was encountered with impurities. 7.8 g. (0.042 mole) of ethyl 10-hydroxycaprate produced 6.0 g. of sodium salt, and upon acidification of this with an excess of glacial acetic acid there was obtained 4.7 g. of mixed acids melting over a wide range. After recrystallization from water failed to produce pure material, the remaining 3.2 g. of product were dissolved in 30 ml. of 5% aqueous sodium hydroxide and filtered. The filtrate was then treated dropwise with glacial acetic acid until the *p*H was lowered to 7.5. After chilling in the refrigerator, the white precipitated product was filtered off and dried. The material weighed 2.7 g. and melted over a wide range. Recrystallization from water yielded 2.1 g. (25%) of crystalline product melting at 100–101°, which gave a strong positive test with ferric chloride. A further recrystallization from water afforded an analytical sample.

Anal. Calcd. for $C_{10}H_{21}NO_3$: C, 59.1; H, 10.4; N, 6.9. Found: C, 59.8; H, 10.4; N, 6.8.

The *p*H of the filtrate of the precipitation solution was lowered to 2.1 by the addition of 10% hydrochloric acid, the mixture cooled, and the white precipitate filtered off and dried. There was obtained 0.48 g. of a compound melting at 72–74°, evidently 10-hydroxycapric acid (lit. m.p. 75–76° corr.)[19] resulting from saponification of the ester.

B. *Hexanehydroxamic acid* was synthesized from ethyl caproate by the general procedure given above, except that the solution of the ester and hydroxylamine was permitted to stand at room temperature for 4 hr. before addition of the sodium ethoxide, and an equal volume of absolute ether was added. Only a small amount of solid had separated after standing in the refrigerator for several days, but concentration of the solution and further addition of absolute ether produced several crops of the salt, the total weight of which was 9.8 g. This was dissolved in the minimum amount of water (*ca.* 40 ml.) and the *p*H was adjusted to 7.4 by the addition of glacial acetic acid. After chilling in ice, the white solid precipitate was filtered off, washed with a little ice cold water, and dried. Recrystallization from benzene produced 4.2 g. (47% yield) of mica-like plates melting at 61.5–63.5° and giving an intense red-violet coloration with ferric chloride. The melting point reported in the literature is 63.5–64°.[22]

C. *D-Gluconohydroxamic acid* was prepared from delta-gluconolactone as directed by Mathis,[23] with the substitution of ethanol for methanol as the reaction solvent. The weight of material melting at 136.5–138.5° (dec.) was 22.5 g. (95% yield). The literature melting point is 138–140° (dec.).[23] For kinetic studies, the material was recrystallized twice from water-ethanol. It was found that under the conditions of the kinetic runs D-gluconohydroxamic acid takes up alkali at an appreciable rate, probably due to hydrolysis of the hydroxamic acid function. The data were accordingly corrected for this.

D. *Carboxy derivatives. N-hydroxysuccinamic acid.* A sample of this compound was prepared by the action of hydroxylamine on succinic anhydride in ethanol solution,[24] and recrystallized once from methyl ethyl ketone. This material melted at 101–106°, while the literature value is 105–106° (sample prepared by the action of benzyloxyamine on succinic anhydride, followed by catalytic hydrogenation of the product[25]). An attempt to further purify the compound by recrystallization from methyl ethyl ketone was

(22) Y. Inoue and H. Yukawa, *J. Agr Chem. Soc. Japan*, 16, 504 (1940); *Chem. Abstr.*, 35, 731[1] (1941).

(23) F. Mathis, *Compt. rend.*, 229, 226 (1949).

(24) G. Errera, *Gaz. Chim. ital.*, 25II, 25 (1895).

(25) D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 631 (1955).

unsuccessful. Titration revealed that the sample was only 69.7% pure, and probably contaminated by succinic acid.

*N-Hydroxymaleamic acid** was synthesized in a similar manner from maleic anhydride. There was obtained a 48.5% yield of tan triangular plates, melting at 121–128° (dec.). Ferric chloride in aqueous solution produced an intense reddish purple color. According to titration data, this material is 72.5% pure, but attempts to improve it by recrystallization were unsuccessful.

Anal. Calcd. for $C_4H_5NO_4$: C, 36.7; H, 3.8; N, 10.7. Found: C, 35.1; H, 3.8; N, 10.2.

*N-Hydroxyoxalamic acid** (oxalomonohydroxamic acid). Although this compound has not been prepared previously, the sodium, copper, barium, and lead salts have been reported.[26] The copper salt, however, was probably the mixed copper–sodium salt $(NaOOCCONHO)_2Cu$, since upon treatment with hydrogen sulfide it produced the monosodium salt NaOOCCONHOH.

The potassium salt KOOCCONHOH was prepared by the action of hydroxylamine in ethanol on potassium ethyl oxalate. This compound is unchanged on heating to 250°, but decomposes suddenly when held near a flame. Aqueous ferric chloride yields a deep red-brown colored complex, and aqueous cupric acetate a bright green precipitate, probably $(KOOCCONHO)_2Cu$.

The free hydroxamic acid is believed to have been isolated in low yield as follows. The *p*H of a solution of the potassium salt was lowered to 0.19 by the addition of dilute hydrochloric acid, at which point 90% of the carboxyl groups should be in the undissociated form, assuming that the *p*K of the carboxyl group of oxalomonohydroxamic acid is the same as the first *p*K of oxalic acid (1.19). Addition of cupric chloride to this solution yielded a cupric salt, probably $(HOOCCONHO)_2Cu$, which liberated the hydroxamic acid on treatment with hydrogen sulfide.

14.3 g. (0.1 mole) of the potassium salt was dissolved in 150 ml. of water, and the *p*H lowered to 0.19 by the dropwise addition of 3*N* hydrochloric acid with vigorous stirring. At this point there was added dropwise a solution of 25.6 g. (0.15 mole) of cupric chloride dihydrate in 50 ml. of water, which had been adjusted to *p*H 0.15 with concentrated hydrochloric acid. The light green precipitate of copper salt began to separate, and the mixture was allowed to stand in the refrigerator overnight. The copper salt was then filtered off under suction, washed with water and then methanol, and dried on the filter, weight 7.57 g. This was suspended in 150 ml. of methanol and hydrogen sulfide was passed in with occasional shaking. When it was judged that all of the copper salt had reacted, the copper sulfide was filtered off and washed with methanol. The combined filtrate and washings were evaporated under reduced pressure to produce a moist white solid, which was redissolved in 25 ml. absolute ethanol, filtered, and treated with several volumes of petroleum ether (34.5–55°). Since only a very small amount of material had appeared after standing for 3 days in the refrigerator, the solvents were evaporated once more to yield an oil, which on trituration with petroleum ether produced a solid. After filtration, washing with petroleum ether and drying, there was obtained 0.22 g. (2% yield) of a white product melting with vigorous decomposition at 130.5–134° to a white solid residue, which in turn melted at about 195° (dec.). The color produced with aqueous ferric chloride seemed to depend on the concentrations used and the *p*H, ranging from intense violet to red-brown. Although a satisfactory elemental analysis was not obtained, the titration curve was in good agreement with theory. Neutral equivalents: monobasic, 106 (calcd., 105); dibasic, 53.6 (calcd., 52.5).

Anal. Calcd. for $C_2H_3NO_4$: C, 22.9; H, 2.9; N, 13.3. Found: C, 20.3; H, 2.4; N, 12.1.

Acknowledgment. It is a pleasure to acknowledge the assistance of Mr. R. Proper in the synthetic work.

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(26) O. Dimroth and O. Dienstbach, *Ber.*, 41, 4077 (1908).

[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, INDIANA]

The Reaction of Maleic Hydrazide with Formaldehyde and Alcohols in Acidic Medium[1,2]

HENRY FEUER AND RONALD HARMETZ

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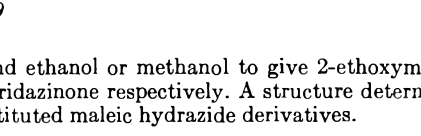
Maleic hydrazide reacts in the presence of acid with formaldehyde and ethanol or methanol to give 2-ethoxymethyl-6-hydroxy-3(2H)-pyridazinone and 2-methoxymethyl-6-hydroxy-3(2H)-pyridazinone respectively. A structure determination is presented which unambiguously proves that these products are *N*-substituted maleic hydrazide derivatives.

Maleic hydrazide (I) has been reported to undergo a number of reactions with substitution on oxygen or nitrogen. Feuer and Rubinstein[3] recently reported that acylation and benzenesulfonylation of compound I resulted in the exclusive



I

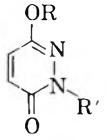
formation of 3-(1H-6-pyridazinonyl) acetate (II) and 3-(1H-6-pyridazinonyl) benzenesulfonate (III) respectively. The present authors established[4] that compound I underwent the Michael type reaction

(1) Paper VI in the series, "The Chemistry of Cyclic Hydrazides."

(2) (a) From the Ph.D. thesis of Ronald Harmetz; (b) presented before the Division of Organic Chemistry at the New York City Meeting of the American Chemical Society, September, 1957.

(3) H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.*, 80, 5873 (1958).

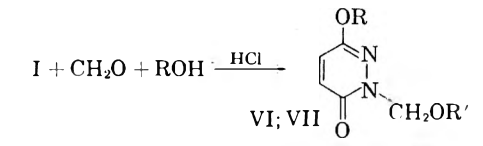
(4) H. Feuer and R. Harmetz, *J. Am. Chem. Soc.*, 80, 5877 (1958).



II, R = $-\overset{O}{\overset{\|}{C}}-CH_3$; R′ = H
III, R = $SO_2\phi$; R′ = H
IV, R = H; R′ = $CH_2-CH_2-COCH_3$
V, R = H; R′ = CH_2NR_2''

with methyl vinyl ketone and other activated double bonded compounds to afford *N*-substituted products (IV), and Hellmann and Löschmann[5] claimed to have obtained *N*-substituted Mannich products (V) by treating compound I with various amines and formaldehyde.

When compound I was treated with formaldehyde and dimethylamine hydrochloride in an ethanolic solution containing a small quantity of hydrochloric acid, the expected Mannich-type product was not obtained. Instead, a small amount of product was isolated, the neutralization equiva-



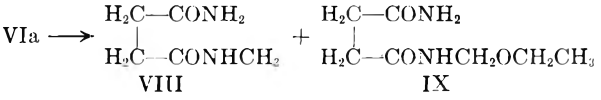
VIa; R=H; R′=C_2H_5 VIIa; R=H; R′=CH_3
VIb; R=C_2H_5; R′=H VIIb; R=CH_3; R′=H

lent and elemental analysis of which were consistent with structures VIa and VIb. The same compound was obtained in an 82% yield (23% conversion), when dimethylamine hydrochloride was omitted from the reaction mixture.

When an analogous reaction was carried out with methanol, a white crystalline solid was secured in 34% yield (7% conversion). The elemental analysis of this material was in agreement with structures VIIa and VIIb.

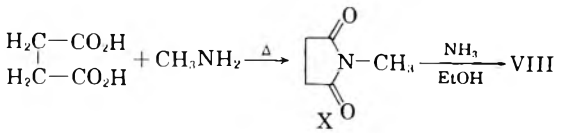
The presence of an alkoxy group in compounds VI and VII was indicated by their infrared spectra, which showed a characteristic ether band at 9.15 μ. Further confirmation of an ether linkage was secured when both compounds gave a positive Zeisel alkoxy test.

In order to determine its structure unambiguously, compound VI was treated with Raney nickel in refluxing ethanol, because it has been recently established[4] that *N*-substituted maleic hydrazides were converted by this procedure to substituted succinamides. When compound VI was subjected to these hydrogenolysis conditions, two compounds VIII and IX, m.p. 160–161° and 142–144°, were obtained. They were identified as amides by their infrared spectra. Compound



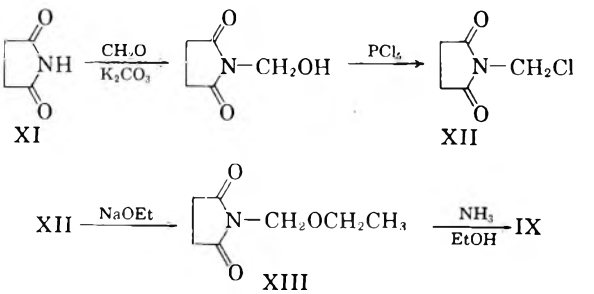
VIII

VIII was identified as *N*-methylsuccinamide by its elemental analysis and comparison with an authentic sample. Authentic *N*-methylsuccinamide (VIII) was prepared by the ammonolysis of *N*-methylsuccinimide (X).



Compound IX could not be sufficiently purified for elemental analysis, but was definitely identified as *N*-ethoxymethylsuccinamide (IX), by comparison with an authentic sample which was prepared as shown in Scheme I.

SCHEME I



N-Ethoxymethylsuccinimide (XIII) was prepared in a 75% yield from succinimide (XI) by following the procedure of Cherbuliez and Sulzer.[6] The desired compound *N*-ethoxymethylsuccinamide (IX) was obtained in a 47% yield by heating compound XIII at 100° in a sealed tube containing 95% ethanol saturated with ammonia. It was identified by its elemental analysis and infrared spectrum, which was identical with that of compound IX obtained from the hydrogenolysis of compound VIa. Also, a mixed melting point determination of these two products did not show a depression.

The above data unambiguously established that maleic hydrazide reacted in the presence of hydrochloric acid with formaldehyde and ethanol or methanol to afford the *N*-substituted maleic hydrazide derivatives VIa and VIIa.

The ultraviolet spectra of compounds VIa and VIIa showed absorption maxima at 315 mμ, which is in agreement with our previous findings[4] that *N*-substituted maleic hydrazide derivatives show absorption maxima in the region 316–318 mμ, while the *O*-substituted compounds absorb in the region 306–308 mμ.

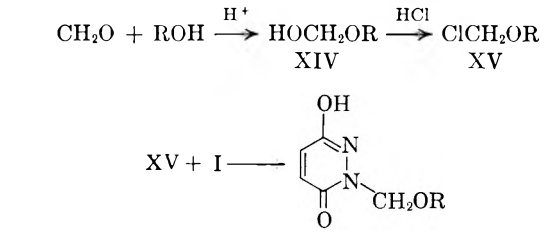
PROPOSED REACTION PATH

Two possible reaction paths leading to the formation of compounds VIa and VIIa may be postulated.

The first involves an initial condensation between formaldehyde and the alcohol to produce a hemiacetal (XIV), which in turn reacts with the

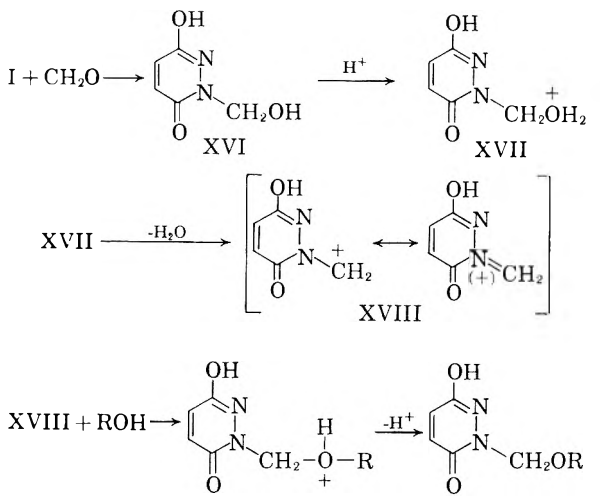
(5) H. Hellmann and I. Löschmann, *Angew. Chem.*, **67**, 110 (1955); *Chem. Ber.*, **89**, 594 (1956).

(6) E. Cherbuliez and G. Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925).



hydrochloric acid to yield a chloromethyl alkyl alkyl ether (XV). The latter then reacts with maleic hydrazide to give the final product. The postulated formation of a chloromethyl alkyl ether (XV) as an intermediate receives support from the reports of Farren[7] and Reychler[8] that chloromethyl ethyl ether and chlorodimethyl ether can be prepared by treating ethanol or methanol with paraformaldehyde and hydrogen chloride. Additional support for intermediate XV was obtained when the reaction of maleic hydrazide with chloromethyl ethyl ether gave a 67% yield (12% conversion) of VIa.

The other reaction path for the formation of compounds VIa and VIIa involves an initial reaction between maleic hydrazide (I) and formaldehyde to yield *N*-hydroxymethylmaleic hydrazide



(XVI) which, after protonation and loss of a molecule of water, is converted to the carbonium ion XVIII. This intermediate is then transformed, by nucleophilic attack of the alcohol and subsequent loss of a proton, to the final product.

EXPERIMENTAL

2-Ethoxymethyl-6-hydroxy-3(2H)-pyridazinone (VIa). (a) *Using Hydrochloric Acid.* In a 200 ml. flask were placed 11.2 g. (0.1 mole) of maleic hydrazide, 3.3 g. (0.11 mole) of paraformaldehyde, 125 ml. of absolute ethanol, and 10 ml. of concd. hydrochloric acid. The mixture was refluxed for 24 hr. and then kept at 5° for several more hr. Filtration afforded 6.3 g. of unreacted maleic hydrazide. The filtrate was evaporated to one half its volume and kept at 5° overnight. Three g. of product, m.p. 138–139° was obtained which was recrystallized from benzene, m.p. 142–143°. The filtrate was evaporated to approximately 20 ml. and placed at −15° for several hr. Upon filtration a solid was obtained which was extracted with hot benzene until no precipitate formed on cooling the extract. By this method an additional 1.0 g. (82% yield, 23% conversion) of *2-ethoxymethyl-6-hydroxy-3(2H)-pyridazinone* (VIa) was obtained.

Anal. Calcd. for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46; neut. equiv., 170. Found: C, 49.44; H, 5.98; N, 17.04; neut. equiv., 168.

(b) *Employing Chloromethyl Ethyl Ether.* A mixture of 5.6 g. (0.05 mole) of maleic hydrazide, 4.7 g. (0.05 mole) of chloromethyl ethyl ether, and 50 ml. of absolute ethanol was refluxed for 24 hr. and then kept at 10° for several more. Upon filtration 2.1 g. of unreacted maleic hydrazide was obtained. Evaporation of the filtrate afforded 4.5 g. of solid, m.p. 140–300°, which was subsequently extracted with 200 ml. of hot benzene, which yielded on cooling 1.0 g. (67% yield, 12% conversion) of *2-ethoxymethyl-6-hydroxy-3(2H)-pyridazinone* (VIa), m.p. 135–136°. Recrystallization from benzene raised the melting point to 141–142°.

The infrared spectra of compound VIa prepared by methods "a" and "b" were superimposable and showed a band at 9.15 μ for the ether linkage and a medium band at 6.00 μ (ring carbonyl). λ_{max} 95% EtOH 315 (log ϵ 4.48).

2-Methoxymethyl-6-hydroxy-3(2H)-pyridazinone (VIIa). In a 200 ml. round-bottom flask, equipped with a stirrer and reflux condenser, were placed 11.21 g. (0.1 mole) of maleic hydrazide, 3.0 g. (0.1 mole) of paraformaldehyde, 10 ml. of concd. hydrochloric acid, and 125 ml. of methanol. The mixture was refluxed for 22 hr. and then filtered to remove 2.1 g. of unreacted maleic hydrazide. An additional 7.0 g. of maleic hydrazide was recovered by cooling the filtrate to 5°. The filtrate was concentrated to 20 ml. and cooled to 10° for several hours. Subsequent filtration yielded 1.0 g. (34% yield, 7% conversion) of *2-methoxymethyl-6-hydroxy-3(2H)-pyridazinone* (VIIa) m.p. 149–153°. After recrystallization from toluene the melting point was raised to 153–154°. The infrared spectrum showed a strong band at 9.15 μ for the ether linkage and a medium band at 6.02 μ (ring carbonyl). λ_{max} 95% EtOH 315 (log ϵ 3.52).

Anal. Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.13; H, 5.08; N, 18.18.

Hydrogenolysis of 2-Ethoxymethyl-6-hydroxy-3(2H)-pyridazinone (VIa). In a 500 ml. round-bottom flask, equipped with a reflux condenser, were placed 70 ml. of settled Raney nickel,[9] 250 ml. of 70% ethanol and 3.4 g. (0.02 mole) of compound VIa. The mixture was refluxed for 5 hr., centrifuged, and decanted while still hot. The Raney nickel was washed with 500 ml. of boiling 95% ethanol, centrifuged, and the supernatant liquid decanted. Combination and subsequent evaporation of the ethanolic solutions afforded 2.3 g. of a mixture, m.p. 95–125°, containing *N*-methylsuccinamide and *N*-ethoxymethylsuccinamide. The mixture was extracted with 100 ml. of warm ethylene dichloride and upon evaporation of the solvent a solid was obtained which was wastefully recrystallized twice from ethylene dichloride, and four times from acetonitrile to afford *N-ethoxymethylsuccinamide*, m.p. 142–144°. Further purification of this compound was unsuccessful. Recrystallization of the solid, which remained after the ethylene dichloride extraction, from acetonitrile yielded pure *N-methylsuccinamide*, m.p. 160–161°.

Anal. Calcd. for $C_5H_{10}O_2N_2$: C, 46.16; H, 7.75; N, 21.53. Found: C, 46.15; H, 7.94; N, 21.67.

N-Methylsuccinamide (VIII). *N*-Methylsuccinimide[10] (11.3 g., 0.1 mole), and 50 ml. of 95% ethanol were placed in a combustion tube and ammonia was bubbled into the mixture until the solution was saturated. The tube was then

(7) J. W. Farren, H. R. Fife, F. E. Clark and C. E. Garland, *J. Am. Chem. Soc.*, **47**, 2419 (1925).

(8) A. Reychler, *Bull. soc. chim.*, [4] **1**, 1195 (1907).

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

(10) N. Menschutkin, *Ann.*, **182**, 92 (1877).

sealed and heated for 6 hr. at 100°. The mixture was evaporated to dryness and the solid obtained was treated with 50 ml. of cold acetonitrile. Filtration afforded 3 g. (23% conversion) of *N-methylsuccinamide*, m.p. 154–156°, and evaporation of the filtrate yielded unreacted *N*-methylsuccinimide. Recrystallization of the product from acetonitrile raised the melting point to 160–161° (lit. value,[11] m.p. 158–162°).

A mixed melting point between this compound and the higher melting product obtained by the hydrogenolysis of compound VIa gave no depression. The infrared spectra of these two substances were superimposable and showed strong characteristic amide bands at 3.08, 3.21, and 6.10 μ.

Anal. Calcd. for $C_5H_{10}O_2N_2$: C, 46.16; H, 7.75; N, 21.53. Found: C, 46.15; H, 7.83; N, 21.46.

N-Ethoxymethylsuccinamide (IX). In a combustion tube were placed 12.5 g. (0.079 mole) of *N*-ethoxymethylsuccinimide[6] and 50 ml. of 95% ethanol. After saturating the solution with liquid ammonia, the tube was sealed and heated for 6 hr. at 100°. Subsequent evaporation of the solvent afforded a mixture of solid product and liquid starting material which was separated by filtration. Recrystallization of the solid from acetonitrile afforded 6.5 g. (47% conversion) of *N-ethoxymethylsuccinamide*, m.p. 138–145°. Two additional recrystallizations raised the melting point to 146–146.5°.

A mixed melting point determination between this compound and the lower melting product obtained from the reduction of compound VIa showed no depression (m.p. 144–146°). The infrared spectra of these two substances were superimposable and showed strong characteristic amide bands at 2.95, 3.01, 3.12 and 6.08 μ and an aliphatic ether band at 9.05 μ.

Anal. Calcd. for $C_7H_{14}O_3N_2$: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.17; H, 8.09; N, 16.34.

LAFAYETTE, INDIANA

(11) F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 628 (1945).

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Synthesis of Methylenedioxyphenyl Compounds from Isosafrole and Sesamol

B. H. ALEXANDER, S. I. GERTLER, R. T. BROWN, T. A. ODA, AND M. BEROZA

Received April 17, 1959

During a search for compounds with improved insecticidal activity, 31 new ethers and esters were synthesized from sesamol and isosafrole. Methods of preparation, physical constants, and some biological information are reported herein.

As part of our search for new compounds with improved insecticidal activity, 3,4-methylenedioxyphenyl compounds containing a halogen in the 6- position of the phenyl group were synthesized. Their preparation and that of their intermediates, totaling 31 new compounds, are given. Most were obtained in good or high yield.

Some of the compounds are related to the insecticide 6-chloropiperonyl chrysanthemumate (barthrin)[1]; *i.e.*, they contain a bromine instead of a chlorine atom in the 6- position of the 3,4-methylenedioxyphenyl group. Unfortunately, no substantial improvement in insecticidal activity over barthrin was attained. The addition of bromine usually increased insecticidal activity over the unbrominated analog, but it also decreased activity in several instances.

The derivatives of isosafrole (1,2-methylenedioxy-4-propenylbenzene), given in Table I, were prepared essentially as outlined by Pond and coworkers[2] with one improvement. These investigators brominated isosafrole in ether and reported no yields; we used both ether and glacial acetic acid as solvents and obtained higher yields and a purer product with the latter.

Derivatives of sesamol (3,4-methylenedioxyphenol), given in Table II, were prepared according to published procedures.[3] The shift of the double bond (conversion of an allyl to a propenyl group) and the preparation of allylmethylenedioxyphenol from its ether precursor, by the Claisen rearrangement, were carried out in the usual way.[4] Bromination of the double bond took place readily in a solution of glacial acetic acid at 10°.

Results of screening the compounds as chigger and body louse toxicants, mosquito larvicides, and mosquito repellents are given in Table III. The methods of test and classification of activity are the same as those given by King.[5a] Some of the ethers (I–X) of Table I showed excellent activity as mosquito larvicides; however, the corresponding activity of the esters (XI–XVIII) was nil. Good larvicidal and pediculocidal activities were shown by the sesamol ethers (XX–XXVI); one of these (XX) is a positional isomer of myristicin (3,4-methylenedioxy-5-methoxy-1-allylbenzene), a natural product known to be synergistic with pyrethrins.[6] The best pediculocide (XXIII) differs

(1) W. F. Barthel and B. H. Alexander, *J. Org. Chem.*, **23**, 1012 (1958); W. A. Gersdorff and P. G. Piquett, *J. Econ. Entomol.*, **62**, 85 (1959).

(2) F. J. Pond, E. S. Erb, and A. G. Ford, *J. Am. Chem. Soc.*, **24**, 327 (1902); F. J. Pond and C. R. Siegfried, *J. Am. Chem. Soc.*, **25**, 262 (1903).

(3) L. Claisen and O. Eisleb, *Ann.*, **401**, 36 (1913); C. F. H. Allen and J. W. Gates, Jr., *Org. Syntheses*, Coll. Vol. III, 140 (1955).

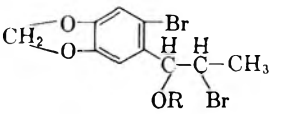
(4) D. S. Tarbell, *Org. Reactions*, **2**, 26 (1944).

(5a) W. V. King, *U. S. Dept. Agr. Handbook*, No. 69, 397 pp. (1954). (b) p. 2.

(6) R. Kerr, Australia, *Commonwealth Sci. and Ind. Res. Bull.* **261** (1951).

TABLE I

ETHERS FROM 1,2-DIBROMO-1-(2-BROMO-4,5-METHYLENEDIOXYPHENYL)PROPANE AND ESTERS FROM 6-BROMO-*alpha*-(1-BROMOETHYL)PIPERONYL ALCOHOL



No.	R	Yield, %	B.P./ (Mm.)	n_D^{25} or M.P.	Molecular Formula	Analysis			
						Carbon		Hydrogen	
						Calcd.	Found	Calcd.	Found
I	C_3H_7	82	125–127/0.03	1.5587	$C_{13}H_{16}Br_2O_3$	41.07	41.11	4.21	4.37
II	C_4H_9	85	138–140/0.05	1.5536	$C_{14}H_{18}Br_2O_3$	42.64	42.57	4.57	4.46
III	C_5H_{11}	78	146–148/0.03	1.5488	$C_{15}H_{20}Br_2O_3$	44.12	44.40	4.90	5.39
IV	$CH_2(CH_2)_4CH_3$	86	150–152/0.03	1.5449	$C_{16}H_{22}Br_2O_3$	45.50	45.61	5.21	4.87
V	$CH_2CH_2OCH_3$	62	153–154/0.05	1.5659	$C_{13}H_{16}Br_2O_4$	39.39	39.74	4.04	4.31
VI	$CH_2CH_2OC_2H_5$	75	147–149/0.03	1.5577	$C_{14}H_{18}Br_2O_4$	40.97	41.10	4.39	4.27
VII	$CH_2CH_2OC_4H_9$	68	163–164/0.03	1.5467	$C_{16}H_{22}Br_2O_4$	43.84	42.73[a]	5.02	5.17
VIII	$CH(CH_3)_2$	79		58–59 (alcohol)	$C_{13}H_{16}Br_2O_3$	41.07	39.47[a]	4.21	5.06
IX	$CH_2CH(CH_3)_2$	87	137–138/0.04	1.5547	$C_{14}H_{18}Br_2O_3$	42.64	42.08	4.57	4.96
X	$CH_2CH_2CH(CH_3)_2$	92	141–142/0.03	1.5487	$C_{15}H_{20}Br_2O_3$	44.12	43.54	4.90	5.09
XI	$C(=O)CH_2Cl$	61	180/0.6	1.5808	$C_{12}H_{11}Br_2ClO_4$	34.74	34.96	2.65	2.89
XII	$C(=O)CH(CH_3)_2$	66	162/0.1	1.5608	$C_{14}H_{16}Br_2O_4$	41.17	41.17	3.92	4.02
XIII	$C(=O)C_2H_5$	90	162–175/0.7	1.5683	$C_{13}H_{14}Br_2O_4$	39.62	40.16	3.58	3.72
XIV	$C(=O)C_{10}H_7$	80		130–132 (benzene and methanol)	$C_{21}H_{16}Br_2O_4$	51.24	51.34	3.28	3.49
XV	$C(=O)C_6H_4Cl$	87		93–94 (alcohol)	$C_{17}H_{13}Br_2ClO_4$	42.84	43.09	2.75	2.97
XVI	$C(=O)C_4H_3O$	88		111–112 (methanol and water)	$C_{15}H_{12}Br_2O_5$	41.69	41.92	2.80	3.12
XVII	$C(=O)CCl_3$	83		103–105 (alcohol)	$C_{12}H_9Br_2Cl_3O_4$	29.81	29.77	1.88	2.09
XVIII	$C(=O)C_6H_4OCH_3$	87		118–119 (alcohol)	$C_{18}H_{16}Br_2O_5$	45.79	45.30	3.42	3.44

[a] The low values are probably due to some impurity which we were not able to remove.

from the other sesamol ethers in that it contains a triple bond.

The striking feature of Table III is the variation in effectiveness shown by the compounds against different species of arthropods. As in the King report,[5b] the results indicate that compounds ineffective against one species may be effective against another.

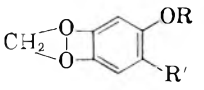
Several of the compounds were not subjected to all the entomological tests because of insolubility in solvents, obnoxious odor, toxicity to warm-blooded animals, or skin irritation.

EXPERIMENTAL

The physical properties, yields, and elemental analyses of the individual compounds are given in Tables I and II.

TABLE II

COMPOUNDS DERIVED FROM SESAMOL (3,4-METHYLENEDIOXYPHENOL)



No.	R	R′	Yield, %	B.P./ (Mm.)	n_D^{25} or M.P.	Molecular Formula	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XIX	H	$CH_2CH{:}CH_2$	77	122–128/ 1.3	76–77 (benzene[a])	$C_{10}H_{10}O_3$	67.40	67.80	5.66	5.97
XX	CH_3	$CH_2CH{:}CH_2$	63	119–124/ 2.5	1.5412	$C_{11}H_{12}O_3$	68.73	68.84	6.30	6.44
XXI	C_3H_7	$CH_2CH{:}CH_2$	51	108–114/ 0.4	1.5268	$C_{13}H_{16}O_3$	70.88	69.91	7.32	7.18
XXII	$CH_2C(CH_3){:}CH_2$	H	63	100–101/ 0.9	1.5324	$C_{11}H_{12}O_3$	68.73	68.17	6.30	6.17
XXIII	$CH_2C{:}CH$	$CH_2CH{:}CH_2$	73	113–121/ 0.5	1.5482	$C_{13}H_{12}O_3$	72.20	72.08	5.60	5.54
XXIV	$CH(CH_3)_2$	$CH_2CH{:}CH_2$	45	98–100/ 0.2	1.5242	$C_{13}H_{16}O_3$	70.88	71.44	7.32	7.33
XXV	C_3H_7	C_3H_7	79	157–162/ 18	1.5119	$C_{13}H_{18}O_3$	70.24	69.73	8.16	8.01
XXVI	CH_3	$CH_2C(CH_3){:}CH_2$	74	93–110/ 0.6	1.5510	$C_{12}H_{14}O_3$	69.88	69.31	6.84	6.58
XXVII	O ‖ C—C_9H_{15}	$CH_2C(CH_3){:}CH_2$	44	133–160/ 1.0	1.4968	$C_{21}H_{26}O_4$	73.66	73.96	7.65	7.85
XXVIII	CH_3	$CH{:}CHCH_3$	37		48–49 (alcohol)	$C_{11}H_{12}O_3$	68.73	68.97	6.30	6.23
XXIX	$CH_2CHBrCH_2Br$	Br	80		67–68 (methanol)	$C_{10}H_9Br_3O_3$	28.81	28.96	2.18	2.45
XXX	CH_3	$CH_2CHBrCH_2Br$	46		121–122 (methanol and acetone)	$C_{11}H_{12}Br_2O_3$	37.53	37.94	3.44	3.61
XXXI	C_2H_5	$CH_2CHBrCH_2Br$	64		70–71 (methanol)	$C_{12}H_{14}Br_2O_3$	39.37	39.53	3.86	3.95

[a] Product quite soluble in benzene.

1,2-Dibromo-1-(2-bromo-4,5-methylenedioxyphenyl)propane. A mixture of isosafrole (324 g.) and glacial acetic acid (700 ml.) was cooled to 0° in a 4 l. beaker, and a solution of bromine (640 g.) in glacial acetic acid (400 ml.) was added dropwise with stirring over a period of 2 hr., while the temperature was kept below 15°. Crystallization occurred, and the mixture was allowed to stand at 25° overnight. After filtering off and washing the crystals with normal pentane and then water, a crude product melting at 101–106° (lit. 110–111°[2]) was obtained in 76% yield. Recrystallization from acetone and ether produced a pure product; however, the crude material was pure enough for use as an intermediate.

Ethers prepared from 1,2-dibromo-1-(2-bromo-4,5-methylenedioxyphenyl)propane (Table I, I–X). The preparation of 4-bromo-5-[2-bromo-1-(2-ethoxyethoxy)propyl]-1,2-methylenedioxybenzene (VI) illustrates the procedure. 1,2-Dibromo-1-(2-bromo-4,5-methylenedioxyphenyl)propane (40 g.) was mixed with redistilled 2-ethoxyethanol (100 ml.) and heated gently under reflux for several hours. The excess 2-ethoxyethanol was removed by distillation and the residue distilled *in vacuo*.

Esters prepared from 6-bromo-α-(1-bromoethyl)piperonyl alcohol (Table I, XI–XVIII). The preparation of 6-bromo-α-(1-bromoethyl)piperonyl ester of 1-naphthoic acid (XIV) is typical. 6-Bromo-α-(1-bromoethyl)piperonyl alcohol[2] (34 g.), dry benzene (300 ml.), and pyridine (10 ml.) were mixed and 1-naphthoyl chloride (19.4 g.) was added with stirring. The mixture was heated gently at 40° for 6 hr. and allowed to stand at 25° overnight. The product was poured into a separatory funnel containing water, and the separated benzene layer was washed with 5% aqueous hydrochloric acid, water, saturated sodium bicarbonate, and finally with a saturated salt solution. The benzene layer was dried over anhydrous sodium sulfate, filtered, and after removal of the benzene a crystalline product was obtained. The noncrystalline esters were distilled for final purification.

2-Allyl-4,5-methylenedioxyphenol (Table II, XIX) *and related phenols.* The preparation of XIX is typical. 3,4-Methylenedioxyphenyl allyl ether[7] (89 g.) was heated under reflux in a stream of nitrogen to 220°, at which point the heating bath was removed and a very vigorous reaction (can get violent) took place raising the liquid temperature rapidly to 270°. When the temperature had fallen to 210°, heating with the bath was resumed for 0.5 hr. keeping the temperature at 210–220°. Distillation *in vacuo* gave the desired product.

(7) M. Beroza, *J. Agr. Food Chem.*, 4, 49 (1956).

TABLE III

RESULTS OF BIOLOGICAL TESTS WITH COMPOUNDS IN TABLES I AND II AGAINST VARIOUS ARTHROPODS[a]

No.	Chigger[b] Toxicant	Body Louse[c] Toxicant	Mosquito[d] Larvicide	Mosquito[e] Repellent
I	1	1	1	1
II	1	1	4	1
III	1	1	4	1
IV	1	1	2	1
V	1	1	2	1
VI	1	1	3	1
VII	1	2	4	1
VIII	1	1	4	1
IX	1	1	4	1
X	1	1	4	1
XI	1	1	1	1
XII	1	1	1	1
XIII	2	1	1	1
XIV	1	2	1	1
XV	1	1	1	1
XVI	1	1	1	...
XVII	...	3	1	...
XVIII	1	1	1	...
XIX	3	1	1	2
XX	...	3	2	1
XXI	...	4	3	1
XXII	...	3	3	1
XXIII	...	4A	3	1
XXIV	...	3	3	1
XXV	...	4	3	1
XXVI	...	4	3	1
XXVII	...	1	1	1
XXVIII	...	...	...	...
XXIX	1	1	2	1
XXX	...	1	1	1
XXXI	...	1	1	1

[a] Classification same as that given by King,[5a] class 1 least and class 4 or 4A most effective. [b] *Trombicula splendens* Ewing. [c] *Pediculus humanus humanus* L. [d] *Anopheles quadrimaculatus* Say. [e] *Aedes aegypti* (L.).

Ethers and esters (Table II, XX–XXI, XXIII–XXXI) *from phenols.* The ethers were prepared from the phenol, alkyl bromide, potassium carbonate, and dry acetone according to published procedures.[3] The ester was prepared in the usual way from a mixture of the phenol, benzene, pyridine, and the acid chloride.

1,2-Methylenedioxy-5-methoxy-4-propenylbenzene (Table II, XXVIII). XX (64 g.) was dissolved in 150 ml. of a saturated solution of potassium hydroxide in methanol.[4] Methanol was removed by distillation until a liquid temperature of 110° was reached, and the solution was then refluxed for 6 hr. After cooling, the mixture was poured into cold water and extracted with ether. The ether layer was washed with a saturated salt solution and dried over anhydrous sodium sulfate. After filtering and evaporating the ether, the residue (XXVIII) crystallized.

5-Bromo-1,2-methylenedioxy-4-(2,3-dibromopropoxy)-benzene (XXIX). A mixture of 3,4-methylenedioxyphenyl allyl ether[7] (47 g.) and glacial acetic acid (200 ml.) was cooled to 0°, and bromine (86 g.) was added with stirring at such a rate as to maintain the temperature below 15°. Stirring was continued for an additional hour at 15° and the mixture was allowed to stand at 25° overnight, after which it was poured into ice and water with stirring. After several hours the supernatant was decanted from the dark residue, and the latter was washed twice with cold water. Cold water was again added to the residue, and it was scratched to produce crystallization. The crystals were filtered, washed with cold water, and dried.

4-(2,3-Dibromopropyl)-5-methoxy-1,2-methylenedioxybenzene (XXX). This compound was prepared as above from XX (0.2 mole) and bromine (0.2 mole). The corresponding ethoxy compound (XXXI) was prepared from the ethoxy derivative in the same manner.

Acknowledgment. We are grateful to Shulton Inc., Clifton, N. J., for the sesamol used in this study, and to Dr. Carroll N. Smith and others of the staff of the Orlando, Fla., laboratory of the Entomology Research Division for conducting the biological tests.

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

Ocimene

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This paper describes an improved apparatus for preparing ocimene from α-pinene. It also outlines the method of analysis of the product mixture. Infrared absorption curves of ocimene, alloöcimene, dipentene, α-pinene, alloöcimene dimer, and a synthetic mixture of the products are included. The values calculated for ocimene were n_D^{25} 1.4851, d^{25} 0.7926 g./cc.

In 1907, Enklaar[1] stated that he obtained some ocimene by the isomerization of alloöcimene under the influence of a mixture of sulfuric and acetic acids. The known behavior of ocimene and alloöcimene makes such an isomerization unlikely. Several attempts in this laboratory to verify Enklaar's statement were unsuccessful.

In 1940, Rice[2] reported the vapor phase formation of ocimene from α-pinene. In 1951, Hawkins and Hunt[3] published a description and method of operating an apparatus for the production of ocimene from α-pinene in the vapor phase. More recently O'Connor and Goldblatt[4] indicated that they have prepared ocimene by the isomerization

(1) C. J. Enklaar, *Rec. trav. chim.*, **26**, 157 (1907).
(2) F. O. Rice, U. S. Patent **2,190,369**, Feb. 13, 1940.
(3) J. E. Hawkins and H. G. Hunt, *J. Am. Chem. Soc.*, **73**, 5379 (1951).
(4) R. T. O'Connor and L. A. Goldblatt, *Anal. Chem.*, **26**, 1726 (1954).

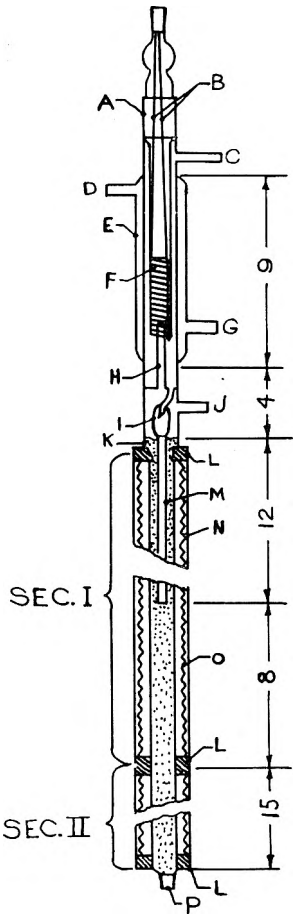
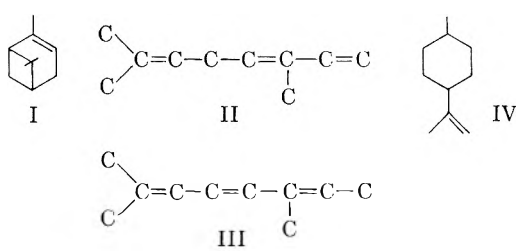


Fig. 1. Apparatus for production of ocimene by vapor phase pyrolysis of α-pinene

of α-pinene, but gave no description of the method used.

In view of the above it appeared profitable to construct a more efficient apparatus for the preparation of ocimene. This would then provide a more convenient source of ocimene for use in the determination of its physical and chemical properties.

When α-pinene is isomerized the principal components present in the product are α-pinene, I, ocimene, II, alloöcimene, III, and dipentene, IV.



Apparatus. The glass apparatus used for the preparation is shown in Fig. 1. The design is for a continuous process and involves the principle of reverse take-off.

A is a standard-taper joint, 45/50, *D* and *G* are the condenser water outlet and inlet respectively, and *L* is asbestos packing.

Liquid α-pinene from a reservoir enters the apparatus at tube *J* and runs into the protruded packing *K* where it is vaporized by the column heater, *N*.

The α-pinene vapor then passes up through tube *H* and over the electrically heated nichrome spiral *F*. This spiral is supported by a cage of glass rods. One lead wire passes through the one hollow tube used in the cage and is sealed through glass at the bottom end of this tube. The other lead wire is sealed through glass just above the pyrolysis spiral. These two lead wires *B* are connected to a variable autotransformer. Tube *C* is connected to a vacuum system. The pyrolysed α-pinene vapor is condensed in *E*. The condensed pyrolysate drains into the column through the tube *M*. A drop counter 1 is provided above the packing so that the rate of liquid passing over the pyrolysis spiral can be observed. Tube *M* directs the pyrolysate into the column packing to a sufficient depth so that recycling of ocimene is prevented. The column heating jacket is divided into two separately controlled sections. These heating jackets consist of six nichrome wire spirals running the length of the heating section. Operation is improved by insulating the column with glass wool.

The primary purpose of Section I is to vaporize the α-pinene and prevent the recycling of the ocimene. The liquid α-pinene from the reservoir serves as reflux in Section I. Section II is for the purpose of returning the unreacted α-pinene to Section I and allowing only the higher boiling alloöcimene, ocimene, and dipentene to pass down into the receiver connected at *P*. This receiver is cooled by passing cold water through its jacket. An outlet, attached to the water-cooled receiver, is connected to a three-way stopcock for evacuating a second receiver, which is detachable while the process is in operation.

The liquid pinene is delivered to tube *J* from a three-liter reservoir, connected to the vacuum line through a three-way stopcock. The vacuum lines from the reservoir, tube *C*, and the detachable receiver all lead to a cold finger dry ice trap. Any material trapped by the dry ice cold finger can be drained into the detachable receiver through its vacuum line. A drop counter is provided in the line from the reservoir to tube *J* for measuring the rate of introduction of α-pinene. This rate was regulated by a Hoke valve.

EXPERIMENTAL

Material used. The α-pinene used was obtained from the Glidden Company, Jacksonville, Fla., and was redistilled until $n_D^{25} = 1.4632 \pm 0.0001$.

Production of ocimene. The pyrolysis of α-pinene was usually carried out at about 5 mm. pressure to permit operation at lower temperatures. Once the proper vacuum had been established, the column heaters were turned on. The heaters were allowed to come to temperature at the operating voltage before α-pinene was introduced into the

TABLE I

COMPOSITIONS OF MIXTURES OBTAINED AT DIFFERENT VOLTAGES ACROSS THE PYROLYSIS SPIRAL

Volts	% Ocimene	% Alloöcimene	% α-Pinene	% Dipentene	Dipentene/ Ocimene	Alloöcimene + Ocimene/ Dipentene
27	14	0	62	15	1.1	0.9
28	29	9	40	27	0.9	1.4
30	29	19	16	29	1.0	1.7
33	19	25	14	35	1.8	1.3
35	29	28	10	35	1.2	1.6

column. The temperatures of the heating sections were indicated by thermocouples attached to an electronic recorder. After the introduction of liquid α-pinene, the column heating jacket temperatures quickly dropped to the operating level. The current in the pyrolysis spiral was not turned on until reflux appears at drop counter 1.

The four controllable variables of the apparatus are the power input to the pyrolysis spiral, the wattages developed in the two heating jackets, and the rate of introduction of the α-pinene. The power input to the pyrolysis spiral affects the heat transfer to the α-pinene vapor. A combination of this heat transfer rate and the rate of passage of α-pinene vapor over the spiral determines the temperature to which the vapor is heated. This temperature in turn determines the percentage of α-pinene which is isomerized in one pass over the spiral, the ratio of the dipentene to ocimene in the product, and the possible further isomerization of ocimene to alloöcimene before it is condensed. The α-pinene drop rate affects the column temperatures which in turn affect the efficiency of separating the α-pinene from the product.

The temperature of the upper column heater must be high enough to provide sufficient heat to vaporize the liquid α-pinene entering Section I and to vaporize the α-pinene in the liquid reflux from the pyrolysis spiral. The best indication of proper setting of the voltage across this heater is the ratio of the drop rate in the drop counter, 1, Figure 1, to the α-pinene drop rate from the reservoir. Under usual conditions this should be a minimum of 5 to 1. The amount of insulation on the outside of the heater must be kept constant after the proper setting is determined.

The temperature in the lower column must be high enough to strip practically all the α-pinene from the product before it enters the receiver. If either the percentage of α-pinene in the material coming into Section II or the rate of all material coming into Section II is too high, this section will be overloaded and the product will contain a substantial amount of α-pinene. If, on the other hand, the temperature of the lower heater is increased too much in order to compensate for this factor, the ocimene will be isomerized to alloöcimene. As long as this section is not overloaded, the proper voltage setting can be determined by the percentage of α-pinene in the product.

Low drop rate increases the percentage conversion on one pass over the spiral and the efficiency of α-pinene separation from the product, but may increase the proportion of alloöcimene found. The optimum drop rate, in the apparatus studied during this investigation, seemed to be between 5 and 30 drops a minute. Drop rates over 60 per minute tended to require excessive column temperatures to maintain reflux.

It is impossible to apply these optimum conditions to the operation of another apparatus; so, this information can be used only as a guide.

Experiments were run on the present column at various drop rates with 27, 28, 30, 33, 35, 36, and 37 volts across the pyrolysis spiral. Some of the mixtures obtained at the various voltages are shown in Table 1.

The important information given by these percentages is the ratios. The amount of α-pinene is not important since apparently it can be reduced to a low value by lowering the drop rate. Approximately the same amounts of ocimene were produced by the different voltages, so the optimum operating voltage is that which produces the smallest amounts of alloöcimene and dipentene. The dipentene is the most important impurity to keep at a low value since its removal by distillation is very difficult. It appears that the optimum voltage is 28–30 volts.

The ratios of alloöcimene plus ocimene to dipentene were somewhat better than obtained by hot tube pyrolysis at 350°.[5] By operating at a very high column temperature, a high spiral temperature and low drop rates, a very high concentration of alloöcimene can be obtained if alloöcimene is desired rather than ocimene.

Analysis of product. Separation of ocimene proved to be difficult. Even at 5 mm. it is believed that some ocimene isomerized due to the length of the heating period. The product was distilled at 5 mm. Hg pressure in a protruded packing distillation column, 3.5 cm. O.D. and 140 cm. long. Material boiling at 54° was collected. It contained some dipentene. This distillate was analyzed by the method of Hawkins and Hunt[3] for per cent ocimene by isomerizing it and a sample of pure alloöcimene in separate sealed tubes for 1 hr. at about 200°. This heating isomerized the ocimene to alloöcimene and caused some of the alloocimene formed, and some of the pure alloöcimene, to dimerize. Before heating, the alloöcimene had an n_D^{25} of 1.5424 and the ocimene, 1.4842. After heating, the alloöcimene was 1.5360 and the ocimene 1.5320. The difference between the refractive indices of the heated alloöcimene and dipentene (n_D^{25}, 1.4702) is divided into the difference between the refractive indices of the heated impure ocimene and dipentene. This is justified as the relation between the refractive index and the composition of alloöcimene-dipentene mixtures is nearly linear.[6] The calculation gave 94% ocimene. Since the ocimene isomerizes almost immediately at 200°, the alloöcimene produced from ocimene and the pure alloöcimene have nearly the same length of time to dimerize. Thus, using the refractive index of the heated pure alloöcimene as equivalent to that of heated pure ocimene is valid.

The 94% ocimene produced, boiling at 54°, at 5 mm., was found to have a refractive index of 1.4842, a density of 0.7953 g./cc. at 25°, a viscosity of 0.680 centipoise, and a surface tension of 25.4 dynes per cm.

The viscosity was obtained with an Ostwald viscometer. The surface tension was obtained with a Colthup and Torly maximum bubble pressure type apparatus.

If the refractive index of the 94% ocimene is corrected

(5) L. A. Goldblatt and S. Palkin, *J. Am. Chem. Soc.*, **63**, 3517 (1941).

(6) R. E. Fuguitt and J. E. Hawkins, *J. Am. Chem. Soc.*, **69**, 319 (1947).

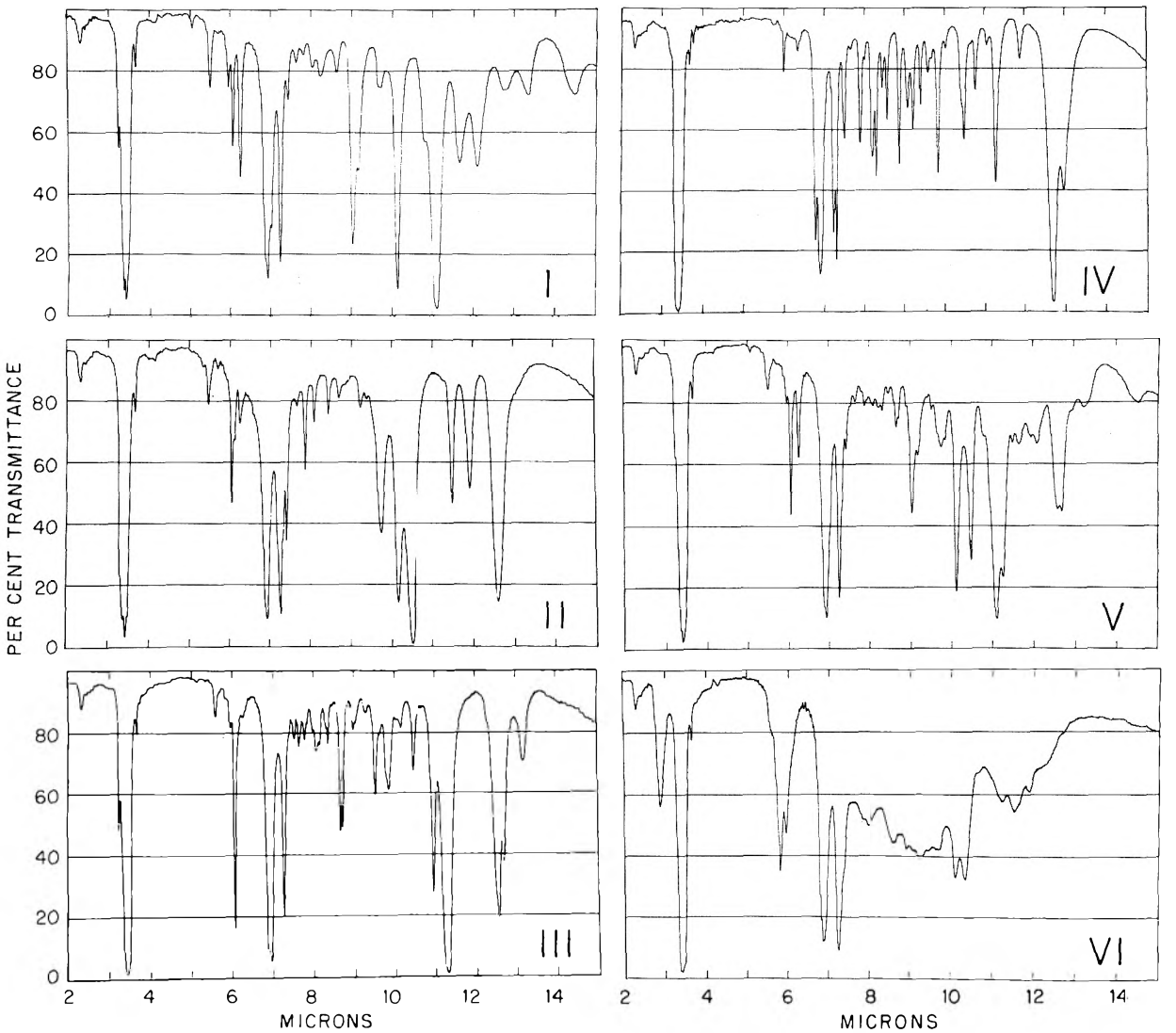


Fig. 2. Infrared absorption spectra (in a 0.0288 mm. cell). I. 94% Ocimene. II. Alloöcimene. III. Dipentene. IV. α-Pinene. V. Synthetic pyrolysis mixture. VI. Alloöcimene dimer.

by dividing the difference between the refractive index of dipentene, 1.4702, and that of the 94% ocimene by 0.94, and adding this to the refractive index of dipentene, a value of n_D^{25} 1.4851 is obtained for pure ocimene. If the density is corrected by dividing the difference between the impure ocimene density found and that of dipentene, 0.8370, by 0.94 and subtracting this from the density of dipentene, a value of 0.7926 at 25° is obtained. These values compare favorably with those of n_D^{20} 1.4873 and density at 20° of 0.8034 reported by O'Connor and Goldblatt.[4]

In order to determine optimum operating conditions of the ocimene apparatus it is necessary to analyze the pyrolysis product. The most convenient available method of analysis was by infrared. The infrared spectra of ocimene, alloöcimene from hot spiral pyrolysis, dipentene, α-pinene, and a synthetic pyrolysis mixture will be found in Figure 2.

These spectra are included as they were obtained with an instrument which was capable of greater resolution than shown by previously published spectra and cover a wider range of wave lengths which furnishes additional information.[4] The spectrum of the dimer is included as it readily forms from alloöcimene and has not been published previously.

The optical densities of the principal pyrolysis components at their characteristic infrared wave lengths also are given in Table II. The wave lengths suitable for quantitative work are given in Table III. The ocimene absorbancies in these tables were corrected for the presence of 6% dipentene by subtracting 0.06 times the dipentene absorbancy and adjusted to 100% ocimene by division by 0.94. An approximate method of analysis was developed using four wave lengths, at each of which only one component was a major absorber and all others absorbed at essentially the same low value. Using the equation of composition and average values of absorbance for the low absorbers, the following relations were developed for a 0.0288 mm. cell. $V_1 \cdots V_4$ = volume fractions of the various components. As = the optical density of the mixture at the particular wave length.

At 12.09 microns, $0.04\ (1 - V_1) + 0.32\ V_1 = As$, where V_1 = vol. fraction of ocimene

TABLE II

OPTICAL DENSITY AT CHARACTERISTIC INFRARED WAVE LENGTHS OF PURE COMPONENTS OF PYROLYSIS MIXTURE IN 0.0288 MM. CELL

Part I Alloöcimene		Part II Dipentene	
Wave Length, Microns	Optical Density	Wave Length, Microns	Optical Density
3.42	1.30	3.43	1.6
6.03	0.300	6.05	0.740
6.91	1.02	6.93	1.23
7.24	0.928	7.25	0.670
7.40	0.460	8.65	0.292
7.85	0.223	8.70	0.285
9.73	0.440	10.94	0.530
10.15	0.838	11.27	1.8
10.50	1.7	12.54	0.685
11.47	0.320	12.67	0.440
11.92	0.300		
12.59	0.770		

Part III α-Pinene		Part IV Ocimene	
Wave Length, Microns	Optical Density	Wave Length, Microns	Optical Density
3.40	2.00	3.40	1.10
6.77	0.635	6.05	0.244
6.88	0.925	6.23	0.372
7.22	0.580	6.91	0.892
7.38	0.790	7.24	0.408
7.50	0.285	9.02	0.645
7.89	0.250	10.12	1.08
8.18	0.290	11.10	1.7
8.87	0.313	11.66	0.310
9.21	0.260	12.10	0.292
9.84	0.350		
10.49	0.250		
11.27	0.384		
12.70	1.32		
12.96	0.287		

TABLE III

OPTICAL DENSITY OF PURE COMPONENTS OF PYROLYSIS MIXTURE IN 0.0288 CELL AT INFRARED WAVE LENGTHS MOST USEFUL IN QUANTITATIVE DETERMINATIONS

Wave Length, Microns	Ocimene	Allo-ocimene	Dipentene	α-Pinene
6.05	0.204	0.240	0.740[a]	0.043
8.65	0.066	0.065	0.292[a]	0.035
8.70	0.044	0.082	0.285[a]	0.032
8.87	0.072	0.057	0.040	0.313[a]
9.02	0.644[a]	0.046	0.076	0.110
9.73	0.118	0.440[a]	0.125	0.118
10.94	0.016	0.450	0.530[a]	0.022
11.64	0.307[a]	0.064	0.060	0.008
12.09	0.319[a]	0.066	0.028	0.013
12.96	0.100	0.067	0.078	0.287[a]

[a] Values, used in calculating composition of mixtures, determined at appropriate wave lengths.

At 9.74 microns, $0.12 (1 - V_2) + 0.44 V_2 = As$, where V_2 = vol. fraction of alloöcimene

At 12.96 microns, $0.08 (1 - V_3) + 0.29 V_3 = As$, where V_3 = vol. fraction of α-pinene

At 8.70 microns, $0.05 (1 - V_4) + 0.285 V_4 = As$, where V_4 = vol. fraction of dipentene

In these equations everything but the component being determined, $(1 - V)$, is treated as one component. A synthetic pyrolysis mixture, Fig. 2, was made with the composition in volume per cent as follows, ocimene 47, dipentene 23, alloöcimene 20, and α-pinene 10. This mixture had an optical density at 12.09 microns of 0.168, at 9.74 microns of 0.183, at 12.96 microns of 0.108, and at 8.70 microns of 0.104. Using the above equations, the following values were obtained: ocimene, 46%; dipentene, 23%; alloöcimene, 20%; and α-pinene, 13%. This is an excellent check with the known values.

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[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE[1]]

Nitration of 1- and 3-Fluorofluorene

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The nitration of either 1- or 3-fluorofluorene led to a mixture of isomers. In each case, the main product was the 7-nitro derivative, but small amounts of the 2- and 4-nitro compounds were also isolated. The halogen fluorine hinders substitution in the same ring of the polynuclear hydrocarbon fluorene and directs the entering group chiefly into the unsubstituted ring. A number of derivatives of these compounds, including the fluorenones, and the amino and acetylamino derivatives were prepared.

Substitution by the halogen fluorine in molecules with physiological activity has in many cases resulted in a profound alteration of the biological effect tending in general towards an increased activity.[3] With the carcinogen *N*-2-fluorenylacetamide substitution of fluorine at the 7-position served to enhance the carcinogenicity appreciably.[4] The 7-carbon atom is one of the positions at which hydroxylation occurs during the metabolism of

(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

(2) Visiting Scientist, National Cancer Institute. On leave of absence from Yamaguchi University, Ube, Japan.

(3) (a) E. C. Miller and J. A. Miller, *J. Natl. Cancer Inst.*, 15, 1571 (1955). (b) J. Fried, *Cancer*, 10, 752 (1957). (c) J. Fried and A. Borman, *Vitamins and Hormones*, 16, 303 (1958).

(4) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Research*, 15, 188 (1955).

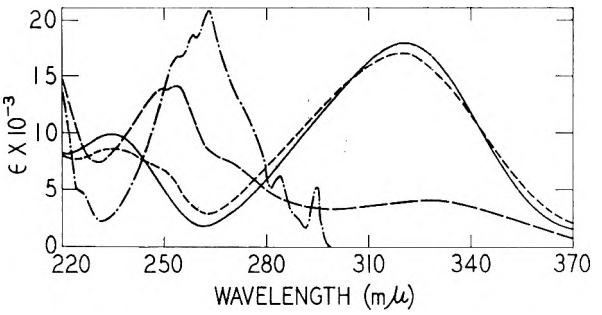


Fig. 1. Ultraviolet absorption spectra: ——— 1-Fluoro-7-nitrofluorene [λ max 234 mμ (ε = 9,800), 320 (17,900); λ min 221 (8,200), 261 (1,800)]: - - - - 1-fluoro-2-nitrofluorene [λ max 230 (8,470), 237 (8,530), 318 (16,900); λ min 224 (7,670), 234 (8,370), 262 (2,800)]; — — 1-fluoro-4-nitrofluorene [λ max 247 (13,400), 253 (14,000), 336 (4,200); λ min 321 (7,400); 300 (3,400)]; — · — 1-fluorofluorene [λ max 219 (13,800), 227 (4,400), 254 (16,800), 258 (18,600), 263 (20,800), 284 (6,200), 295 (5,100); λ min 232 (2,200), 260 (18,400), 282 (5,100), 292 (1,400). Inflection points are underlined

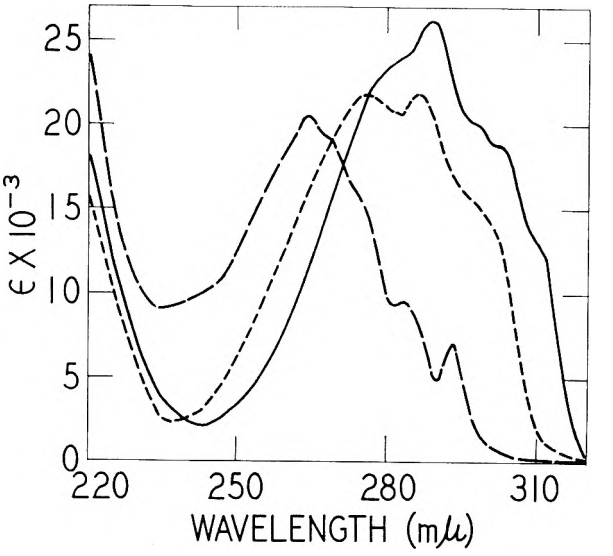


Fig. 2. Ultraviolet absorption spectra: ——— *N*-(8-Fluoro-2-fluorenyl)acetamide [λ max 277 mμ (ε 22,200), 289 (26,200), 297 (20,600), 303 (18,800), 311 (12,600); λ min 243 (2,000), 296 (20,000), 302 (18,600)]; - - - - *N*-(1-fluoro-2-fluorenyl)acetamide [λ max 275 (22,000), 287 (22,000), 302 (14,000); λ min 237 (2,500), 282 (20,800)]; — — *N*-(1-fluoro-4-fluorenyl)acetamide [λ max 264 (20,600), 283 (9,500), 293 (6,000); λ min 235 (9,200), 281 (9,400), 290 (4,800)]

N-2-fluorenylacetamide.[5] Recently the synthesis of *N*-(4- and 5-fluoro-2-fluorenyl)acetamides has been described[6] and the biological testing of these fluoro-substituted derivatives of the carcinogen will be of interest.

Differences in the metabolism of *N*-2-fluorenylacetamide in rats and guinea pigs, species susceptible and nonsusceptible, respectively, to the carcinogenic effect, have focused attention on the *ortho*-hydroxylated derivatives of the carcinogen as possible factors or mediators in the initiation of the carcinogenic process.[7] The question, thus, arose whether carcinogenicity in this series of compounds could be abolished by blocking these *ortho* positions. In this case, also, fluorine was a useful substituent, as carbon-fluorine bonds are stable and the atomic radius of fluorine is not much greater than that of hydrogen.[8] Thus, it was desired to develop syntheses leading to *N*-(1- and 3-fluoro-2-fluorenyl)-acetamides, in which one of the *ortho* positions is occupied by the halogen fluorine.

Initially, it was planned to prepare the intermediates required by nitrating 1- or 3-fluorofluorenes, themselves readily available from the known corresponding amines.[9,10] The experiments, however, indicated that nitration of 1- or 3-fluorofluorene did not occur exclusively at the 2-position but showed instead that a number of isomeric nitro derivatives resulted. The details of the separation and proof of structure of these products form the substance of the present paper.

Compounds derived from 1-fluorofluorene. Nitration of 1-fluorofluorene occurred readily at a temperature of 80° with concentrated nitric acid in acetic acid. The major part of the products crystallized in the reaction mixture in the form of a powder. This material was subjected to a crude fractionation by means of steam distillation. The compounds *A*, m.p. 103°, *A'*, m.p. 112°, *B*, m.p. 133°, and *C*, m.p. 174° were then isolated by a series of systematic fractional crystallizations. The identity of these isomeric 1-fluoro-*x*-nitrofluorenes was ascertained by comparison with an authentic sample, in the case of *B*, and by spectroscopy for the remaining products.

Compound *A'* exhibited an ultraviolet spectrum (Figure 1) remindful of that of 4-nitrofluorene,[11] in contrast to compounds *B* and *C*, whose spectrum was more nearly like that of 2-nitrofluorene. Further evidence for assigning the substituent in compound *A'* to the 4-position was derived from an examination of the spectra of the amine and acetylamino derivative (Experimental and Fig. 2),

(5) J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *Arch. Biochem. Biophys.*, **80**, 187 (1959).

(6) T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H.-L. Pan, *J. Am. Chem. Soc.*, **81**, 1092 (1959).

(7) (a) J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *Cancer Research*, **18**, 1039 (1958). (b) J. H. Weisburger, E. K. Weisburger, P. H. Grantham, and H. P. Morris, *J. Natl. Cancer Inst.*, **22**, 825 (1959).

(8) (a) L. Pauling, *Nature of the Chemical Bond*, 2nd Ed., Cornell Univ. Press, Ithaca, N. Y., 1940, pp. 160–168. (b) G. W. Wheland, *The Theory of Resonance*, J. Wiley and Sons, Inc., New York, 1944, pp. 97–103.

(9) (a) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **18**, 864 (1953). (b) E. Sawicki and B. Chastain, *J. Org. Chem.*, **21**, 1028 (1956). (c) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **23**, 1193 (1958).

(10) The technical assistance of Mr. Lawrence Shaw in the preparation of 1-fluorenamine is gratefully acknowledged.

(11) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **19**, 964 (1954).

as compared to the curves of similarly 2- and 4-substituted fluorenes.[12] Thus, compound *A'* was 1-fluoro-4-nitrofluorene. Compound *A*, isolated in larger quantities, had an infrared spectrum almost superposable with that of compound *A'*. However, even extensive crystallizations failed to increase the melting point above 103°. Solid solutions and cocrystallizations appear to occur readily in this series of compounds, for similar phenomena were encountered also with the isomeric compound *B*.

Diazotization of 7-nitro-1-fluorenamine[13] in hydrofluoric acid gave a sample of 1-fluoro-7-nitrofluorene, m.p. 145.5°. The infrared spectrum of this compound coincided exactly with that of *B*, m.p. 133°, but the curve of the latter substance exhibited two small additional peaks at 12.87 and 14.30 μ. This quasi-identity of the spectra suggested that these compounds were the same despite the difference in melting points. A phase diagram plotting the melting points versus composition of synthetic mixtures of authentic 1-fluoro-7-nitrofluorene and 1-fluoro-2-nitrofluorene (product *C*) indicates that a material with the melting point of *B* would correspond to a solid solution[14] of about 20% *C* in 80% 1-fluoro-7-nitrofluorene (Figure 3).

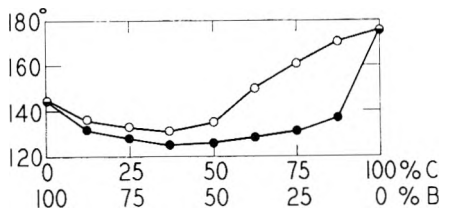


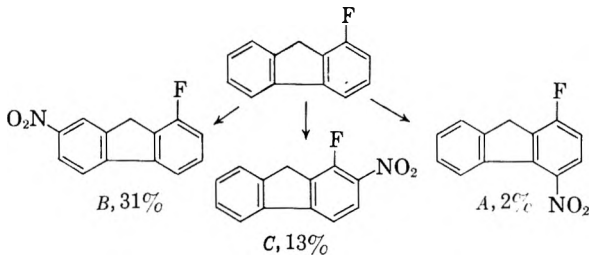
Fig. 3. Phase diagram showing the melting range of mixtures of 1-fluoro-2-nitrofluorene, *C*, and 1-fluoro-7-nitrofluorene, *B*. The mixtures were prepared by taking suitable aliquots of solutions of the pure compounds, followed by removal of the solvent. It seems noteworthy that small amounts of *C* cause but little depression in melting point of *B*, whereas *B* affects the melting point of *C* considerably

The infrared spectrum of such a mixture matched that of *B*. In addition, reduction of *B* gave a crude amine which was resolved by fractional recrystallization into two materials in the ratio of 91 to 9%. The first corresponded to 1-fluoro-7-fluorenamine, the second to 1-fluoro-2-fluorenamine.

Compound *C* also showed an ultraviolet spectrum not unlike that of a 2-substituted fluorene. In view of the fact that the nitro group in *B* was in the 7-position the nitro group in *C* would necessarily be in the symmetrical 2-position. Hence, *C* was 1-fluoro-2-nitrofluorene. A further consideration of the spectra of the amino and acetylamino derivatives likewise confirmed this assignment (*cf.* Experimental Part, Figure 2, and refs. 11,15).

Product *G*, isolated in small amounts from the nitration mixture had an infrared spectrum suggesting the presence of a ketonic function. Oxidation of 1-fluoro-7-nitrofluorene to the fluorenone gave yellow plates, m.p. 212°, identical to compound *G*. Thus, some oxidation to fluorenones occurred during nitration of fluorene derivatives even when the temperature of the reaction was carefully controlled. This observation was made previously in this laboratory with other fluorenes.

These experiments show that 1-fluorofluorene nitrated mainly at the 7-position (31%), and to a lesser extent at the 2- (13%) and 4-positions (2%). The nitration reaction took place at about



the same temperature as that of fluorene itself, and proceeded in a manner similar to that of the unsubstituted hydrocarbon.[16] Nevertheless, the fluorine atom at the 1-position appeared to have some deactivating effect[17] on substitution within the same ring, as the nitration affected chiefly the 7-carbon atom. However, the halogen atom did exhibit some *ortho, para* directivity within the same ring, as demonstrated by the isolation of the 2- and 4-nitro substituted products. Dewar and Urch[15]

(12) J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *J. Am. Chem. Soc.*, 74, 4540 (1952).

(13) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, 21, 1386 (1956).

(14) It seems that polarizability of the nitro and fluoro radicals in these molecules confers upon them a certain degree of mutual attraction favoring the crystallization of mixtures. The well-known complexing ability of 2,4,7-trinitrofluorenone is based on the presence of 4 such active centers. Reduction of the fluoro-nitro derivatives to the amines removed one of the polarizable groups with a consequent loss of complexing tendencies. Therefore the amines could be readily separated by simple crystallization.

(15) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 3079 (1958).

(16) W. E. Kuhn, *Org. Syntheses*, Coll. Vol. II, 447 (1943).

(17) (a) L. N. Ferguson, *Electron Structures of Organic Molecules*, Prentice-Hall, Inc., New York, N. Y., 1952, p. 296 ff. (b) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 359. (c) In analogy with these findings, it might be expected that fluorine would decrease appreciably the reactivity of the *K* region in the fluoro derivatives of the polycyclic carcinogenic compounds prepared by E. D. Bergmann, J. Blum, S. Butanaro, and A. Heller [*Tetrahedron Letters*, no. 1, 15 1959)]. Since the initiation of the carcinogenic process appears to require reaction at the *K* region [V. T. Oliverio and C. Heidelberger, *Cancer Research*, 18, 1094 (1958)] it follows that substitution of fluorine at the *K* region would reduce carcinogenicity, rather than increase it, as suggested by Bergmann, *et al.*

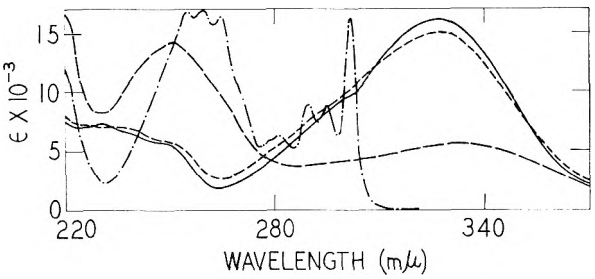


Fig. 4. Ultraviolet absorption spectra: ——— 3-Fluoro-7-nitrofluorene [λ max 230 mμ (ε 7,180), 250 (5,380), 326 (16,100); λ min 224 (6,780), 264 (1,800)]; - - - - 3-fluoro-2-nitrofluorene [λ max 230 (8,270), 245 (5,980), 325 (14,900); λ min 225 (8,170), 264 (2,790)]; — — 3-fluoro-4-nitrofluorene [λ max 220 (16,300), 250 (14,200), 332 (5,600); λ min 230 (8,200), 288 (3,700)]; —·—· 3-fluorofluorene [λ max 221 (11,200), 254 (16,800), 259 (17,000), 265 (16,500), 271 (9,400), 281 (6,300), 290 (9,000), 295 (8,600), 302 (16,200); λ min 231 (2,200), 257 (16,200), 263 (15,400), 275 (5,400), 286 (5,200), 292 (7,600), 298 (6,300)]

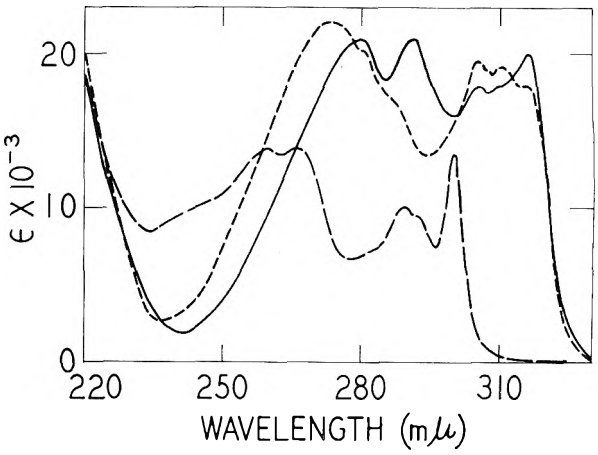


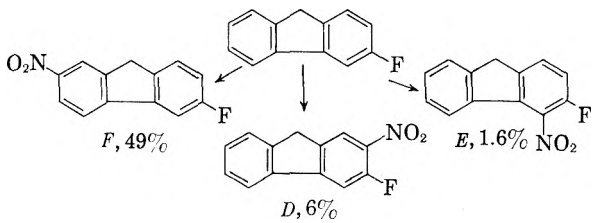
Fig. 5. Ultraviolet absorption spectra: ——— *N*-(6-Fluoro-2-fluorenyl)acetamide [λ max 280 mμ (ε 20,800), 291 (20,800), 304 (17,800), 316 (20,100); λ min 241 (2,000), 285 (18,000), 299 (15,900), 307 (17,600)]; - - - - *N*-(3-fluoro-2-fluorenyl)acetamide [λ max 273 (22,100), 281 (20,300), 305 (19,400), 310 (19,000), 316 (17,900); λ min 237 (2,600), 280 (20,200), 295 (13,400), 308 (18,800), 315 (17,700)]; — — *N*-(3-fluoro-4-fluorenyl)acetamide [λ max 211 (29,800), 259 (13,800), 266 (13,800), 289 (10,000), 300 (13,400); λ min 234 (8,400), 263 (13,400), 278 (6,600), 296 (7,200)]

and we[18] recently reported that fluorene itself upon nitration gave rise to small amounts of 4-nitrofluorene in addition to 2-nitrofluorene.

Compounds derived from 3-fluorofluorene. The nitration of 3-fluorofluorene proceeded under conditions analogous to those used for the 1-isomer. The separation of the isomers produced was somewhat more complex and difficult. However, the combination of fractional crystallizations, steam distillation, and chromatography on alumina yielded four pure compounds: *D*, m.p. 131–132°, *E*, m.p. 146–147°, *F*, 195–196°, and *H*, m.p. 269–271°.

The structure of these compounds was proved, as in the case of the 1-isomer, by comparison with an authentic sample (*F*), and by spectroscopic means for the other materials. The ultraviolet spectrum of 3-fluorofluorene itself, as well as a number of the derived 3-substituted fluorenes (Figs. 4 and 5) have unusual and characteristic features similar to those observed previously with certain other so substituted fluorenes.[9c,19] Compounds *D* and *F* and the amino and acetylamino compounds derived therefrom had spectra which were typically those of a 2-substituted fluorene. In addition, it could be shown by comparison with an authentic sample of 3-fluoro-7-nitrofluorene that the nitro group in compound *F* had entered the 7-position. Thus, it would appear that compound *D* resulted from nitration at the 2-position. Likewise, the spectra of *E*, and compounds derived therefrom were unmistakably those of a 4-substituted fluorene (Figs. 4 and 5), establishing *E* as 3-fluoro-4-nitrofluorene. Oxidation of *D* and *F* produced the corresponding fluorenones. The material *H* was identical to the oxidation product of *F*, 3-fluoro-7-nitrofluorenone.

In essence, the nitration of 3-fluorofluorene produced a complex mixture of isomers. About 49% of the 7-nitro, 6% of the 2-nitro, and 1.6% of the 4-nitro derivatives could be isolated in pure condition.



Catalytic reduction of the nitro derivatives of both 1- and 3-fluorofluorene afforded good yields of the amines,[20] which in turn were acetylated to produce the desired *N*-(fluorofluorenyl)acetamides. However, in view of the preponderance of the materials nitrated at the 7-position, further efforts

(18) E. K. Weisburger and J. H. Weisburger, *Advances in Cancer Research*, V, 331 (1958).

(19) N. Ishikawa and M. Okazaki, *Yûki Gôsei Kagaku Kyôkai Shi*, 16, 610 (1958).

(20) The ionization constants of the amines[21] in 70% ethanol offer further proof that the structures assigned to the nitro compounds are correct. Fluorine in an *ortho* position to the amino group has a larger depressing effect on the *p*K than in other positions. Values, determined at 25°, were as follows: 1-fluoro-2-fluorenamine, 2.59; 1-fluoro-4-fluorenamine, 2.95; 8-fluoro-2-fluorenamine, 3.54; 3-fluoro-2-fluorenamine, 2.69; 3-fluoro-4-fluorenamine, 2.71; 6-fluoro-2-fluorenamine, 3.71; 7-fluoro-2-fluorenamine[4] 3.53; 5-fluoro-2-fluorenamine,[6] 3.93; 4-fluoro-2-fluorenamine[6] 3.05 (we are grateful to Drs. J. and E. Miller, University of Wisconsin, for providing the last 3 compounds). For reference, 2- and 4-fluorenamine had *p*K values of 4.27 and 3.15, respectively.

(21) P. H. Grantham, E. K. Weisburger, and J. H. Weisburger, 125th Meeting, American Association Advancement Science, Washington, D. C., December 1958, General Program, p. 168. Manuscript in preparation.

are required to develop more specific methods of synthesis for the preparation of the larger amounts of the *ortho*-substituted *N*-(1- and 3-fluoro-2-fluorenyl)acetamides necessary for biological experiments.

EXPERIMENTAL

The melting points were determined in a capillary tube and are uncorrected. The ultraviolet absorption spectra were recorded by Mr. P. H. Grantham on a Cary recording spectrophotometer as 5×10^{-5} molar solutions in ethanol and the infrared spectra on a Perkin Elmer spectrophotometer, model 21, as solids in potassium bromide disks. We are indebted to Dr. W. C. Alford, and Mr. R. Koegel, and their staffs, for the microanalyses.

Derivatives of 1-fluorofluorene. 1-Fluorofluorene.[22] Powdered 1-aminofluorene[9a,b] (7.5 g.) was stirred with 375 ml. of 52% technical hydrofluoric acid in a polyethylene beaker, yielding initially a solution from which a salt precipitated on cooling to 5°. Over a period of 30 minutes 2.92 g. of powdered sodium nitrite was added with stirring. The mixture was allowed to stand in the cold for 3–4 hr. and then at 25° 24–48 hr. longer. The precipitated material (8.6 g.) was filtered off and washed with water. Extraction with 0.5*N* potassium hydroxide, followed by acidification of the extract afforded 106 mg. of 1-fluorenol, m.p. and mixed m.p. 117–118°.[9a] The main residue was extracted with 250 ml. of refluxing petroleum ether. The solution was taken to dryness and the residue was sublimed at 1 mm. pressure and a bath temperature of 60°, yielding 6.17 g. (81%) of 1-fluorofluorene, m.p. 81–83°. Recrystallization from dilute ethanol or dilute acetic acid raised the melting point to 83–84°; carbon-fluorine stretching: 8.09 μ.

Anal. Calcd. for $C_{13}H_9F$: C, 84.76; H, 4.92. Found: C, 84.54; H, 5.19.

1-Fluoro-7-nitrofluorene. By a similar procedure, 226 mg. of 7-nitro-1-fluorenamine[13] in 80 ml. of hydrofluoric acid was diazotized with 80 mg. of sodium nitrite yielding 220 mg. of product. Sublimation at 1 mm. pressure for 5 hr. at a bath temperature of 90–100° afforded 160 mg. of almost colorless material, m.p. 144–145°, which when chromatographed on alumina (Merck, suitable for chromatographic adsorption) in benzene solution and recrystallized from cyclohexane gave 126 mg. of 1-fluoro-7-nitrofluorene, m.p. 144–145°. The analytical sample, which was crystallized from ethanol and 50% aqueous acetic acid, melted at 145–145.5°.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.85; H, 3.61.

Nitration of 1-fluorofluorene. The reaction used for fluorene[16] was modified by altering the proportion of nitric to acetic acid. Seventeen ml. of concentrated nitric acid (d = 1.42) was added to a solution of 10 g. of 1-fluorofluorene in 30 ml. of acetic acid at 50°. By means of a water bath the temperature was raised to 80° and maintained thereat for 15 minutes. An exothermic reaction was accompanied by the crystallization of products. After cooling to 25° and standing overnight, the solids weighing 9.9 g., m.p. 120–133°, were filtered off. The filtrate from the reaction mixture was treated as described later.

Steam distillation gave a volatile fraction, 1.92 g., m.p. 79–93°, which by fractional crystallization from petroleum ether gave 535 mg. of compound *B*, m.p. 133°, 5 mg. of A′, *1-fluoro-4-nitrofluorene*, m.p. 111–112°, and 128 mg. of compound *A*, (a mixture of the 4- and 2-nitro isomers), m.p. 100–103°. The analytical sample melted at 103°, and, being a solid solution with an isomer, analyzed correctly.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.91; H, 3.69.

The residue from the steam distillation, 7.5 g., m.p. 130–143°, was extracted twice with 300 ml. of ethanol. The extracts were taken to dryness. The residue was recrystallized from ethanol, yielding 3.25 g. of product *B*, m.p. 130–132°. From the mother liquors 0.2 g. of material, m.p. 157–165° was isolated. This, combined with the insoluble portion, 2.24 g., m.p. 162–165°, from the ethanol extractions, was recrystallized from acetic acid affording 1.62 g. of product *C*, m.p. 173–174°.

The following operations were performed in the hope of purifying 1.08 g. of product *B*. Crystallization from cyclohexane (842 mg., m.p. 132–133°), crystallization from ethanol (420 mg., m.p. 133–134°), sublimation at 1 mm., 90° bath (403 mg. sublimate, m.p. 133–134.5°, and 17 mg. residue, m.p. 133°), recrystallizations of the sublimate from ethanol and cyclohexane (200 mg., m.p. 133.5–134°). Apparently, *1-fluoro-7-nitrofluorene* formed an unresolvable solid solution with the isomeric 1-fluoro-2-nitrofluorene.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.92; H, 3.61.

Product *C*, *1-fluoro-2-nitrofluorene*, was recrystallized twice from acetic acid, m.p. 177–178°.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.89; H, 3.68.

Oxidation of this compound gave *1-fluoro-2-nitrofluorenone*, m.p. 231–232°, after recrystallization from acetic acid. Ultraviolet spectrum: λ_{max} 242 mμ (ϵ = 21,300), 282 (22,100), 375–380 (2,500); λ_{min} 262 (15,100), 350 (2,050).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 64.13; H, 2.79.

The filtrate from the reaction mixture was diluted with water yielding an oil which was taken up in benzene. The extract was washed with 1*N* potassium hydroxide solution and water, then dried over calcium chloride and chromatographed on alumina. The first fraction, a light yellow solution, upon evaporation and crystallization of the residue from ethanol and petroleum ether, afforded 126 mg. of compound *A*. Three further fractions gave brown to reddish oils which were discarded.

The fifth fraction, upon removal of the solvent, left a yellow solid which was crystallized from ethanol to yield 10 mg. of compound *G*, m.p. 211–212°, exhibiting a strong carbonyl absorption at 5.85 μ, and C–F stretching at 8.10 μ. Melting and mixed melting points and infrared spectra proved the identity of this material with authentic 1-fluoro-7-nitrofluorenone.

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 63.97; H, 2.73.

1-Fluoro-7-nitrofluorenone. A mixture of 42 mg. of 1-fluoro-7-nitrofluorene, m.p. 145°, 85 mg. of chromium trioxide, and 5 ml. of acetic acid was refluxed for 3 hr. and poured into cold acidulated water. Upon recrystallization from acetic acid 14 mg. of small yellow plates of the fluorenone, m.p. 211–212° was obtained. Ultraviolet spectrum: λ_{max} 237 mμ (ϵ = 22,800), 282 (22,500), 305 (13,900), 370–375 (2,700); λ_{min} 260 (14,700), 301 (13,300), 353 (2,300).

1-Fluoro-2-fluorenamine. Low pressure catalytic reduction (Parr shaker) over platinum oxide of 2 g. of 1-fluoro-2-nitrofluorene in 80 ml. of ethanol followed by partial evaporation of the solvent (nitrogen atmosphere) and addition of water gave 1.74 g. of the amine, m.p. 109–110°. Recrystallization from water, cyclohexane, and 50% ethanol raised the melting point to 115–116°; λ_{max} 290 mμ (ϵ = 21,900); λ_{min} 244 mμ (ϵ = 1,590); C-F stretching; 8.23 μ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 78.37; H, 5.34.

N-(1-Fluoro-2-fluorenyl)acetamide. Brief refluxing of 1 g. of the amine in 30 ml. of benzene and 1.2 ml. of acetic anhydride gave 1.02 g. of the acetyl derivative, m.p. 178–179°. Crystallization from ethanol afforded 820 mg. of colorless needles, m.p. 179.5–181°. After further crystallizations

(22) The procedure was patterned after that developed by W. M. Stanley, E. McMahon, and R. Adams, *J. Am. Chem. Soc.*, **55**, 706 (1933).

from benzene and ethanol the melting point remained unchanged at 180.5–181.5°.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.41; H, 5.19.

1-Fluoro-4-fluorenamine. Catalytic reduction of 220 mg. of 1-fluoro-4-nitrofluorene, m.p. 103°, gave 147 mg. of amine, m.p. 78°. Crystallization from water, and cyclohexane increased the melting point to 79–80°; λ_{max} (main peaks only given of the characteristically complex curve) 216.5 mμ (ϵ = 29,700), 261.5 (15,100), 266 (14,500), 271 (17,900), 320 (6,280); λ_{min} 214 (29,400), 252.5 (10,400), 287 (3,390). Carbon-fluorine stretching: 8.12 μ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 77.82; H, 4.91.

N-(1-Fluoro-4-fluorenyl)acetamide. A solution of 100 mg. of the amine in 3 ml. of benzene and 0.12 ml. of acetic anhydride was warmed on the steam bath for 25 minutes to give, on cooling, 94 mg. of white crystals, m.p. 218–223°. Crystallizations from benzene, and ethanol left 60 mg. of compound, m.p. 228–230°; C—F stretching: 8.12 μ.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.79; H, 5.63.

1-Fluoro-7-fluorenamine. A. Reduction of 241 mg. of 1-fluoro-7-nitrofluorene, m.p. 143°, afforded 168 mg. of colorless long needles m.p. 143–144°, after one crystallization from cyclohexane.

B. Reduction of 2 g. of compound *B*, m.p. 133°, gave 1.66 g. of product with a melting range of 122–127°. Recrystallization from cyclohexane produced 1.05 g. of crystals, m.p. 137–139°. By evaporation of the mother liquor 109 mg. of material, m.p. 109–110° was obtained. Separate recrystallization of these samples from cyclohexane yielded 53 mg. of 1-fluoro-2-fluorenamine, m.p. 114–115°, identical to the previously described compound, and 888 mg. of 1-fluoro-7-fluorenamine, m.p. 141–143°, equal in all respects to the material obtained under *A* above. λ_{max} 293 mμ (ϵ = 20,900); λ_{min} 246.5 mμ (ϵ = 1,890). C—F stretching: 8.17 mμ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 78.16; H, 5.31.

N-(8-Fluoro-2-fluorenyl)acetamide. Acetylation of 500 mg. of amine in 15 ml. of benzene with 0.6 ml. of acetic anhydride gave 556 mg. of the acetyl derivative, m.p. 186–187°. C—F stretching: 8.11 μ.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.49; H, 5.01.

Derivatives of 3-fluorofluorene. 3-Fluorofluorene. A. An ice-cold solution of 1.9 g. of 3-fluorenamine[9c] in 50 ml. of 52% hydrofluoric acid was treated with 750 mg. of sodium nitrite. After standing at 25° for 2 days, 1.57 g. of brown material was filtered off and washed with water. Sublimation at 1 mm. pressure at a bath temperature of 90–100° yielded 1.02 g. of sublimate which was chromatographed on alumina in benzene solution. Removal of the solvent afforded 863 mg. of slightly yellowish product, m.p. 77–78°, which upon resublimation gave 789 mg. of 3-fluorofluorene as a white powder with the same melting point. Elution of the alumina column, above, with ethanol, followed by crystallization yielded, in addition, 89 mg. of 3-fluorenol, m.p. and mixed m.p. 137–138°.[9o]

B. A hot solution of 30 g. of 3-fluorenamine in 260 ml. of 1*N* hydrochloric acid was filtered and 300 ml. of 12*N* acid was added. The ice-cold mixture was diazotized by introducing 11.8 g. of sodium nitrite in 66 ml. of water all at once. After stirring for 0.5 hr., 158 ml. of a sodium fuoborate solution[23] caused the precipitation of the fluoborate (42.6 g., m.p. 123° with decomposition), which was filtered off after standing overnight at 2°. This material was decomposed by heating cautiously with a direct flame. The product was extracted with hot petroleum ether. After evaporation of the solvent and sublimation of the residue *in vacuo*, recrystallization from 50% ethanol yielded 15 g. of 3-fluorofluorene, m.p. 76°. Further crystallization from dilute ethanol, and acetic acid raised the melting point to 77–78°. C—F stretching: 8.52 μ.

Anal. Calcd. for $C_{13}H_9F$: C, 84.76; H, 4.92. Found: C, 84.91; H, 5.23.

3-Fluoro-7-nitrofluorene. A mixture of 1 g. of 7-nitro-3-fluorenamine,[9c] 90 ml. of 52% hydrofluoric acid, and 335 mg. of sodium nitrite was allowed to stand for 2 days, then was briefly warmed on a steambath. The precipitate was filtered off (342 mg., m.p. 183–189°), and sublimed *in vacuo* at a bath temperature of 170°. A solution of the sublimate in benzene was percolated through an alumina column. The solvent was removed and the residue crystallized from acetic acid yielding 128 mg. of pale yellow needles, m.p. 198°. Further crystallizations from benzene and acetic acid gave a pure sample, m.p. 199–200°. C—F stretching: 8.52 μ.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 68.09; H, 3.75.

Nitration of 3-fluorofluorene. The nitration was performed as described for the 1-isomer, yielding 11.1 g. of solid, m.p. 155–174°, and the mother liquor which was worked up separately. The solid was refluxed with 550 ml. of ethanol (some material remained undissolved) and cooled. The resulting insoluble material was recrystallized from acetic acid to yield 5.4 g. of compound *F*, m.p. 196°. By mixed melting point and identical infrared spectra *F* was shown to be *3-fluoro-7-nitrofluorene.*

The ethanolic mother liquor was steam-distilled. The residue (3.4 g., m.p. 132–140°) was chromatographed on alumina in benzene solution, giving two main fractions weighing 1.3 g., m.p. 147–166°, and 1.1 g., m.p. 125–133°. Fractional crystallizations of each from benzene and ethanol afforded 448 mg. of compound *D*, m.p. 132°, 116 mg. of compound *F*, m.p. 196°, and 562 mg. of an impure fraction *F'*, which when combined with similar fractions obtained in other parts of the isolation steps finally gave 510 mg. of *F*.

The material volatile in steam (1.1 g., m.p. 94–110°) was chromatographed on alumina in cyclohexane-benzene (1:2). Upon recrystallization of the fractions so derived, 177 mg. of *D*, 195 mg. of *E*, m.p. 146°, and 50 mg. of *F'*, could be isolated.

The filtrate from the reaction mother liquor was diluted with water and partially neutralized with sodium acetate. The resulting oil was taken up in benzene. After washing the solution with 1*N* alkali and water and drying, the solution was chromatographed on alumina. Recrystallization of the various fractions obtained by taking the eluates to dryness gave 137 mg. of compound *D*, 18 mg. of compound *E*, 10 mg. of *F'*, and 2.5 mg. of compound *H*, m.p. 271°. The last named material was identical with 3-fluoro-7-nitrofluorenone as proved by mixed melting point and superposable infrared spectra.

Recrystallization of compound *D* from ethanol, dilute acetic acid, and cyclohexane gave small white needles of *3-fluoro-2-nitrofluorene*, m.p. 134.5–135.5°; C—F stretching: 8.40 μ.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 68.01; H, 3.54.

Oxidation of this compound gave *3-fluoro-2-nitrofluorenone*,[24] m.p. 220–221°, after recrystallization from acetic acid. λ_{max} 242 mμ (ϵ = 22,700), 257 (20,100), 277 (22,200), 300 (12,600), 323 (5,960), 338 (5,200); λ_{min} 253 (19,800), 264 (19,100), 317 (5,600), 333 (4,900).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 63.69; H, 2.66.

Similar purification of compound *E* afforded pale yellow,

(23) A. Roe, *Org. Reactions*, V, 193 (1949).

(24) This compound may be identical to a 3-(or 1-)-fluoro-2-nitrofluorenone, m.p. 224–224.5°, described by W. H. Wetzel, M. J. Namkung, H.-L. Pan, and T. L. Fletcher, 134th National Meeting, American Chemical Society, Chicago, Ill., September, 1958, Abstracts of papers, p. 25-0.

long needles of *3-fluoro-4-nitrofluorene*, m.p. 147–147.5°; C—F stretching: 8.44 μ.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.63; H, 3.46.

3-Fluoro-7-nitrofluorenone. Oxidation of 100 mg. of the fluorene derivative by 200 mg. of chromium trioxide in 5 ml. of acetic acid yielded 48 mg. of yellow needles, m.p. 276–277°, after crystallization from acetic acid. Main peaks in ultraviolet spectrum: λ_{max} 241.5 mμ (ϵ = 18,100), 282 (23,100), 323 (4320), 337.5 (3440); λ_{min} 258 (12,600), 317 (3,940), 332 (3250).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 64.34; H, 2.78.

3-Fluorofluorenamines and acetyl derivatives. The isomeric 3-fluoronitrofluorenes were reduced catalytically (platinum oxide) in ethanol solution in 80–90% yields. The acetyl derivatives were produced in similar yields by the action of acetic anhydride on a benzene solution of the amines. Pertinent data for the compounds are listed below. *3-Fluoro-2-fluorenamine*, m.p. 131–131.5° (from water, cyclohexane). λ_{max} 282 mμ (ϵ = 18,700), 320 (12,600); λ_{min} 243.5 (1,790), 308.5 (11,400). C—F band, 8.66 μ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 78.94; H, 5.26.

N-(3-Fluoro-2-fluorenyl)acetamide, m.p. 194–195° (from ethanol). C—F band, 8.64 μ.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.24; H, 4.96.

3-Fluoro-4-fluorenamine, m.p. 118–119° (from water, cyclohexane). Ultraviolet spectrum (main peaks of complex curve): λ_{max} 213 mμ (ϵ = 26,100), 250 (11,400), 261 (11,800), 270 (13,100), 299 (6,400), 315 (6,100); λ_{min} 242 (10,000), 279 (4,300). C—F band, 8.48–8.55 μ.

Anal. Found: C, 78.26; H, 5.31.

N-(3-Fluoro-4-fluorenyl)acetamide, m.p. 227–228° (from benzene). C—F band, 8.55 μ.

Anal. Found: C, 74.57; H, 5.20.

6-Fluoro-2-fluorenamine, m.p. 125–126° (from aqueous ethanol, water, cyclohexane) obtained by reduction of 3-fluoro-7-nitrofluorene. λ_{max} 295 mμ (ϵ = 17,900); λ_{min} 245 (2,090). C—F band, 8.58 μ.

Anal. Found: C, 78.29; H, 5.06.

N-(6-Fluoro-2-fluorenyl)acetamide, m.p. 198–199° (from ethanol). C—F band, 8.52 μ.

Anal. Found: C, 74.71; H, 5.24.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Adrenal Hormones and Related Compounds. V.[1] 2-Fluorinated Cortical Hormones

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A preparation of 2-fluoro-Δ^4-3-ketosteroids is described, making use of the reaction of perchloryl fluoride with the enolates of 2-ethoxyoxalyl-Δ^4-3-ketosteroids. By applying this procedure to the cortical hormone precursors 11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one (Ia) and the corresponding 6α-methyl derivative (Ib), the 2-fluoro derivatives of hydrocortisone acetate (IIIa) and 6α-methylhydrocortisone acetate (IIIb) have been prepared.

Marked modification of hormonal properties of steroids is brought about by substitution of fluorine at the 6[2a], 9[2b], or 12[2c] positions. We have now prepared some cortical hormone derivatives with fluorine substituted at C-2.[3]

The activation of a ring or side chain α-ketone position of a steroid by ethoxalylation to facilitate and direct electrophilic substitution by alkyl halide[4] or halogen,[5] respectively, has been described. Perchloryl fluoride, which has recently been found capable of fluorinating carbanions under mild conditions,[6] has now been employed with steroid 2-ethoxalylates, and has been found to produce simply and in good yields the correspondingly substituted fluoro steroids.

Direct ethoxalylation of the cortical hormones was previously found unsatisfactory[7] as a route to the 2 - methyl derivatives. The preferred intermediate was 11β-hydroxy-21-acetoxy-4,17(20)-[*cis*]-pregnadien-3-one (Ia, R′ = Ac),[4] which was

(1) Paper IV: G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956).

(2) (a) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. & Ind. (London)*, 1002 (1958); A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 4423 (1958). (b) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953); *J. Am. Chem. Soc.*, **79**, 1130 (1957). (c) J. E. Herz, J. Fried, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 2017 (1956); D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **79**, 452 (1957).

(3) A communication reporting the preparation of 2-fluorocholestanone appeared after this work was completed: R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958). After preparation of this manuscript the synthesis of 2-fluorohydrocortisone was reported by H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **81**, 1262 (1959).

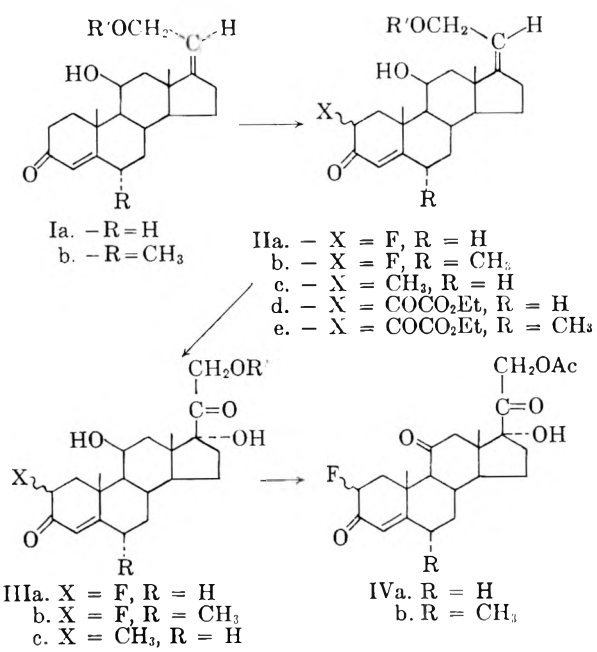
(4) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(5) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

(6) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling, and F. L. Scott, Abstracts of Papers, 134th National Meeting, ACS, Chicago, Ill., Sept. 7–12, 1958; C. E. Inman, E. A. Tyczkowski, R. E. Oesterling, and F. L. Scott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 6533 (1958).

(7) Unpublished results obtained in connection with the work reported in ref. (4).

methylated *via* its 2-ethoxyoxalyl derivative (IId), and then converted by oxidative hydroxylation of the side chain to the cortical hormone analog (IIIc).[4] IId proved also to be a suitable intermediate for the present fluorination studies. The major product of the reaction of IId with perchloryl fluoride, obtained in yields up to 59% after removal of the ethoxyoxalyl group and chromatographic purification, was 2-fluoro-11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one (IIa). After reacetylation at C-21, the cortical side chain was introduced by oxidation with *N*-methylmorpholine oxide–hydrogen peroxide in the presence of catalytic amounts of osmium tetroxide,[8] or with phenyliodosoacetate and osmium tetroxide,[4] giving 2-fluorohydrocortisone acetate (IIIa, R′ = Ac) in 72% yield. 2-Fluorocortisone acetate (IVa) was prepared by oxidation of IIIa with sodium dichromate.



Ia. – R = H
b. – R = CH_3

IIa. – X = F, R = H
b. – X = F, R = CH_3
c. – X = CH_3, R = H
d. – X = $COCO_2Et$, R = H
e. – X = $COCO_2Et$, R = CH_3

IIIa. X = F, R = H
b. X = F, R = CH_3
c. X = CH_3, R = H

IVa. R = H
b. R = CH_3

An analogous series of reactions carried out on 6α-methyl-11β-hydroxy-21-acetoxy-4,17(20)-[*cis*]-pregnadien-3-one[1] (Ib) afforded the corresponding 2-fluoro-6α-methyl derivatives IIb (R′ = H), IIb, (R′ = Ac) and IIIb (R′ = Ac). The 2-fluoro-6α-methylhydrocortisone acetate so obtained resisted crystallization; although it remained amorphous after chromatographic purification it appeared homogeneous, and afforded a crystalline 11-ketone (IVb) on oxidation with sodium dichromate.

The newly introduced fluorine atom is considered to be in the stable configuration on the basis of the following observation. Attempts to isomerize 2-fluorohydrocortisone acetate (IIIb) with dry hydrogen chloride in chloroform at 0° for 2 hr. did not alter the rotatory dispersion curve of the crude product. Recrystallization afforded pure 2-fluorohydrocortisone acetate identical in all respects to the starting sample. No other material could be isolated.

The stable configurations of α-halocyclohexanones have been related to differences in energy due to (1) electrostatic interaction in the equatorial conformer and (2) steric compression in the axial conformer.[9] Thus the equatorial isomer is more stable in the 2-chloro and 2-bromo-3-keto-Δ^4 steroids. The energetics have not been extended to include fluorine which is both the smallest halogen and the most electro-negative element known. While the stable conformer in the 2-fluoro steroids may well be *equatorial*, rotatory dispersion curves of hydrocortisone acetate and of its 2-fluoro derivative exhibit differences in the characteristic double trough[10] in the 300–360 mμ region which may be attributed to the influence of an axial substituent adjacent to the chromophore.[11] Accordingly, a definitive assignment is not being made at this time.

The infrared absorption maximum for the Δ^4-3-ketone is displaced by fluorine toward higher wave numbers by about 30 cm.$^{-1}$ This shift is in good agreement with that observed by Jensen for 2-fluorocholestan-3-one and appears consistent with that to be expected for equatorial α-fluorocyclohexanones.[12] Studies are presently underway to permit a definitive assignment of configuration. This work, as well as a description of a number of other 2-fluoro-Δ^4-3-ketosteroids which have been prepared in these laboratories, will be reported in future publications.

The physiological properties of these 2-fluorocorticoids are under investigation in the Endocrinology Department of these laboratories. Preliminary biological assay[13] of 2-fluorohydrocortisone acetate and of 2-fluoro-6α-methylhydrocortisone acetate in general corroborated the conclusions reported by Kissman, *et al.*,[3] that the 2-fluoro substituent apparently lacked the remarkable potentiating action shown by the 9α-fluoro-, 2α-methyl- and 6α-fluoro groups.

(8) U. S. Patent 2,769,823; B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, 80, 2326 (1958).

(9) E. J. Corey, *J. Am. Chem. Soc.*, 75, 2301 (1953); *J. Am. Chem. Soc.*, 76, 175 (1954).

(10) C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

(11) Unpublished studies by W. A. Struck and R. A. Houtman of these laboratories.

(12) Reported shifts for α-halocyclohexanones are:
equatorial: bromine, 17–23 cm.$^{-1}$; chlorine, 26–31 cm.$^{-1}$
axial: bromine, −2–8 cm.$^{-1}$; chlorine, 10–18 cm.$^{-1}$
For axial fluorine, the 9α-fluoro-11-ketosteroids exhibit a shift of 20 cm.$^{-1}$ while the corresponding chloro and bromo compounds exhibit shifts of 8 and 2 cm.$^{-1}$, respectively.

(13) Private communication from Drs. R. O. Stafford, W. E. Dulin, and F. L. Schmidt, to whom we are grateful for the biological studies.

EXPERIMENTAL

General procedure for preparing 2-fluoro-Δ⁴-3-ketosteroids. A solution of 0.02 mole of the steroid in 100 ml. of commercial tertiary butyl alcohol was prepared by heating to 55–80°, while stirring and flushing the atmosphere above the solution with a gentle stream of nitrogen. The source of heat was removed and 5.45 ml. (0.04 mole) of ethyl oxalate was added all at once to the warm solution, followed immediately by sufficient methanolic sodium methoxide solution[14] to contain 1.62 g. (0.03 mole) of sodium methoxide. Generally the yellow sodium enolates of the 2-ethoxalylates began to precipitate within a few minutes. The mixture was stirred under nitrogen, without further heating, for about 1.5 hr.; then 300 ml. of absolute ether was added to the suspension of the sodium enolate, and the latter was collected by filtration on a Büchner funnel. These sodium salts were all hygroscopic in varying degrees, so that care had to be taken not to condense atmospheric moisture on them by virtue of the large cooling effect of evaporating ether. In highly humid atmospheres, therefore, the precipitate was covered by a rubber dam while applying vacuum in order to express all possible solvent. By the time nearly all the ether had evaporated and the precipitate had warmed up to ambient temperature again, handling difficulties usually became negligible. The precipitate could be stored conveniently in a desiccator over Drierite.

The dry sodium enolate was dissolved in 170 ml. of methanol and the solution cooled to −10 to −15° in an ice salt bath, with protection from atmospheric moisture. A nitrogen atmosphere was again maintained. Perchloryl fluoride gas from a cylinder was passed into 100 ml. of methanol at 0 to +5°, until the weight gain was 2.9 to 3.4 g. The cold solution of perchloryl fluoride was added to the solution of sodium enolate with stirring, at a rate such as to keep the temperature below −5°. Five to 10 min. were generally required for the addition. The solution was stirred for 0.5 hr. longer in the ice salt bath, and then an amount of methanolic sodium methoxide solution calculated to neutralize all the perchloryl fluoride originally weighed was added. The solution was stirred an additional 0.5 hr., concentrated to about 1/3 its volume under reduced pressure, and then poured into about 750 ml. of cold water. The precipitate of crude product was collected, washed with water, and dried in a vacuum desiccator over Drierite. It was purified by chromatography on Florisil, using about 40 g. of Florisil per gram of crude steroid, and developing the column with increasing concentrations of acetone in hexanes (Skellysolve B), starting with 5% and increasing to 20% acetone, by volume. The steroidal products were generally eluted by 10% or 20% acetone, and were isolated from the appropriate column fractions in fairly pure condition. A single recrystallization usually sufficed to give a sample pure enough for analysis.

2ζ-Fluoro-11β,21-dihydroxy-4,17(20)-[cis]-pregnadien-3-one (IIa, R′ = H). Application of the general procedure to 7.45 g. of 11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one-21-acetate[5] (Ia, R′ = Ac) furnished 3.43 g.[15] (49.2%) of 2ζ-fluoro-11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one, m.p. 155–162°, as isolated in crystalline state from the 20% acetone–Skellysolve B eluates of the chromatographic column. After two recrystallizations from a mixture of ethyl acetate and Skellysolve B, a sample of the compound melted at 176.5–178.5°; however the m.p. was not reproducible even under controlled rates of heating, and samples that were indistinguishable analytically melted at various ranges between 170–186°.

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39; F, 5.45. Found: C, 72.49; H, 8.21; F, 5.35. $[\alpha]_D$ +195° ($CHCl_3$). λ_{max} 241.5 mμ, ε 13,850.

In addition to the free alcohol, the *21-acetate* (IIa, R′ = Ac) was isolated in 2–5% yields from the 7% acetone in Skellysolve B eluates of the column, as crystals melting at 163–169°. The melting point of this compound was elevated to a fairly reproducible value of 201–210°. by recrystallization from 95% alcohol.

Anal. Calcd. for $C_{23}H_{31}FO_4$: C, 70.74; H, 8.00; F, 4.87. Found: C, 70.95; H, 8.00; F, 4.61. $[\alpha]_D$ +185°. λ_{max} 251 mμ, ε 14,775.

The *21-acetate* (IIa, R′ = Ac) was also prepared by acetylation of the 21-alcohol with acetic anhydride in pyridine at room temperature. A solution of 2.97 g. of the alcohol in 20 ml. of pyridine and 25 ml. of acetic anhydride was kept at room temperature in a nitrogen atmosphere for 20 hr. The crystalline acetate, m.p. 178–200°, was isolated in practically quantitative yield by pouring the mixture into ice water. Its identity with the 21-acetate described above was confirmed after recrystallizing a sample, by finding the melting points, mixed m.p., and infrared spectra identical.

2ζ-Fluorohydrocortisone acetate (IIIa, R′ = Ac). A solution of 3.24 g. of 2ζ-fluoro-11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one 21-acetate in a mixture of 110 ml. of tertiary butyl alcohol, 30 ml. of methylene chloride, and 4.1 ml. of pyridine was treated with 10.9 ml. of a solution of *N*-methylmorpholine oxide–hydrogen peroxide complex in tertiary butyl alcohol[8] and 5.0 mg. of osmium tetroxide in 1.7 ml. of tertiary butyl alcohol. The solution was stirred at room temperature overnight, then 30 ml. of 0.5% aqueous sodium hydrosulfite and 2 g. of Magnesol were added, and stirring was continued for 0.5 hr. more. The solution was filtered and the solids were washed with 40 ml. of 75% tertiary butyl alcohol in water. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in methylene chloride, which was then washed with 10% aqueous sodium dihydrogen phosphate and with water, dried over sodium sulfate, and passed through a column of 220 g. of Florisil. The column was developed with 2.4 l. of 10% acetone in Skellysolve B, 2.8 l. of 15% acetone in Skellysolve B, and 2.0 l. of 25% acetone in Skellysolve B, collecting 400-ml. fractions. The 15% acetone contained 2.55 g. (72.5%) of 2-fluorohydrocortisone acetate, which after one recrystallization from a mixture of ethyl acetate and Skellysolve B, melted at 194–199°. Further recrystallizations raised the m.p. to 208–210.5°, and a sample of this quality gave the following analysis.

Anal. Calcd. for $C_{23}H_{31}FO_6$: C, 65.38; H, 7.40; F, 4.50. Found: C, 65.74; H, 7.03; F, 4.6. $[\alpha]_D$ +198° ($CHCl_3$). λ_{max} 243 mμ, ε 14,100.

2ζ-Fluoro-11β,21-dihydroxy-6α-methyl-4,17(20)-[cis]-pregnadien-3-one. Starting with 7.73 g. of 11β,21-dihydroxy-6α-methyl-4,17(20)-[*cis*]-pregnadien-3-one 21-acetate (Ib, R′ = Ac) the 2ζ-fluoro derivative was obtained as the free 21-alcohol (IIb, R′ = H) by the general procedure described above in yields of 62.5%. The compound crystallized well from ethyl acetate, but its m.p. was not precisely reproducible. Samples of apparently equal purity melted over short ranges that varied from 170–194°. A sample melting at 188–189° was analyzed.

Anal. Calcd. for $C_{22}H_{31}FO_3$: C, 72.89; H, 8.62; F, 5.24. Found: C, 72.73; H, 8.61; F, 5.14. λ_{max} 243 mμ.

The corresponding *21-acetate* (IIb, R′ = Ac), prepared by acetylation with acetic anhydride in pyridine at room temperature overnight, as described for the lower homolog, could be crystallized from tertiary butyl alcohol as a solvate which lost its appearance of crystallinity at 80° (on a Kofler block, viewed in polarized light), and melted at about 147–156°.

(14) Commercial 25% sodium methoxide in methanol, obtained from Olin Mathieson Chemical Corp. was assayed titrimetrically for total alkali, calculated as grams of sodium methoxide per 100 grams of solution. The required amounts were weighed in a syringe whose tare weight was obtained with the walls wetted by the solution; the weighed amounts were then injected rapidly into the reaction vessels.

(15) This figure is an average of eight runs, in which the yields varied from 2.91 g. (41.6%) to 4.10 g. (58.9%).

2ζ-Fluoro-6α-methylhydrocortisone acetate (IIIb, R′ = Ac). By means of the oxidative hydroxylation procedure described above for preparing 2ζ-fluorohydrocortisone acetate, 1.84 g. of the amorphous 21-acetate described above was converted to 1.30 g. of 2ζ-fluoro-6α-methylhydrocortisone acetate. The latter was eluted by 15% acetone in Skellysolve B from the column of 130 g. of Florisil upon which the total crude reaction product was adsorbed. The chromatographically purified product was amorphous and no solvent was found from which it could be crystallized. A sample eluted from the column was analyzed.

Anal. Calcd. for $C_{24}H_{33}FO_6$: C, 66.03; H, 7.62; F, 4.35. Found: C, 66.69; H, 7.66; F, 3.25. λ_{max} 242 mμ, ε 13,280. The infrared spectrum exhibited the expected absorption bands, including one at 1685 cm.$^{-1}$, attributable to the conjugated carbonyl at C-3, raised by the adjacent fluorine.

2ζ-Fluorocortisone acetate (IVa). A solution of 0.5 g. of 2ζ-fluorohydrocortisone acetate in 15 ml. of methylene chloride was mixed with a solution of 0.35 g. of sodium dichromate dihydrate in 5.0 ml. of water and 0.8 ml. of concentrated sulfuric acid at room temperature. The mixture was stirred for 4 hr. The methylene chloride layer was separated, washed with dilute sodium sulfite solution, saturated aqueous sodium bicarbonate and dried over sodium sulfate. Evaporation to dryness left a white crystalline solid, which, after 2 recrystallizations from ethanol, melted at 229–244° (Kofler block). The infrared spectrum of this substance showed bands at 3565 cm.$^{-1}$ (OH); 1743 cm.$^{-1}$ (acetate); 1730 cm.$^{-1}$ (20-ketone); 1700 cm.$^{-1}$ (11-ketone); 1667 cm.$^{-1}$ (conjugated carbonyl at C-3); and 1617 cm.$^{-1}$ (4:5 double bond). The band at 1667 cm.$^{-1}$ is typical of a Δ^4-3-ketone without α-halo substitution, and would be expected to be raised 10–20 cm.$^{-1}$ by the presence of the adjacent fluorine; analysis also indicated partial loss of fluorine.

Anal. Calcd. for $C_{23}H_{29}FO_6$: C, 65.70; H, 6.95; F, 4.52 Found: C, 66.05; H, 6.93; F, 3.43. λ_{max} 237 mμ, ε 14,175. $[\alpha]_D$ +240° ($CHCl_3$).

Descending chromatography on paper, using formamide as the stationary phase and Skellysolve B as the mobile phase, showed that the compound moved faster than 2-fluorohydrocortisone acetate, but slower than cortisone acetate

2ζ-Fluoro-6α-methylcortisone acetate (IVb). A sample of the chromatographed, amorphous 2-fluoro-6α-methylhydrocortisone acetate was oxidized with a solution of sodium dichromate in acetic acid for 1 hr. at room temperature. The mixture was poured into cold water and extracted with methylene chloride; the latter solution was washed successively with sodium sulfite solution, sodium bicarbonate solution, and water, then dried and evaporated. The residue crystallized from methanol, and melted at 222–225° with sintering at 207°. Evidence that this was 2ζ-fluoro-6α-methylcortisone acetate was given by a positive Tollens test, an infrared absorption spectrum of the expected type, an ultraviolet absorption maximum at 237 mμ (ε 14,250), and the following analysis:

Anal. Calcd. for $C_{24}H_{31}FO_6$: C, 66.34; H, 7.19; F, 4.37. Found: C, 66.94; H, 7.25; F, 3.30. $[\alpha]_D$ +216° ($CHCl_3$).

Acknowledgment. We wish to express our appreciation to Messrs. R. A. Houtman, W. A. Struck, R. C. Anderson, and S. R. Shaw for analyses and rotatory dispersion curves, to Dr. J. L. Johnson, M. F. Grostic, and J. E. Stafford for infrared and ultraviolet spectroscopy, and to J. D. Highstrete for technical assistance.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH]

Hypotensive Agents. XI. 3-Azabicyclohexane and 3-Azabicycloheptane Derivatives

LEONARD M. RICE

Received April 27, 1959

Dialkylaminoalkyl substituted bases containing the 3-azabicyclo[3:1:0]hexane[1] and 3-azabicyclo[3:1:1]heptane ring systems have been prepared and quaternized to asymmetric bis-quaternary salts. The 3-azabicyclo[3:1:0]hexane derivatives were synthesized from 1,2-cyclopropane dicarboxylic acid anhydride and caronic anhydride respectively. The 3-azabicyclo[3:1:1]heptane derivatives were prepared by employing norpinic anhydride. Reaction of the anhydrides with appropriate dialkylaminoalkylamines yielded the corresponding imides, by way of the amic acids, which were subjected to lithium aluminum hydride reduction to give the bicyclic bases. Quaternization yielded the bis-ammonium salts which were screened for hypotensive activity.

The high biological activity which we have previously encountered in many series of unsymmetrical bis-ammonium salts containing bi- and tricyclic nitrogen heterocycles has led us to extend this work and synthesize derivatives of 3-azabicyclo[3:1:0]hexane, VII and VIII, and 3-azabicyclo[3:1:1]heptane, IX. Prior studies of related bicyclic ring systems have been concerned with quaternary derivatives containing the 3-azabicyclo[3:2:0]heptane nucleus I,[2] the 3-azabicyclo[3:2:1]-octane nucleus II[3] and III,[4] the 3-azabicyclo[3:3:0]octane nucleus IV,[5] the 3-azabicyclo[3:3:1]-

(1) Other compounds containing this ring system have recently been prepared wherein the substitution was 6,6-diaryl. Private communication, Dr. P. B. Russell, Abstracts, 135th National Meeting, ACS, Boston, Mass., April 1959. Organic division 59.

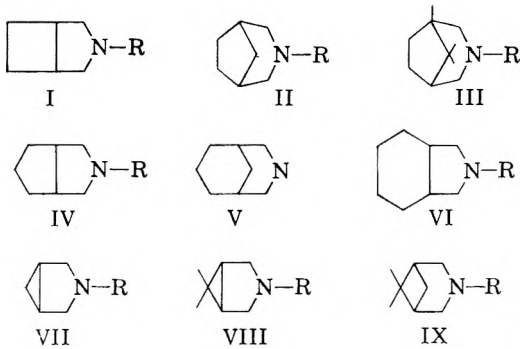
(2) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 22, 1100 (1957).

(3) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 22, 185 (1957).

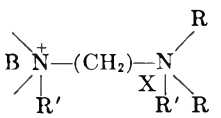
(4) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, 22, 1223 (1957).

(5) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 24, 7 (1959).

nonane nucleus V,[6] and many derivatives of the 3-azabicyclo[4:3:0]nonane nucleus, VI.[7]



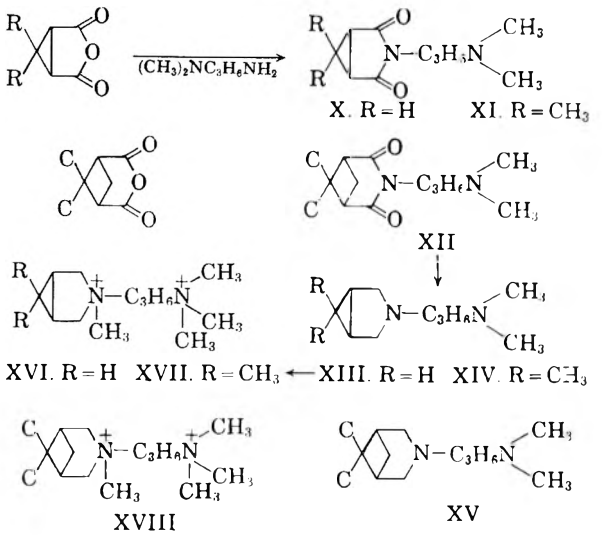
Early in our work it was noted that the most favorable arrangement of atoms for good hypotensive response was contained in the structure as shown below[7] where R′ is methyl or ethyl or a part of a small heterocycle, R′ is methyl or ethyl, X is 2 or 3 and B is a bi- or tricyclic ring.



This has since been confirmed by Cavallito and his co-workers.[8–10] Because in all these series of unsymmetrical bis-ammonium salts the most effective combination was found to be either the dimethylaminoethyl or dimethylaminopropyl side chain in which the quaternizing group was also methyl, we have used this grouping in the present investigation.

It is to be noted that all of the compounds prepared are either 3,4-polymethylene bridged pyrrolidines or 3,5-polymethylene bridged piperidines with or without additional bridging or substitution. To date the most favorable ring systems for good hypotensive response have been found in those compounds containing the dimethylene, trimethylene, and tetramethylene bridged pyrrolidine rings or the dimethylene bridged piperidine types. To further study and clarify the structure activity relationship in these series, it was desirable to prepare compounds wherein the bridging consisted of a lone methylene carbon atom. This report is concerned with the synthesis of bases containing such ring systems, which have not been previously reported in the literature in their completely reduced states.

The synthesis of the *N*-substituted ring system, 3-azabicyclo[3:1:0]hexane and its 6,6-dimethyl substituted analogue, was achieved by employing cyclopropane dicarboxylic anhydride and caronic anhydride respectively as the key intermediates. Cyclopropane dicarboxylic anhydride was prepared by both the methods of Guthzeit[11,12] and of Wiberg.[13] Caronic anhydride was synthesized by the elegant method of Perkin.[14] The corresponding *N*-substituted 3-azabicyclo[3:1:1]heptane was obtained employing norpinic anhydride as the starting material. Norpinic anhydride was obtained by the method of Kerr[15] as modified by Guha.[16] In general, the appropriate anhydride was reacted with a slight excess of dimethylaminopropylamine.



The resultant mixture of imide and amic acid was heated and maintained at 180–190° for two hours in order to complete the cyclization. The dione bases were obtained in good yields as distillable colorless oils. These imide bases and their corresponding hydrochloride and methonium salts are listed in Table I together with pertinent data.

Reduction of the imides was carried out by the addition of an ethereal solution of the dione to an ethereal solution of lithium aluminum hydride at such a rate as to just maintain reflux of the reaction solvent. The reduction products were isolated by distillation in excellent yields as colorless oils. The relevant data are shown in Table II.

A related dione, caronimide, containing the azabicyclohexane structure has been previously reported but attempted electrolytic reduction re-

(6) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **23**, 844 (1958).
(7) L. M. Rice and C. H. Grogan, *J. Am. Chem. Soc.*, **75**, 4911 (1953).
(8) C. J. Cavallito, A. P. Gray, and E. E. Spinner, *J. Am. Chem. Soc.*, **76**, 1862 (1954).
(9) C. J. Cavallito, A. P. Gray, and T. B. O'Dell, *Arch. intern. pharmacodynamie*, **101**, 38 (1955).
(10) A. P. Gray, D. E. Heitmeier, and C. J. Cavallito, *J. Am. Chem. Soc.*, **81**, 728 (1959).
(11) M. Conrad and M. Guthzeit, *Ber.*, **1185** (1884).
(12) A. Wasserman, *Helv. Chim. Acta*, **13**, 213, 229 (1930).
(13) K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Am. Chem. Soc.*, **79**, 4997 (1957).
(14) W. H. Perkin, Jr., and J. F. Thorpe, *J. Chem. Soc.*, **75**, 57-60 (1899).
(15) C. A. Kerr, *J. Am. Chem. Soc.*, **51**, 614 (1929).
(16) P. C. Guha and K. Ganapathi, *Ber.*, **69**, 1189 (1936).

TABLE I

N-DIMETHYLAMINOPROPYL-3-AZABICYCLOALKANEDIONES AND DERIVATIVES

Compound	Formula	B.P., °C.	Mm.	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Ionic Halogen Calcd.	Ionic Halogen Found
X	$C_{10}H_{16}N_2O_2$	106–107	0.4	61.20	60.97	8.22	8.13	14.28	14.29		
XI	$C_{12}H_{20}N_2O_2$	101–111	0.3	64.25	64.34	8.99	8.87	12.49	12.41		
XII	$C_{13}H_{22}N_2O_2$	90–92	0.1	65.51	65.12	9.31	9.42	11.75	11.50		
				HYDROCHLORIDES							
X	$C_{10}H_{17}N_2O_2Cl$	215–216[a]		51.61	51.63	7.36	7.47	12.04	11.76	15.23	14.95
XI	$C_{12}H_{21}N_2O_2Cl$	162–163[a]		55.27	55.28	8.12	8.04	10.74	10.53	13.60	13.50
XII	$C_{13}H_{23}N_2O_2Cl$	214–215[a]		56.82	56.89	8.44	8.72	10.20	10.27	12.90	13.02
				METHIODIDES							
X	$C_{11}H_{19}N_2O_2I$	200–201[a]		39.06	39.27	5.66	5.92	8.28	8.15	37.53	37.40
XI	$C_{13}H_{23}N_2O_2I$	237–238[a]		42.63	42.36	6.33	6.33	7.65	7.43	34.65	34.40
XII	$C_{14}H_{25}N_2O_2I$	215–216[a]		44.22	44.39	6.63	6.35	7.37	7.41	33.38	33.34

[a] M.p., °C.

TABLE II

N-DIMETHYLAMINOPROPYL-3-AZABICYCLOALKANES

Compound	Formula	B.P., °C.	Mm.	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Ionic Halogen Calcd.	Ionic Halogen Found
XIII	$C_{10}H_{20}N_2$	84–85	10	71.37	70.19[a]	11.98	11.91	16.65	16.38		
XIV	$C_{12}H_{24}N_2$	104–106	14	73.41	72.62[a]	12.32	12.17	14.27	14.00		
XV	$C_{13}H_{26}N_2$	118–120	12	74.22	74.35	12.46	12.20	13.32	12.95		
				DIHYDROCHLORIDES							
XIII	$C_{10}H_{22}N_2Cl_2$	237–238[b]		49.79	49.65	9.19	9.27	11.62	11.61	29.40	29.50
XIV	$C_{12}H_{26}N_2Cl_2$	230–231[b]		53.52	53.28	9.73	9.43	10.41	10.27	26.34	26.30
XV	$C_{13}H_{28}N_2Cl_2$	248–249[b]		55.12	55.21	9.96	10.01	9.89	9.68	25.03	25.48
				DIMETHIODIDES							
XVI	$C_{12}H_{26}N_2I_2$	277–278[b]		31.89	32.17	5.80	5.85	6.19	6.02	56.14	56.10
XVII	$C_{14}H_{30}N_2I_2$	227–228[b]		35.01	34.95	6.36	6.02	5.83	5.59	52.86	52.53
XVIII	$C_{15}H_{32}N_2I_2$	230–231[b]		36.45	36.51	6.53	6.49	5.69	5.44	51.36	51.40

[a] Analysis of the free base invariably gave a low carbon due to difficulty of complete combustion. [b] M.p., °C.

sulted in ring cleavage.[17] In view of this and other work by Simonsen *et al.*,[18,19] it was thought possible in the case of 3-azabicyclo(3:1:0]hexane that the reduction might open the cyclopropane ring yielding a monocyclic compound. We therefore prepared the corresponding *N*-substituted dimethylaminopropyl piperidine for direct comparison. The infrared spectra of the two compounds was different as well as the melting points of their respective hydrochloride salts. The refractive indexes of the two bases were also different, *N*-dimethylaminopropyl-3-azabicyclo[3:1:0]hexane n_D^{26} 1.463, *N*-dimethylaminopropyl piperidine n_D^{26} 1.458.

Quaternization by methyl iodide of the 3-azabicyclo[3:1:0]-hexane bases proceeded readily to yield the bis-ammonium salts. In the case of 3-azabicyclo[3:1:1]heptane, however, the quaternization was more difficult and had to be performed in a bomb tube. This is in keeping with most other 3,5-polymethylene bridged piperidines which we have worked with previously.

Pharmacology. The hypotensive activity of these compounds was evaluated on dogs by means of the cannulation technique under nembutal anesthesia. As expected from previous studies, diones, when tested as either their hydrochloride or methonium salts, were inactive. The dihydrochlorides of the reduced bases were also inactive. The bis-quaternary methonium salts of the base were of graded activity. Dimethylaminopropyl-3-azabicyclo[3:1:0]-hexane dimethiodide had a low order of activity whereas its dimethyl analogue had increased activity. The introduction of another carbon in the bridging, as in XVIII, resulted in increased biological potency. This compound was approxi-

(17) K. N. Menon and J. L. Simonsen, *J. Chem. Soc.*, 303 (1929).

(18) S. N. Iyer and J. L. Simonsen, *J. Chem. Soc.*, 2049 (1926).

(19) K. V. Hariharan, K. N. Menon, and J. L. Simonsen, *J. Chem. Soc.*, 431 (1928).

mately $^1/_2$ the potency of the ring system III bearing the same side chain.[20,21]

EXPERIMENTAL

N-Dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]-hexane-2,4-dione. A total of 16.8 g. (0.15 mole + 10% excess) of dimethylaminopropylamine was added to 21 g. (0.15 mole) of caronic anhydride contained in a 50-ml. round bottom flask. After the immediate exothermic reaction subsided, the reaction mixture was stirred and heated gently until a homogeneous melt was obtained. The temperature was slowly raised to 180–190° and maintained for 2 hr. The imide was isolated by distillation *in vacuo* to yield 28 g., 83%, of product, b.p. 101–111° at 0.3 mm.

The *hydrochloride* was prepared in isopropyl alcohol with excess alcoholic HCl and precipitated with ether. On recrystallization from isopropyl alcohol–ether it melted at 162–163°.

The *methiodide* was prepared in ethyl acetate with a slight excess of methyl iodide and recrystallized from isopropanol-ether, m.p. 237–238°.

N-Dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]-hexane. A solution of 12 g. (excess) of lithium aluminum hydride in 800 ml. of anhydrous ether was prepared in a 2-liter, 3-necked reaction flask fitted with a stirrer, dropping funnel, and condenser, and protected from atmospheric moisture. A solution of 22.4 g. (0.1 mole) of 3-dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]hexane-2,4-dione in 400 ml. of anhydrous ether was added dropwise with stirring at such a rate as to just maintain reflux of the ether. The reaction mixture was stirred an additional 2 hr. and then decomposed by dropwise addition of water. After an hour of additional stirring the inorganic precipitate was filtered and washed with 3 portions of ether, which were combined with the filtrate and dried over anhydrous sodium sulfate. The ether was stripped off and the residue distilled under reduced pressure to yield the base, 18 g., 91%, b.p. 104–106° at 14 mm.

The *hydrochloride* was prepared in the usual manner, m.p. 230–231°.

The *dimethiodide* was prepared by refluxing the base dissolved in absolute alcohol with a 10% excess of methyl iodide for several hours, m.p. 227–228°.

All of the compounds were prepared as outlined in the above examples except the *dimethiodide of N-dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:1]heptane.* In this case, the base dissolved in methanol was heated in a bomb tube for 4 hr. with a 10% excess of methyl iodide. The product was washed out of the bomb tube, precipitated with ether and recrystallized several times from alcohol ether, m.p. 231°.

RADNOR, PA.

(20) W. E. O'Malley, G. W. Haemmerli, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci. Ed.*, **47**, 263 (1958).

(21) This compound is known as Wy-1395, Trimethidinium, and OSTENSIN.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, DIAMOND ALKALI COMPANY]

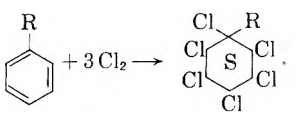
The Addition-Chlorination of Phenol[1]

IRVING ROSEN AND JOHN P. STALLINGS

Received April 28, 1959

Benzene derivatives with strong electron releasing groups such as phenol have not been addition-chlorinated in the past because of the ease with which they undergo substitution. The modification of the electron releasing properties of the hydroxy group in phenol by the use of electron withdrawing groups attached to the oxygen atom permits addition-chlorination to take place readily. Phenyl haloacetates were addition-chlorinated in good yields. Hydrolysis of the addition products suggests that the major stable product from the addition-chlorination of phenol is 2,4,6-trichlorophenol.

The literature contains descriptions of the addition-chlorination of several substituted benzenes. The most comprehensive study of these reactions was made by T. van der Linden.[2] The reactions he studied are summarized below. The most recent work reported on this reaction with substituted benzenes dwelled upon the effect of reaction conditions on the product yields.[3,4]



where R = F, CN, COCl, COOH, NO_2, CCl_3, $CHCl_2$, CH_2Cl, CH_3

A common property of these substituted benzenes is that they do not readily undergo chlorine substitution without the presence of an acid catalyst. Under conditions favorable for addition-chlorination, the addition reaction can take place instead of the substitution reaction. In some cases both reactions have occurred. Some of the major products isolated from reactions of this sort have been substituted by chlorine and then addition-chlorinated.

Among the compounds missing from the above are those which contain strong electron releasing groups and which readily undergo substitution-chlorination, even in the absence of an acid catalyst, *i.e.*, compounds such as phenol and aniline.

(1) Presented before the Organic Division at the 135th Meeting of the American Chemical Society, Boston, Mass., April 10, 1959.

(2) T. van der Linden, *Rec. trav. chim.*, **53**, 45 (1934); **53**, 703 (1934); **55**, 282 (1936); **57**, 342 (1938); **57**, 1075 (1938).

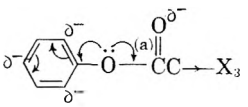
(3) D. E. Harmer, *AECU-3077* (1955).

(4) I. Rosen and J. P. Stallings, *Ind. & Eng. Chem.*, **50**, 1511 (1958).

It was the purpose of this work to addition-chlorinate phenol, or a phenol derivative, and to determine the nature of the product of the addition-chlorination of phenol.

In order to achieve the addition-chlorination of phenol, it appeared necessary either to conduct the chlorination at very low temperatures, or to so modify the phenolic OH group that the tendency of the molecule to undergo substitution would be considerably curtailed. The first alternative did not appear attractive because of the probable low reaction speeds at the low temperatures required. Furthermore, if low-temperature addition had taken place, a *gem* chlorohydrin, II, would have been formed, the isolation of which did not appear possible, because of the instability of such structures. For these reasons, the latter alternative appeared to offer the best route.

To modify the activating influence of the phenolic OH group, it is necessary to reduce its electron donating properties towards the benzene ring. It seemed that this could be accomplished by combining the phenolic oxygen atom with groups exerting a negative inductive effect. A strong inductive effect by this new group upon the electrons surrounding the phenolic oxygen atom would reduce their contribution towards activation of any positions on the benzene ring. In the case of phenol, it is known that the *ortho-para*-orienting power is considerably reduced after it has been converted to the acetate.[5] The use of the haloacetates should diminish this *ortho-para*-orienting power even more by virtue of the added inductive effect of the halogens upon the unshared electrons on the oxygen. Because of the displacement (a),



the unshared electrons on the oxygen are less available for activation of the aromatic nucleus. Consequently, the haloacetate group is less powerfully *ortho-para* directing than the unsubstituted hydroxy group and should be less directing than the acetate group. The deactivation of the nucleus reduces the rate of the substitution-chlorination reaction and should permit the addition-chlorination to take place more readily under favorable conditions.

The first strong electron withdrawing group used to deactivate the phenol was the trichloroacetyl radical. The phenyl trichloroacetate was prepared by conventional means. The mixture of phenyl trichloroacetate, together with CCl_4 and the theoretical amount of chlorine for addition was sealed in a borosilicate glass tube and exposed to ultraviolet irradiation for 22 hr. The phenyl trichloroacetate was readily addition-chlorinated in quantitative yields. The first evidence for the complete addition chlorination was afforded by the absence of the chlorine color in the reaction vessel and by the absence of HCl when the reaction tube was opened. The ease with which the addition-chlorination reaction took place and the quantitative yields were obtained was very gratifying. The crude reaction product was many times found pure enough for use in other reactions.

The structure of the 1,2,3,4,5,6-hexachlorocyclohexyl trichloroacetate was confirmed by infrared analyses. It was suspected that the product could be a mixture of unsaturated chlorinated products and overchlorinated products which fortuitously gave the correct analysis. The spectrogram contained no evidence of benzene unsaturation or aliphatic unsaturation, resembled that of the 1,2,3,-4,5,6-hexachlorocyclohexanes to a modified extent, and contained strong bands supporting the acetate group.

After it was found that phenyl trichloroacetate was readily addition-chlorinated, several other phenol esters were prepared and investigated in this reaction. Table I summarizes the results obtained with the phenyl haloacetates. The wide range in the boiling points of the products in Table I is probably due to the number of stereoisomers present. Elemental and infrared analyses of various fractions of the same product showed little variation.

To determine if the halogen substituent in the haloacetate were necessary for the addition-chlorination, an attempt was made to carry out the addition reaction with phenyl acetate. The product consisted of a mixture of substitution-chlorinated materials, and no addition-chlorinated material. Thus it appears that the additional deactivating influence of the halogen ester is necessary to obtain the desired reaction.

Some esters other than the haloacetates were found to permit addition-chlorination. Table II summarizes the results of the addition chlorination of diphenyl carbonate and triphenyl phosphate. The analyses of these materials indicate that the products were not completely addition-chlorinated. The products, however, were difficult to purify because of a tendency to decompose during heating. This is not surprising in view of the steric strain which is probably present in these crowded molecules. The infrared spectra of the compounds contained only weak bands for benzene unsaturation and many bands supporting the saturated structure.

To determine the product of the addition-chlorination of phenol, I was hydrolyzed by dilute acid under mild conditions. The product of the acid hydrolysis consisted of a 90% yield of 2,4,6-trichlorophenol (V).

(5) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 239.

TABLE I

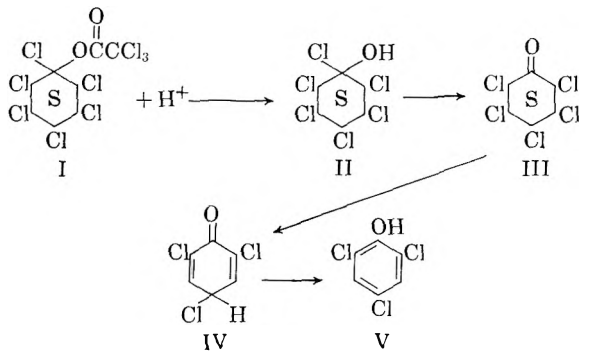
ADDITION-CHLORINATION OF PHENYL HALOACETATES

Phenyl haloacetate	Products B.p., °C./mm.	n_D^{25}	Yield, %	Formula	Analyses, % Calculated C	H	Cl	Found C	H	Cl
$C_6H_5OCOCCl_3$	160-164/0.3-0.4	1.5532	90	$C_8H_5O_2Cl_9$	21.25	1.11	70.5	21.15	1.16	70.6
$C_6H_5OCOCHCl_2$	162-175/0.7		79	$C_8H_6Cl_8O_2$	22.95	1.44	67.8	22.58	1.77	66.8
$C_6H_5OCOCH_2Cl$	166-172/1.2	1.5558	43	$C_8H_5Cl_7O_2$	25.05	1.84	64.9	25.00	1.92	65.6
	172-176/1.2		51					23.64	1.68	65.1
$C_6H_5OCOCF_3$	120-126/1.1	1.4910	65	$C_8H_5F_3Cl_6O_2$	23.82	1.25	52.8	23.22	1.27	53.3
p-$ClC_6H_4OCOCCl_3$	180-192/1.0	1.5624	76	$C_8H_4Cl_{10}O_2$	19.73	0.83	72.8	19.79	0.93	72.3

TABLE II

ADDITION-CHLORINATION OF DIPHENYL CARBONATE AND TRIPHENYL PHOSPHATE

Starting Material	Products M.p., °C.	Yield, %	Formula	Analyses, % Calculated C	H	Cl	Found C	H	Cl
Diphenyl carbonate	84–90°	47	$C_{13}H_{10}Cl_{12}O_3$	24.4	1.6	66.5	25.3	1.7	63.4
Triphenyl phosphate	120° (dec.)	62	$C_{18}H_{15}Cl_{18}PO_4$	22.4	1.6	66.2	26.2	2.2	60.6



The proposed explanation for the formation of the 2,4,6-trichlorophenol rather than other isomers is represented by the above sequence of steps. Initially, the ester I should be hydrolyzed to the *gem* chlorohydrin, II, which is the product of the addition chlorination of phenol. The *gem* chlorohydrin, II, then undergoes dehydrochlorination to the 2,3,4,5,6-pentachlorocyclohexanone, III. The *beta* chlorine atoms of ketones are easily eliminated. It is postulated that III preferentially eliminates the *beta* chlorine atoms and forms a dienone such as IV which rapidly undergoes the dienone-phenol rearrangement to the product, V. An inference of the results is that if phenol were addition-chlorinated to II, II would probably undergo the same dehydrochlorination path and sequence of steps and yield V as the major stable product.

EXPERIMENTAL

Preparation of the Phenyl Haloacetates. Most of the phenyl haloacetates were prepared in better than 80% yields by refluxing equimolar quantities of the phenol and the appropriate acid chloride until the evolution of HCl ceased. The product was then purified by distillation or recrystallization.

Phenyl trichloroacetate. B.p. 122°/14 mm. and 137–138°/24 mm.; n_D^{20} 1.5233 (lit. b.p. 125–126°/14 mm.[6]).

Phenyl dichloroacetate was recrystallized from hexane, m.p. 48.5–49.5° (lit. m.p. 48°[7]).

Phenyl chloroacetate. B.p. 140–141°/31 mm. (lit. b.p. 155°/65 mm.[8]).

p-Chlorophenyl trichloroacetate. B.p. 170–172°/34 mm. and 108/110°/0.8–0.9 mm. Bhargava and Sen[9] reported a b.p. of 94–98°/4 mm. Because of the discrepancy in boiling points, our material was subjected to infrared and elemental analyses. The infrared spectrum showed a strong absorption band at 1200 $cm.^{-1}$ plus the carbonyl band to support the acetate group. There was also support for 1,4 substitution in the benzene ring, n_D^{25} 1.5383.

Anal. Calcd. for $C_8H_4Cl_4O_2$: C, 35.0; H, 1.47; Cl, 51.6. Found: C, 34.9; H, 1.70; Cl, 51.2.

Phenyl trifluoroacetate was prepared in 83% yield by refluxing phenol with trifluoroacetic anhydride at 100–120° for 2 hr., b.p. 146.5–147° (lit. b.p. 146.5–147.0°[10]).

2,4,6-Trichlorophenyl trichloroacetate was prepared by refluxing the mixture of the sodium salt of 2,4,6-trichlorophenol with trichloroacetyl chloride in dry dioxane for 2.5 hours. Evaporation of the dioxane and distillation of the residue gave the product, b.p. 110–112°/0.09 mm., n_D^{25} 1.5597, in 40% yield.

Anal. Calcd. for $C_8H_2Cl_6O_2$: C, 28.1; H, 0.58; Cl, 62.0. Found: C, 28.6; H, 0.87; Cl, 61.5.

Addition Chlorination of the Phenol Esters. The esters were generally addition-chlorinated by irradiating the ester and liquid chlorine, with or without CCl_4 as a solvent, in a sealed borosilicate glass tube with a 15 watt General Electric Company black light fluorescent lamp (catalogue no. F15T8-BL). The following examples illustrate the method.

Preparation of 1,2,3,4,5,6-hexachlorocyclohexyl trichloroacetate (1). In a thick-walled borosilicate glass tube of 2.5 cm. i.d. were placed 24.0 g. (0.10 mole) of phenyl trichloroacetate and 21.4 g. (0.30 mole) of chlorine. The tube was sealed and placed adjacent to a black light fluorescent lamp for 22 hr. When the tube was opened, no HCl was detected. After venting, the gain in weight of the non-volatile contents

(6) W. Kuster and G. Koppenhoffer, *Ber.*, 60, 1778 (1927).

(7) H. Crompton and P. M. Triffitt, *J. Chem. Soc.*, 119, 1874 (1921).

(8) K. Fries and W. Pfaffendorf, *Ber.*, 43, 214 (1910).

(9) P. M. Bhargava and A. B. Sen, *J. Sci. Food and Agr.*, 1, 178 (1950).

(10) R. F. Clark and J. H. Simons, *J. Am. Chem. Soc.*, 75, 6306 (1953).

of the tube corresponded to complete addition of the chlorine. The reaction product was a nearly colorless, dense, highly viscous liquid. Distillation gave about 90% of the theoretical quantity of product, b.p. 160–164°/0.4 mm., d_{20}^{20} 1.745. Calcd.: Mr_D^{20} 82.40. Found: 82.98.

Anal. Calcd. for $C_8H_5O_2Cl_9$: C, 21.25; H, 1.11; Cl, 70.5. Found: C, 21.15; H, 1.16; Cl, 70.6.

Because the reaction product was very viscous, some product was held up in parts of the distillation apparatus, lowering the yield. The crude undistilled reaction mixture was analyzed.

Anal. Found: C, 21.03; H, 1.02; Cl, 71.0.

Preparation of bis(1,2,3,4,5,6-hexachlorocyclohexyl) carbonate. In a thick-walled borosilicate glass tube were placed 10.7 g. (0.050*M*) of diphenyl carbonate, 31.6 g. (0.44*M*) of chlorine, and 18.0 ml. of carbon tetrachloride. The tube was sealed and irradiated by a black light fluorescent lamp for 17 hr. After the tube was vented, there was a 29.6 g. weight gain in the nonvolatile materials. The product was dissolved in methanol, precipitated by the addition of water, and rapidly filtered and dried. In the first crop, 15.0 g. of product was obtained, m.p. 84–90°.

Anal. Calcd. for $C_{13}H_{10}Cl_{12}O_3$: C, 24.4; H, 1.58; Cl, 66.5. Found: C, 25.3; H, 1.7; Cl, 63.4.

Subsequent materials which were precipitated were lower melting and gave greater deviations from the theoretical values in the elemental anaylsis.

Hydrolysis Experiments. The acid hydrolysis of I was effected by stirring a mixture of 15.0 g. (0.0332*M*) of I, 60 ml. of dioxane, 30 ml. of conc. HCl, and 60 ml. of water at reflux for one hour. The hydrolysis mixture was saturated with salt and the organic material separated by extraction with chloroform. After evaporation of the chloroform, distillation of the residue gave 8.3 g. of one fraction, b.p. 120–124°/39 mm. and 1.4 g. of 2,4,6-trichlorophenol, identified by elemental analysis and a mixed m.p. with an authentic sample. The first fraction was a binary mixture (apparently azeotropic) containing about an equimolar ratio of 2,4,6-trichlorophenol to trichloroacetic acid. The total amount of 2,4,6-trichlorophenol obtained was 5.9 g., or a 90% yield.

The hydrolysis of 0.08*M* of the addition-chlorinated phenyl trifluoroacetate in dioxane-water at 10–25° followed by chloroform extraction and distillation of the extract gave a 70% yield of the 2,4,6-trichlorophenol. The phenol was identified by a mixed melting point; benzoate, m.p. 74–75°.

PAINESVILLE, OHIO

[FROM THE DEPARTMENT OF BACTERIOLOGY, THE UNIVERSITY OF KANSAS]

Adduct Formation between Chloroacetone and *N'*-Alkyl Substituted Pyridine Bases and Its Biological Significance[1-3]

J. M. AKAGI* AND D. PARETSKY

Received April 29, 1959

The reaction involving adduct formation between DPN[4] and various carbonyl compounds have been extensively studied by Burton and Kaplan.[5,6] The mechanism for this reaction, proposed by these workers, involves a prior ionization of a proton from the carbon alpha to the carbonyl carbon, resulting in the formation of a negatively charged molecule. This is followed by an addition reaction with the positively-charged 4-carbon of the pyridinium moiety of DPN. The reaction can be followed by the appearance of a characteristic maximum absorption for that particular adduct. In this report will be presented results of adduct formation obtained between chloroacetone and *N'*-alkyl substituted pyridinium bases. When *N'*MeN is caused to react with chloroacetone in basic solutions, the formation of an adduct is apparent by the formation of a new maximum in the 360 mμ region of the absorption spectrum. Substituting the carbamoyl for a carboxaldehyde group resulted in a pyridinium compound (*N'*MePyAl), which in smaller quantities was capable of reacting with chloroacetone at a rate faster than *N'*MeN. When, instead of aldehyde, an acetyl group was attached to the pyridine ring, a compound was obtained which was intermediate between *N'*MeN and *N'*MePyAl in adduct-forming abilities. Table 1 summarizes these findings.

In order to determine whether or not the group attached to the positive nitrogen atom influenced adduct formation, the carbon density around the ring nitrogen was increased by preparing the ethyl, isopropyl, and tertiary butyl derivatives of the pyridine bases. Rate studies comparing adduct formation between *N'*-methyl and the larger alkyl derivatives showed that with increasing carbon density around the ring nitrogen decreasing rates of addition reactions were obtained. This can be seen in Fig. 1 where the reactivity of *N'*MePyAl

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(1) Taken from a thesis submitted by J. M. Akagi in partial fulfillment of the requirement for the degree of Doctor of Philosophy.

(2) This investigation was supported in part by the American Cancer Society, Institutional Grant 57 M 578-G, and by the University of Kansas General Research Fund.

(3) This report was presented at the Missouri Branch, Society of American Bacteriologists' Meeting in Manhattan, Kansas, in April 1958, and at the Midwest Regional Biochemistry Meeting in Lawrence, Kansas, October 1958.

(4) The following abbreviations will be employed in this paper: diphosphopyridine nucleotide (oxidized), DPN; *N'*-methylnicotinamide, *N'*-MeN; *N'*-ethylnicotinamide, *N'*-EtN; *N'*-isopropylnicotinamide, *N'*iPrN; *N'*-methyl-3-acetylpyridine, *N'*MeAP; *N'*-methyl-pyridine-3-carboxaldehyde, *N'*MePyAl; *N'*-tertiary butylpyridine-3-carboxaldehyde, *N'*-*tert*-BuPyAl.

(5) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, **206**, 283 (1954).

(6) N. O. Kaplan, *Record of Chem. Prog.*, **16**, 177 (1955).

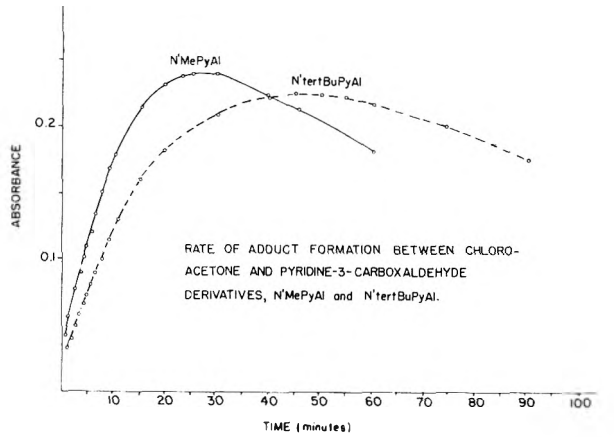


Fig. 1. Reaction rates were measured at the maximum absorption peaks of the respective chloroacetone adducts, *i.e.*, N^{1}MePyAl-chloroacetone = 340 mμ; N^{1}tertBuPyAl-chloroacetone = 390 mμ. Each reaction mixture consisted of 1.0 μmole pyridinium base; Tris buffer, 0.1 M, pH 10.2; reaction initiated by addition of 75 μmoles chloroacetone; the entire system made to a volume of 4.0 ml. with distilled water; temperature, 25°.

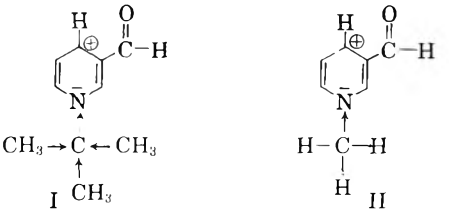
TABLE I

ADDUCT FORMATION BETWEEN CHLOROACETONE AND PYRIDINIUM BASES

Compound	Conc. μmoles per 4.0 ml.	Adduct observed formed with chloro-acetone	Relative rate of reaction[a]
*N'*MeN	1.0	–	—
*N'*MeN	10.0	+	100
*N'*MePyAl	1.0	+	203
*N'*MePyAl	10.0	+	Too rapid to be measured
*N'*MeAP	1.0	–	—[b]
*N'*MeAP	10.0	+	—[b]

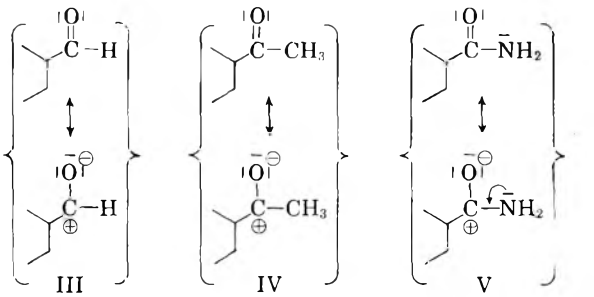
[a] Each system consisted of the pyridinium compounds which were caused to react with 75 μmoles of chloroacetone (with *N'*MeAP, 5 μmoles of chloroacetone were employed); Tris buffer, 0.1*M*, *p*H 10.2; made to a final volume of 4.0 ml. with distilled water. An arbitrary value of 100 was given to *N'*MeN expressed as the change in absorbancy per unit time (5 min.). The wave lengths at which the reactions were measured were: *N'*MeN = 365 mμ; *N'*MePyAl = 340 mμ; for *N'*MeAP there was an initial peak at 310 mμ followed by the slow formation of a new peak at 390 mμ after 24 hr. [b] The rate studies could not be made, since there was apparently rearrangement of the adduct to another product indicated by a shift in the absorption peak, as indicated above.

is compared with that of *N'-tert*-BuPyAl. The latter compound forms an adduct at a slower rate than the corresponding *N'*-methyl compound. This is in accordance with the fact that alkyl groups repel electrons through an inductive effect; a higher carbon density around the nitrogen would be expected to alleviate the positivity of this atom. Thus, the resonance structure in which the formal positive charge appears on the 4-carbon makes less of a contribution to the state of the pyridinium ion when the *N'*-substituent is *tert*-butyl (I) rather than methyl (II). Similar results were obtained



I II

with the nicotinamide series when *N'*-MeN was compared with *N'*EtN and *N'*iPrN. The *N'*EtN reactivity was very close to that of *N'*MeN, but there was a noticeable difference in rate between *N'*MeN and *N'*iPrN. Two conclusions may be drawn from the results obtained in these studies: 1. The side chain moiety of the pyridinium compound controls to a large extent the reactivity of the molecule. It appears that the more positive the carbonyl carbon of this side chain, the more reactive the compound as illustrated below:



III IV V

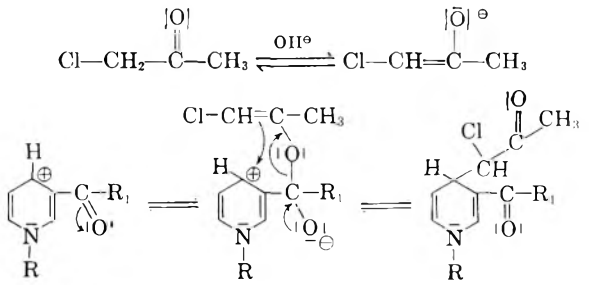
The carbonyl carbon atom of the carboxaldehyde, III, exhibits a greater electrophilic character than the carbonyl carbon atom of IV or V. Structure IV has a carbonyl carbon atom with a greater electrophilic character than V, since the amide group in V can help share the positive charge on the carbonyl carbon by donating its free pair of electrons of the nitrogen atom. The order of reactivity of the pyridinium compounds was found to be *N'*RPyAl>*N'*RAP>*N'*RN; *i.e.*, in the contribution of the side chain ($-\overset{\overset{O}{\|}}{C}-R^1$) to pyridinium reactivity, $R^1 = H > CH_3NH_2$.

2. The group linked to the positive nitrogen atom is partly responsible for the shift of electrons from the ring to the nitrogen. This results in the formation of the positive center at the 4-carbon. It has been suggested that the side chain moiety of the pyridinium compound has an influence on the electrophilic nature of the 4-carbon.[7]

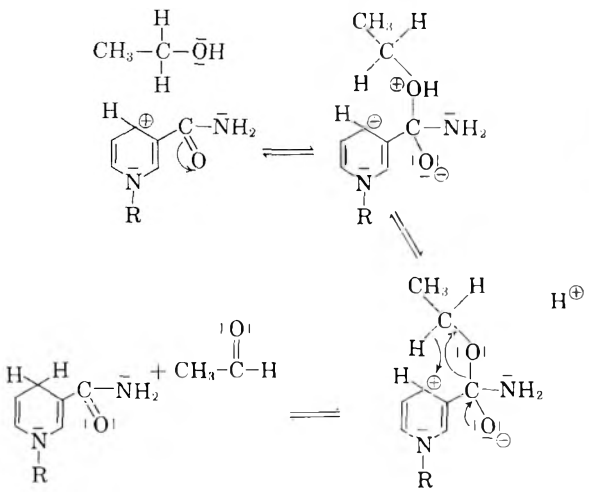
Although this effect is undoubtedly partially operative, it is the opinion of the authors that the main function of the side chain is to participate in addition reactions by coordinating with the nucleophilic carbonyl compound. The interaction of

(7) N. O. Kaplan and M. Ciotti, *J. Biol. Chem.*, 221, 823 (1956).

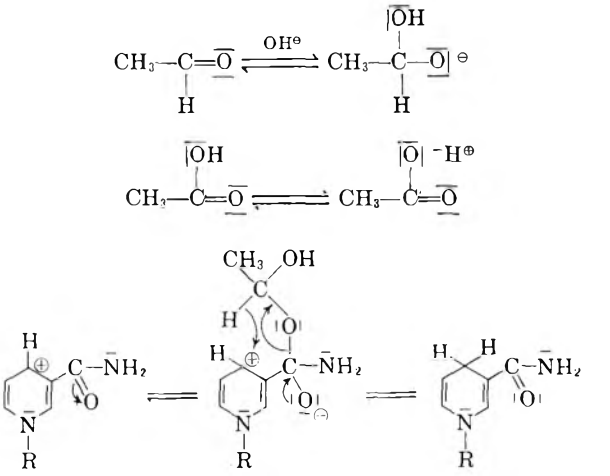
chloroacetone and the pyridinium bases employed in these studies may be explained as follows:



Extending this hypothesis to biological systems such as ethanol oxidation, a possible mechanism for the reduction of DPN would be as follows:



This is related to the Meerwein-Ponndorf-Verley reduction mechanism involving a hydride ion transfer as proposed by Woodward *et al.*[8] Mahler and Douglas[9] have considered a similar mechanism for DPN reduction involving zinc as a participant in the reaction. Wallenfels and Sund[10] also presented a mechanism for DPN reduction involving zinc; the metal is proposed to coordinate with enzyme, substrate, and the adenine moiety of DPN. In contrast are the views of van Eys and Kaplan[11] who suggested that zinc is linked to DPN through a pyrophosphate bond. In a subsequent report, van Eys *et al.*[12] stated that zinc is not an integral part in the actual catalysis of substrate oxidation. The action of aldehyde dehydrogenases may be explained by the mechanism which we propose in the present communication. Aldehyde dehydrogenases are pyridine nucleotide-linked enzymes which catalyze the oxidation of aldehydes to the respective acids. This can be visualized by an initial attack on the carbonyl group of the aldehyde by a hydroxyl ion in a manner similar to that found in the Cannizzaro reaction.[13] The following scheme demonstrates this reaction:



Aldehyde dehydrogenases and alcohol dehydrogenases may operate under the same mechanism as proposed in this communication.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were prepared by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Rate studies were measured in the Beckman Model B spectrophotometer while the maximum absorption curves were determined in the Beckman DU spectrophotometer, employing cuvettes having a 1.0 cm. light path.

Pyridinium compounds. The compounds employed during this investigation, *N'*MeN,[14] *N'*EtN,[15] *N'*PrN, *N'*MePyAl[16] and *N'*tertBuPyAl iodides were prepared by the methods of Karrer *et al.*[14]

N'-Isopropylnicotinamide iodide. Yellow crystalline product, m.p. 185–186°. *Anal.* Calcd. for $C_9H_{13}N_2IO$: C, 36.96; H, 4.45; N, 9.58; I, 43.49; O, 5.48. Found: C, 37.45; H, 4.54; N, 9.69; I, 43.7; O, 4.62.

N'-Methyl-3-acetylpyridine iodide. Yellow shiny powder, m.p. 160–163°. *Anal.* Calcd. for $C_8H_{10}NIO$: C, 36.5; H, 3.8; N, 5.33; I, 48.3; O, 6.08. Found: C, 36.94; H, 3.9; N, 5.43; I, 48.22; O, 5.51.

N'-tert-Butylpyridine-3-carboxaldehyde iodide. Yellow flaky powder, m.p. 192°. *Anal.* Calcd. for $C_{10}H_{14}NIO$: C, 41.2; H, 4.81; N, 4.81; I, 43.7; O, 5.5. Found: C, 41.0; H, 4.92; N, 4.81; I, 43.5; O, 5.77.

Adduct formation. The procedures employed during this investigation consisted of reacting the cited concentrations of pyridinium salts with chloroacetone in the presence of Tris buffer, 0.1*M*, *p*H 10.2, made to a final volume of 4.0

(8) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Amer. Chem. Soc.*, **67**, 1425 (1945).

(9) H. R. Mahler and J. J. Douglas, *J. Amer. Chem. Soc.*, **79**, 1159 (1957).

(10) K. Wallenfels and H. Sund, *Biochem. Z.*, **329**, 59 (1957).

(11) J. van Eys and N. O. Kaplan, *Biochim. Biophys. Acta*, **23**, 574 (1957).

(12) J. van Eys, A. San Pietro, and N. O. Kaplan, *Science*, **127**, 1443 (1958).

(13) E. R. Alexander, *J. Amer. Chem. Soc.*, **69**, 289 (1947).

(14) P. Karrer, G. Schwarzenbach, F. Benz, and U. Solmssen, *Helv. Chim. Acta* **19**, 811 (1936).

(15) P. Karrer and F. J. Stare, *Helv. Chim. Acta*, **20**, 418 (1937).

(16) L. Pannizzon, *Helv. Chim. Acta*, **24**, 24E (1941).

ml. with distilled water. All reactions were conducted at room temperature (23–25°).

Acknowledgment. The authors wish to acknowledge their indebtedness to Dr. W. E. McEwen, Department of Chemistry, for his helpful suggestions and constructive criticisms during the course of this work.

Addendum. During the preparation of this report an abstract by B. Kadis[17] appeared which proposed a similar Meerwein-Ponndorf-Verley reduction mechanism for DPN reduction.

LAWRENCE, KAN.

(17) B. Kadis, Abstracts, 135th Meeting of the American Chemical Society, Boston, Mass., April 1959, page 24-O.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Ethyl 1-Thio-α-D-galactofuranoside

M. L. WOLFROM, Z. YOSIZAWA,[1] AND B. O. JULIANO[1]

Received April 30, 1959

Partial demercaptalation of D-galactose diethyl dithioacetal (mercaptal) (I) leads to the synthesis of ethyl 1-thio-α-D-galactofuranoside (II) characterized by periodate oxidation and by its crystalline tetraacetate IV.

Schneider and co-workers[2,3] synthesized alkyl 1-thio-α-D-glucosides by treating an aqueous solution of D-glucose dialkyl dithioacetal (mercaptal) at room temperature with one mole of mercuric chloride and neutralizing the acid formed with alkali. With more mercuric chloride, complete demercaptalation occurred to produce the free sugar in aqueous solution or the alkyl glycoside in alcohol solution. However, attempts to prepare an ethyl 1-thio-D-galactoside (II) by treatment of D-galactose diethyl dithioacetal (I) with one mole of mercuric chloride, under neutral conditions, failed.[3,4] There was obtained instead, in ethanolic solution, equimolar amounts of ethyl β-D-galactofuranoside and starting material (I), which Green and Pacsu[4] ascribed to the reactivity of the thioglycoside (II) to solvolysis promoted by mercuric chloride. Green and Pacsu[4] concluded, on the basis of rotation values and ease of acid hydrolysis, that the glycosides formed from the dithioacetals were furanosides. Utilizing periodate oxidation data, Wolfrom and co-workers[5] verified this ring assignment for ethyl 1-thio-α-D-glucofuranoside derived from the dithioacetal.

We report herein the synthesis of sirupy ethyl 1-thio-α-D-galactofuranoside (II) and its crystalline tetraacetate (IV), using essentially the method of Green and Pacsu[4] but supplemented with chromatographic techniques not at the time available to these workers. A reappraisal of the feasibility of partial demercaptalation of I to II stemmed from the need of the analogous 2-acetamido-2-deoxy-1-thio-α-D-galactofuranoside as an intermediate in the synthesis of 2-amino-2-deoxy-L-arabinose from 2-amino-2-deoxy-D-galactose.[6] D-Galactose diethyl dithioacetal (I) was treated with an aqueous solution of mercuric chloride in the presence of mercuric oxide, to produce nearly equimolar amounts of ethyl 1-thio-α-D-galactofuranoside (II) and D-galactose (III). The latter substance (III) was removed by its exhaustive fractional precipitation from alcoholic solution. The mother liquor was acetylated and further purified by silicate column elution chromatography to give crystalline IV, recrystallized from diethyl ether–petroleum ether, m.p. 50.5–51.5°, $[\alpha]_D$ +118° (chloroform) and +127° (ethanol). This substance showed weak infrared absorption at 648 and 682 cm.$^{-1}$ Sheppard[7] cites 600–700 cm.$^{-1}$ as the region for C—S bond absorption.

The ring structures of II and IV were assigned on the basis of sodium metaperiodate oxidation (Table I) of sirupy II, $[\alpha]_D$ +124° (water), obtained from pure IV by deacetylation. The oxidation conditions employed were essentially those of Wolfrom and Yosizawa.[6] It has been shown[5,6] that the rapid liberation of one mole of formaldehyde by periodate ion is characteristic of 1-thiohexofuranosides and it is further known that the presence of the thioethoxyl group results in some overoxidation of an obscure nature.[8] Although a number of 1-thio-β-D-glycopyranosides have been reported,[3,9] to our knowledge II is the first 1-thio-D-galactoside to be recorded.

(1) National Science Foundation Research Associate (Z. Y.) and Predoctoral Fellow (B. O. J.), 1957–1958, under Grant NSF-G4494 to The Ohio State University.

(2) W. Schneider and Johanna Sepp, *Ber.*, 49, 2054 (1916).

(3) W. Schneider, Johanna Sepp, and Ottilie Stiehler, *Ber.*, 51, 220 (1918).

(4) J. W. Green and E. Pacsu, *J. Am. Chem. Soc.*, 59, 1205 (1937).

(5) M. L. Wolfrom, S. W. Waisbrot, D. I. Weisblat, and A. Thompson, *J. Am. Chem. Soc.*, 66, 2063 (1944).

(6) M. L. Wolfrom and Z. Yosizawa, *J. Am. Chem. Soc.*, 81, 3474, 3477 (1959).

(7) N. Sheppard, *Trans. Faraday Soc.*, 46, 429 (1950).

(8) L. Hough and M. I. Taha, *J. Chem. Soc.*, 3994 (1957).

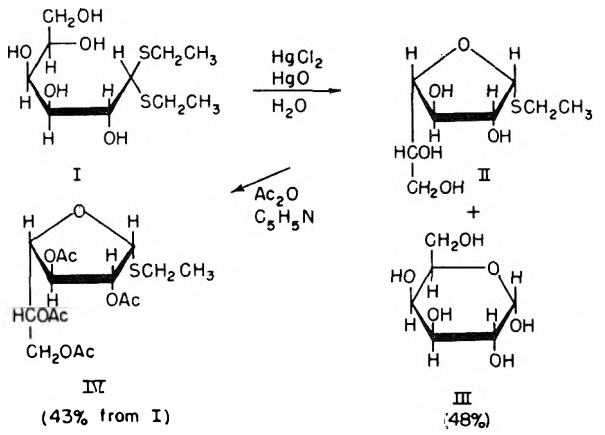
(9) E. Fischer and K. Delbrück, *Ber.*, 42, 1476 (1909); C. B. Purves, *J. Am. Chem. Soc.*, 51, 3619, 3631 (1929).

TABLE I

SODIUM METAPERIODATE OXIDATION OF ETHYL 1-THIO-α-D-GALACTOFURANOSIDE (II, 1%) AT 5°, *p*H 4.5 IN THE DARK

Time, Hr.	Oxidant[a] Added	Oxidant[a] Used[b]	Formaldehyde[a] Formed[c]	Formic Acid[a] Formed[d]
0.5	6	2.76	0.99	<0.10
1.0	6	3.12	—	<0.10
2.0	6	3.65	—	—
4.0	6	4.38	—	0.25
24.0	6	5.23	—	0.30
0.5	2	1.46	0.98	0.00
1.8	2	1.83	—	—

[a] Moles per mole of sample. [b] Determined iodometrically. [c] By dimedon assay. [d] Titrable acidity, phenolphthalein endpoint.



EXPERIMENTAL

Ethyl tetra-O-acetyl-1-thio-α-D-galactofuranoside (IV). The preparation of ethyl 1-thio-α-D-galactofuranoside (II) essentially followed the procedure of Green and Pacsu[4] for preparing ethyl 1-thio-α-D-glucofuranoside from D-glucose diethyl dithioacetal. D-Galactose diethyl dithioacetal[10] (I, 19 g., m.p. 140–142°) was dissolved in 800 ml. of water at 70°, and the solution cooled to 50°. In this solution was suspended washed yellow mercuric oxide,[11] prepared from 18.1 g. of mercuric chloride and 5.33 g. of sodium hydroxide, and then an aqueous solution of mercuric chloride (9.04 g. in 500 ml., 0.5 equiv.) was added dropwise, with vigorous stirring, over a period of 30 min. The stirring was continued for 40 min. more, after which 8 ml. of pyridine was added and the reaction mixture was filtered through an asbestos mat. The combined filtrate and washings were concentrated under reduced pressure and the resultant sirup was dried by repeated evaporation from ethanol solution under reduced pressure. Paper chromatography at this stage, using Whatman No. 1 filter paper with 1-butanol, ethanol, and water (40:11:19 by vol.) as developer and periodate-permanganate-benzidine indicator,[12] separated two compounds, one with the same R_F value, 0.22, as D-galactose (III), and a nonreducing substance, R_F 0.67, different from I, R_F 0.79. Separation was made by twice dissolving the sirup in methanol (300 ml.), filtering insoluble material which separated on standing and evaporating the solvent from the filtrate under reduced pressure. The resultant sirup was similarly subjected to two fractional precipitations from ethanol (300 ml.). The final sirup was dissolved in 100 ml. of ethanol and the solution was maintained at 5° for 10 hr. The insoluble material which separated was removed by filtration and, together with the previously collected precipitates, was found to be identical chromatographically with D-galactose (III); total yield 5.75 g. (48% from I). The mother liquor, after concentration to a thick sirup, was dried over phosphorus pentoxide under reduced pressure; yield 9.2 g. The dried sirup was acetylated with a mixture of 50 ml. each of acetic anhydride and pyridine at room temperature for 24 hr. The reaction mixture was then poured into 500 ml. of ice and water and extracted with chloroform. The extract was washed successively with water, sodium bicarbonate aqueous solution, and water and evaporated under reduced pressure to a sirup, which was dried by repeated evaporation from ethanol; yield 14.6 g. This material was dissolved in 50 ml. of benzene and was placed on a column (110 × 75 mm., diam.) of Magnesol[13]–Celite[14] (5:1 by wt.) and developed with 3000 ml. of a mixture of benzene and ethanol (100:1 by vol.). The eluate was concentrated to a sirup and further dried by repeated evaporation with ethanol. On drying over phosphorus pentoxide under reduced pressure, the residual sirup crystallized in long, fine white needles; yield 11.18 g. (43% from I) of ethyl tetra-*O*-acetyl-1-thio-α-D-galactofuranoside (IV), m.p. 50.5–51.5°. Two recrystallizations from diethyl ether–petroleum ether gave essentially the same crystals, m.p. 50.5–51.5°, $[\alpha]_D^{25}$ +118° (c 1.11, chloroform), +127° (c 2.20, ethanol), X-ray powder diffraction data[15]: 9.48 vs (1), 8.82 m, 5.12 s (2, 2), 4.63 s (2, 2), 4.23 vw, 4.09 vw, 3.95 m, 3.81 m, 3.60 w, 3.43 m, 3.04 m, 2.66 vw, 2.45 w, 2.22 vw, 1.81 vw. The substance showed weak infrared absorption bands (potassium bromide pellet) at 648 and 682 $cm.^{-1}$

Anal. Calcd. for $C_{16}H_{24}O_9S$: C, 48.97; H, 6.16; S, 8.17; $COCH_3$, 43.87. Found: C, 48.99 H, 6.27; S, 8.03; $COCH_3$ (Kunz[16] method), 43.66; Fehling test (−).

Ethyl 1-thio-α-D-galactofuranoside (II). An amount of 0.4 g. of IV was dissolved in 30 ml. of methanol nearly saturated with anhydrous ammonia at 0°. The solution was maintained at room temperature for 2 hr., filtered and concentrated under reduced pressure below 35° to a thick sirup. This was connected overnight to a vacuum system to sublime traces of acetamide. The sirupy residue was further dried by repeated evaporation of its methanol solution and by storing over phosphorus pentoxide under reduced pressure. It was characterized as ethyl 1-thio-α-D-galactofuranoside (II), $[\alpha]_D^{25}$ +124° (*c* 1.36, water). Attempts to crystallize II failed.

Anal. Calcd. for $C_8H_{16}O_5S$: C, 42.84; H, 7.19; S, 14.30. Found: C, 42.82; H, 7.16; S, 14.02; Fehling test (−).

Periodate oxidation (Table I) together with the above data indicate that II is ethyl 1-thio-α-D-galactofuranoside, and that IV is its tetra-*O*-acetyl derivative. Paper chromatography, using Whatman No. 1 filter paper, with 1-butanol, pyridine, and water (3:2:1.5 by vol.) as developer and periodate permanganate–benzidine indicator[12] showed that II was chromatographically pure, and had a $R_{Galactose}$ value of 3.0 (the R_F values of II and III were 0.67 and 0.22, respectively).

COLUMBUS 10, OHIO

(10) E. Fischer, *Ber.*, **27**, 673 (1894); M. L. Wolfrom, *J. Am. Chem. Soc.*, **52**, 2464 (1930).

(11) E. Pacsu and E. J. Wilson, Jr., *J. Am. Chem. Soc.*, **61**, 1450 (1939).

(12) M. L. Wolfrom and J. B. Miller, *Anal. Chem.*, **28**, 1037 (1956).

(13) A synthetic magnesium silicate produced by the Westvaco Chemical Division of the Food Machinery and Chemical Corp., South Charleston, W. Va.

(14) No. 535, a siliceous filter-aid produced by the Johns-Manville Co., New York, N. Y.

(15) Interplanar spacing, Å, CuK_α radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest); duplicate numbers indicate approximately equal intensities.

(16) A. Kunz and C. S. Hudson, *J. Am. Chem. Soc.*, **48**, 1982 (1926).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

Nitroolefins. I. 2-Nitro-3-hydroxyindene[1]

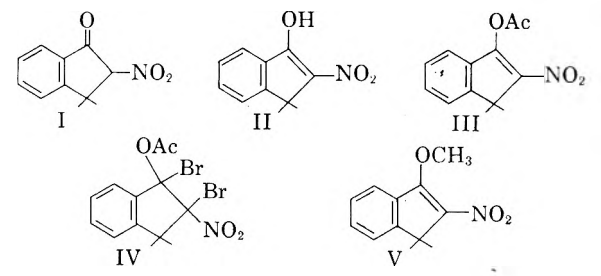
RICHARD D. CAMPBELL AND CHARLES L. PITZER

Received May 4, 1959

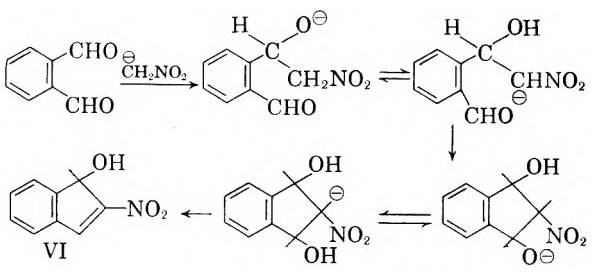
The condensation of nitromethane with *o*-phthalaldehyde has been studied. The product is shown to be a mixture of tautomers of 2-nitro-1-indanone. The tautomeric shift is not rapid. The enol form has been isolated in essentially pure form. The infrared and ultraviolet absorption spectra of this compound, its derivatives, and related compounds are reported and discussed.

In a study of condensation reactions of *o*-phthalaldehyde, Thiele and Weitz[2] reported that the condensation product with nitromethane was 2-nitro-1-indanone (I).

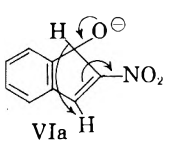
Derivatives of the enol form II were prepared, *viz.*: the acetyl derivatives III, its dibromide IV, and a methoxy compound V.



That I is actually an anomalous product was not discussed or explained. One might expect rather that 1-hydroxy-2-nitroindene (VI) would be formed, as shown.



The formation of II (or I) involves a hydranion migration in structure VI A with an accompanying electron pair shift. Hydranion migration giving rise to a double bond shift in basic conditions is not unusual.[3]



Derivatives that Thiele prepared[2] could as well have been formed from compound VI. Theile reported that the condensation product had a m.p. 117°d. Subsequently the condensation was reported[4] to give a product with m.p. 148° and the correct percentage composition. No comment was made on the structure or the melting point discrepancy.

The possible tautomerism, spectral properties, and chemistry of 2-nitro-1-indanone (I) were of primary interest in this study. Essential to the study was either the establishment of the structures of the two condensation products and their derivatives or the development of an alternative synthesis of I.

Two alternate syntheses of I were attempted without success. The action of alkyl nitrates on indanone was studied, using acidic and basic conditions. Ethyl nitrate with sodium ethoxide in ethanol and with potassium *t*-butoxide in ether, and *iso*-amyl nitrate with potassium *t*-butoxide in ether, and *iso*-amyl nitrate or methyl nitrate in anhydrous ether with dry hydrogen chloride all failed to give the expected product, giving instead intractable tars or recovery of 40–85% of the indanone.

In the second method tried 2-isonitroso-1-indanone was treated with peroxytrifluoroacetic acid by the method of Emmons and Pagano,[5] with the recovery of 60% of the starting material.

The condensation of *o*-phthalaldehyde with nitromethane by the method of Thiele and Weitz was repeated. The product, melting from 117°, actually gave a melting range of 10–20°. Several recrystallizations from various solvents either did not change the melting behavior or raised the melting range without substantially narrowing it (e.g., m.p. 120–135°). Sublimation gave a product with a higher and sharper melting point reported by Schales and Graefe,[4] *viz.* 148°. Thus the former substance must be regarded as a mixture, and the latter, pure.

Derivatives corresponding to those reported by Thiele and Weitz were prepared from the 148°

(1) Taken in part from the M.Sc. Thesis of C. L. Pitzer (1958). Presented before the Division of Organic Chemistry, A. C. S., 135th National Meeting, Boston, April, 1959.

(2) J. Thiele and E. Weitz, *Ann.*, **377**, 1 (1910).

(3) R. C. Fuson, *Advanced Organic Reactions*, John Wiley and Sons, New York, N. Y., 1950, pp. 231–232.

(4) O. Schales and H. A. Graefe, *J. Am. Chem. Soc.*, **74**, 4486 (1952).

(5) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).

TABLE I

INFRARED ABSORPTION BANDS[a]

Substance	OH	C=O	C=C	NO_2[c]	NO_2[d]
II (m. 148°)	3584	—	1611	1577	1357, 1326
I + II (m. 120–134°)	3584	1712	1612	1577	1359, 1326
III	—	1742	1613	1582	1364, 1342, 1321
III[b]	—	1754	1618	1582	1372, 1348, 1323
IV[b]	—	1773	—	1575	1372
α-Nitroacetophenone	—[f]	1709	1605[g]	1565	1379, 1328
1-Indanone[h]	—	1705	1618[g]	—	—
β-Nitrostyrene[b]	—	—	1642	1530	1345
o-Nitrophenol[e]	3270	—	—	1540	1360
2-Nitroindene (VII)	—	—	1600	1570	1379, (1370), 1338

[a] Solvent was chloroform unless specified. Data in cm.$^{-1}$ [b] Solvent was carbon tetrachloride. [c] A symmetrical stretching mode. [d] Symmetrical stretching mode. [e] From R. J. Francel, *J. Am. Chem. Soc.*, **74**, 1265 (1952). [f] A band at 2940 cm.$^{-1}$ was observed using pure crystals. [g] Aromatic ring. [h] Band at 1466 (C—H), weak band at 1325.

melting substance. The acetyl derivative III gave m.p. 130–131°; its dibromide IV gave m.p. 93–94°. The derivatives prepared from the 117° melting substance gave melting points of 120 and 136° respectively.[1] It was supposed at first that the isomerism involved structures I and VI, but further examination, with spectral evidence discussed below, indicated that the isomerism involved structures I and II and that the acetyl derivatives were identical. On subsequent purification dibromide IV gave m.p. 136°, which agrees with Thiele.[1] His sample of the acetyl derivative III was apparently impure.

The substance, m.p. 148°, was found to be soluble in alkali, with decomposition. It gave no reaction with ferric chloride. The compound gave a correct value for percent nitro group. The 2,4-dinitrophenylhydrazine VII formed readily. The compound did not form a quinoxaline derivative with o-phenylene diamine.[6] Neither substance (m.p. 117°, 148°) decolorized bromine in chloroform or acetic acid except on long standing. Both decolorized potassium permanganate in acetone; the higher melting tautomer appeared to react more rapidly. No quantitative determination could be made and no oxidation products were isolated.

On standing for several weeks the pure enol, m.p. 148°, slowly reverted to a mixture of I and II, suggesting that the enol is somewhat less stable.

The infrared and ultraviolet spectra of the compounds studied are listed in Tables I and II respectively. The intense ultraviolet absorption at 3430 Å is expected for the enolic structure of II. The acetyl derivative III (3400 Å) and the unsubstituted nitroindene VIII (3370 Å) exhibit the typical β-nitrostyrene chromophore. The small shifts caused by substituents are in the expected order, if they are explained on the basis of resonance stabilization of the excited state. Such shifts have been[7] smaller in some cyclic systems than in the open chain analogs.

(6) A. Darnow and W. Sassenberg, *Ann.*, **594**, 185 (1955).

(7) R. D. Campbell and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 3456 (1957).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA

Compound	Absorption maxima[a]
3-Hydroxy-2-nitroindene (II)	2430 (7.1), 3430 (9.75)
3-Acetoxy-2-nitroindene (III)	2430 (7.1), 3400 (9.21)
2-Nitroindene (VIII)	2330, 2390 (6.3, 6.2), 3370 (11.0)
α-Nitroacetophenone	2460 (11.4), 3510 (9.3)
β-Nitrostyrene	2280 (7.8), 3110 (16.6)
1-Indanone	2450 (13.2), 2940 (2.8)
1-Acetoxy-1,2-dibromo-2-nitroindane (IV)	No max. ϵ = 3.5 to 2500 Å.

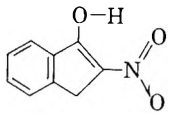
[a] Numbers are wave lengths in angstroms. Numbers in parentheses are $\epsilon = 10^{-3}$.

The analogous α-nitroacetophenone absorbs at 3510Å. Structure I contains the benzoyl chromophore which absorbs at 2450 Å, with a much less intense band at 2940 Å as shown in indanone. Small amounts of I in the presence of II would be difficult to detect by the ultraviolet absorption. Structure VI would absorb below 3400 Å, because the hydroxyl group is not in a position to affect the nitrostyrene chromophore. The acetyl derivative has essentially the same chromophore as II and shows nearly identical ultraviolet absorption. In the dibromide IV the conjugated system is broken and no absorption maximum is observed.

The infrared spectra of the two substances m.p. 117° and m.p. 148° offer the best evidence for their identification as a mixture of I and II, and pure II respectively. Pure enol II gave no carbonyl absorption and showed characteristic bands with assignments indicated in Table I. The enolic O—H stretching frequency at 3584 cm.$^{-1}$ is normal for the unassociated enol group, indicating a lack of hydrogen bonding. Where hydrogen bonding is possible, as in o-nitrophenol, the band is shifted to lower wave number (3270 cm.$^{-1}$). The geometry of the five membered ring in II holds the enol and nitro groups too far apart for effective hydrogen bonding.

The splitting of the symmetrical stretching

frequency of the nitro group has been observed[8] in nitroketones, dinitro compounds, and nitro



alcohols, and may well have been unobserved because of assignment difficulty and proximity of the weaker CH and CH_2 absorptions. We have tentatively assigned two intense bands in the 7.20–7.60 μ region to the symmetric nitro group stretching mode.

The mixture of I and II showed essentially the same bands, with the addition of a medium intensity band at 1710 cm.$^{-1}$. The inductive effect of the nitro group decreases the polar character of the carbonyl group relative to the carbonyl group (1705 cm.) in 1-indanone. The carbonyl adjacent to phenyl normally[9] absorbs at 1686 cm.$^{-1}$, but the effect of the phenyl conjugation is countered by the effect of the five membered ring (cyclopentanone: 1740 cm.$^{-1}$).

The acetyl derivative III has only the expected ester carbonyl band. Again the symmetric nitro band is split. The dibromide IV does not show the splitting seen in the other compounds.

The position of the nitro group bands has been[8] irregularly dependent on structural environment. The nitro group bands in this series do not afford a clear correlation, with the complication of splitting. More extensive studies of the effect of conjugation and of polar groups are planned. The β-nitrostyrene series is now being studied.

The chemistry and tautomerism of nitroketones also are being studied further.

EXPERIMENTAL[10]

2-Nitro-3-hydroxyindene (II). The condensation of *o*-phthalaldehyde with a large excess of nitromethane in methanolic potassium hydroxide was carried out as previously reported.[1] The powdery yellow product was obtained in 65–70% yield and was melted at 110–124°. Recrystallization from benzene several times gave m.p. 117–140°d. Several recrystallizations from isooctane-tetrahydrofuran gave yellow needles, m.p. 120–135°. This sample was identified by the infrared spectrum as a mixture of I and II.

The mixture (m.p. 120–134°) slowly decolorized potassium permanganate in anhydrous acetone. In a preparative run no oxidation product was isolated. The mixture also decolorized bromine in chloroform slowly. No crystalline bromination product was isolated.

The mixture of I and II was sublimed at 100°/3 mm. with a short path (1–1.5 cm.) between hot and cold surfaces. The sublimate, fine pale yellow needles, gave m.p. 148°, identified as II.

Anal. Calcd. for $C_9H_7NO_3$: C, 61.0; H, 3.95; N, 7.91; NO_2, 26.0. Found: C, 60.3; H, 3.91; N, 7.82; NO_2, 25.6.

This product (II) dissolved in 5% sodium hydroxide to give a yellow-orange solution. The ferric chloride test was negative. The pure enol, on standing for several weeks, gave m.p. 120–130°.

The pure enol II decolorized permanganate in acetone rapidly at first, then slowly continued to react. Several attempts were made to titrate II and the mixture with permanganate. The reaction proved to be too slow and ill-defined for titration. No oxidation products were isolated. Bromine in chloroform was decolorized slowly by II.

The reaction reported[6] between *o*-phenylene diamine and α-nitroacetophenone was successfully repeated. When attempted with II, the reaction failed to yield the desired product.

The 2,4-dinitrophenylhydrazone VII was prepared in the usual manner.[11] It formed as red-orange crystals, m.p. 204–205°.

Attempted syntheses of (I). 1-Indanone was treated in anhydrous ether with potassium *t*-butoxide and *iso*-amyl nitrate at −30°. Some tar formation occurred with 40% recovery of 1-indanone. Using the same catalyst, 1-indanone was treated with ethyl nitrate in tetrahydrofuran at −30°. Only a small amount of starting material was obtained by distillation. The same procedure was followed using ether as solvent. Only tars were formed. Treatment of 1-indanone with sodium ethoxide and ethyl nitrate in ethanol gave the same result. The use of methyl nitrate or *iso*-amyl nitrate in ether with dry hydrogen chloride resulted in 80–85% recovery of indanone.

2-Oximino-1-indanone[12] was treated with peroxytrifluoroacetic acid in acetonitrile by the method of Emmons and Pagano.[5] The starting material was recovered in 60% yield.

3-Acetoxy-2-nitroindene (III). The mixture of I and II (m.p. 120–134°) (1.00 gm.) was dissolved in 10 ml. of acetic anhydride. Introduction of a trace of conc. sulfuric acid gave an exothermic reaction. The solution was poured onto crushed ice and water. A yellow solid, m.p. 112–119°, was isolated in 1.2 gm. yield. Recrystallization from petroleum ether (b.p. 60–100°) and from isooctane-tetrahydrofuran (10:1) gave yellow rods, m.p. 133°. Sublimation failed to raise the melting point.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.3; H, 4.11; N, 6.39. Found: C, 60.1; H, 3.88; N, 6.58.

Bromination of III. A solution of 1.5 gm. of the acetate III in glacial acetic acid was treated with 2 gm. of bromine. The solution stood for two days exposed to sunlight. The yellow product isolated was recrystallized from petroleum ether to give a white solid, m.p. 93–94°. Several attempts to recrystallize the product gave oils. Recrystallization from *n*-pentane gave hard white crystals m.p. 136°.

Anal. Calcd. for $C_{11}H_9Br_2NO_4$: C, 34.85; H, 2.39. Found: C, 34.93; H, 2.49.

2-Nitroindene (VIII). The method of Wallach and Beschke[13] was used. The product of the steam distillation was recrystallized from ethyl acetate and petroleum ether. The fine yellow needles melted at 140–141°. (Reported[13] 141°.)

Infrared Spectra. The infrared spectra were determined using a Perkin-Elmer Model 21 double beam recording spectrophotometer over the range from 700 cm.$^{-1}$ to 4000 cm.$^{-1}$ The samples were studied in chloroform or carbon tetrachloride (Brothers Chemical Company) solution freshly prepared at a concentration of 6 mg. per ml., using

(8) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **77**, 6341 (1955).

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, N. Y., 1954, Chapters 9, 17.

(10) Melting points were determined on a Kofler hot stage equipped microscope, and are corrected.

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *Identification of Organic Compounds*, John Wiley and Sons, New York, N. Y., 4th Ed., 1956, p. 219.

(12) N. Levin, B. E. Graham, and H. G. Kolloff, *J. Org. Chem.*, **9**, 380 (1944).

(13) O. Wallach and E. Beschke, *Ann.*, **336**, 2 (1904).

double beam operation and matched cells. The instrument was operated according to the manufacturer's recommendations. The data obtained are listed in Table I.

Ultraviolet Spectra. The ultraviolet spectra were determined using a Cary Model 14 double-beam recording instrument. The solutions were freshly prepared in 95% ethanol and kept in the dark until used. Concentrations were 10^{-3} and 10^{-4} molar. Matched cells were used. The instrument was operated according to manufacturer's recommendations. Extinction coefficients were determined in the usual manner (ref. 11, p. 181). The data obtained are listed in Table II.

Fading absorbance was noted in alcohol solutions of II and III on standing. The 3430 Å band of II decreased to 20% of its initial intensity in 17 hr. on standing in the dark at room temperature. The 3400 Å band of III decreased to 76% of its initial intensity on standing 17 hr. in the dark at room temperature.

Acknowledgment. This work was supported in part by a Summer Faculty Research Grant from E. I. du Pont de Nemours and Company, which is gratefully acknowledged.

The purchase of the infrared spectrophotometer used in this study was made possible by a grant from the National Science Foundation.

IOWA CITY, IOWA

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

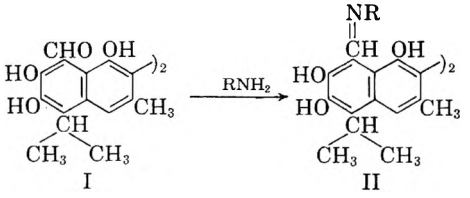
Some New Anil Derivatives of Gossypol[1]

PEGGY W. ALLEY AND DAVID A. SHIRLEY

Received May 25, 1959

The scope of the reaction of Schiff base (anil) formation between gossypol and primary amines has been investigated. Seventeen primary amines of widely varying types were reacted with gossypol and the anil derivates isolated.

It has recently been demonstrated[2] in this laboratory that aliphatic amines form stable derivatives (II) of gossypol (I) analogous to the long known[3] dianilinogossypol (II,R=phenyl) and related aromatic anil derivatives.[4]



I II

We have prepared a variety of new anil derivatives of gossypol in order to determine the scope of the reaction and to obtain potentially useful gossypol derivatives. The amines selected for anil formation with gossypol were in general of the following types: (1) amines containing other functional groups which should permit further reactions of the gossypol anils, (2) physiologically active amines which might impart biological activity to the anil formed, (3) azo dyes containing amino groups, and (4) amino acid and dipeptide esters.

Of particular interest were the anils with the methyl esters of lysine, glycine and the dipeptide glycylglycine. It has been proposed that gossypol becomes chemically bound with protein during the processing of cottonseed meal.[5] The site of the binding is the free amino groups present in the cottonseed protein and the terminal amino groups of lysine has seemed to be a likely spot. While the preparation of these amino acid ester anils does not offer any direct evidence for the site of binding, it demonstates that moderately stable anils of this type may be formed. The reaction product of lysine methyl ester and gossypol contained a 1:1 ratio of the two reactants indicating either anil formation at both amino groups in the lysine molecule (resulting in a polymeric type material) or reaction at only one carbonyl site in the gossypol molecule with one amine function (probably the terminal amino group[6]) in the lysine methyl ester molecule. The analytical data on the product agree more closely with the latter possibility.

The normal product (II,R=CH_2COOCH_3) was obtained from the reaction of gossypol and glycine methyl ester. The product from the reaction of glycylglycine methyl ester and gossypol was identical (analytical data and infrared spectra comparison) with that from glycine methyl ester and gossypol. Hydrolysis of the dipeptide apparently occurred during its liberation from the hydrochloride or during the anil formation.

Gossypol acetic acid complex[7] was used for all reactions. The yields of anils were generally quite satisfactory as indicated in Table I.

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(1) A report of work conducted under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract is being supervised by the Southern Utilization Research and Development Division of the Agricultural Research Service.

(2) D. A. Shirley and W. C. Sheehan, *J. Org. Chem.*, **21**, 251 (1956).

(3) F. E. Carruth, *J. Am. Chem. Soc.*, **40**, 647 (1918).

(4) J. M. Dechary and L. E. Brown, *J. Am. Oil Chemists Soc.*, **33**, 76 (1956).

(5) E. P. Clark, *J. Biol. Chem.*, **76**, 229–235 (1928).

(6) B. Witkop and T. W. Beiler, *J. Am. Chem. Soc.*, **76**, 5589 (1954).

(7) Supplied by Southern Utilization Research and Development Division Laboratory, Agricultural Research Service.

TABLE I

NEW ANIL DERIVATIVES OF GOSSYPOL

Compound (R in II)	Molecular Formula	M.P., °C.	Yield, %	Recrystallization Solvent	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Ethylhexylamine	$C_{46}H_{68}N_2O_6$	200°–201°	78	ethanol-benzene	74.15	9.20	3.76	74.15 74.31	8.99 8.87	3.94 4.07
β-Phenylethylamine	$C_{46}H_{48}N_2O_6$	dec. >225°	91	isopropyl alcohol–benzene	76.22	6.67	3.87	76.37 76.07	6.51 6.71	3.74 3.62
Allylamine	$C_{36}H_{40}N_2O_6$	dec. >200°	97	benzene-ethanol	72.46	6.76	4.70	72.51 72.60	6.53 6.92	4.62 4.47
p-Aminoacetophenone	$C_{46}H_{44}N_2O_8$	dec. >200°	100	.....	73.38	5.89	3.72	73.16	6.08	3.99
N,N-Diethylethylenediamine	$C_{42}H_{58}N_4O$	dec. >200°	72	benzene–isopropyl alcohol	70.6	8.13	7.85	70.00	8.18	7.62
N,N-Dimethyl-1,3-propanediamine	$C_{40}H_{54}N_4O_6$	200° (dec.)	88	benzene-ethanol	69.94	7.92	8.16	69.53 69.32	7.90 7.68	8.29
p-Aminohippuric[a] acid	$C_{48}H_{46}N_4O_{12}$	dec. >200°	80	.....	66.19	5.34	6.43	64.36 64.10	5.84 5.78	5.72 5.92
p-Aminobenzene-[a] sulfonamide	$C_{42}H_{42}N_4O_{10}S_2$	dec. >200°	77	.....	61.26	5.13	6.78	59.63 59.43	5.41 5.53	7.05 6.92
p-Aminoazo-[b] benzene	$C_{54}H_{48}N_6O_6$	280° (dec.)	81	.....	73.95	5.51	9.58	72.93 72.90	5.62 5.54	9.15 9.22
4-*o*-Tolyazo-*o*-[b] toluidine	$C_{58}H_{56}N_6O_6$	270°–273° (dec.)	87	.....	74.68	6.05	9.00	73.10 73.10	5.75 5.86	7.35 7.54
p-Aminobenzoic[a] acid, *n*-butyl-ester	$C_{52}H_{56}N_2O_{10}$	200°–210°, resolidified 230° (dec.)	100	.....	71.86	6.50	3.22	71.15 71.49	6.52 6.52	3.20 3.02
Aminoacetal	$C_{42}H_{58}N_2O_{10}$	207° (dec.)	77	benzene–isopropyl alcohol	67.18	7.79	3.74	67.13 67.08	7.49 7.64	3.88 3.56
p-Bromobenzylamine	$C_{44}H_{42}Br_2N_2O_6$	251°–254° (dec.)	100	chloroform-methanol	61.83	4.96	3.28	62.34 62.43	4.81 5.00	3.08 3.24
p-Nitrobenzylamine	$C_{44}H_{42}N_4O_{10}$	234° (dec.)	97	chloroform-methanol	67.17	5.38	7.12	67.05 66.80	5.61 5.19	7.10 7.23
p-Chlorobenzylamine	$C_{44}H_{42}Cl_2N_2O_6$	236.5°–237.5° (dec.)	94	benzene–ethanol	69.00	5.53	3.66	69.31 68.93	5.67 5.50	3.55 3.53
Glycine methyl ester	$C_{36}H_{40}N_2O_{10}$	205°–210° (dec.)	9	isopropyl alcohol	65.44	6.10	4.24	64.50 64.65	6.23 6.31	3.94 3.95

[a] Insoluble in ordinary organic solvents. [b] Unstable in ordinary organic solvents.

EXPERIMENTAL[8]

Diallylaminogossypol A solution of 1.00 g. (0.00173 mole) of gossypol acetic acid complex[7] in 70 ml. of isopropyl alcohol was heated to boiling and a solution of 2 ml. (excess) of allylamine in 20 ml. of isopropyl alcohol was added. The solution was boiled for several minutes and allowed to stand overnight at 5°. The precipitated yellow crystalline solid was separated by filtration, washed with fresh isopropyl alcohol and dried. The yield was 1.00 g. or 97%. A sample for analysis was recrystallized from a benzene and ethanol mixture.

Anal. Calcd. for $C_{36}H_{40}N_2O_6$: C, 72.46; H, 6.76; N, 4.70. Found: C, 72.51, 72.60; H, 6.53, 6.92; N, 4.62, 4.47.

The compounds listed in Table I were prepared in general accordance with the above procedure except that recrystallization solvents varied as shown. Some of the anils could not be recrystallized because of either solubility difficulties or instability in solution. In cases where recrystallization was not possible, part of the analytical results usually differed somewhat from the calculated values.

(8) Microanalyses by Weiler and Strauss, Oxford, England, and Galbraith Microanalytical Laboratories, Knoxville, Tennessee. All melting points were taken on a Kofler Hot Stage Microscope.

Reaction of gossypol with L-lysine methyl ester. Two and one half grams of L-lysine methyl ester dihydrochloride was mixed with an equal weight of potassium carbonate and slurried in 25 ml. of isopropyl alcohol. Enough water was added to bring the solids into solution, and the resulting solution was extracted with equal volumes of ether. The combined ethereal extracts were added to a hot solution of 1.00 g (0.00173 mole) of gossypol acetic acid in 70 ml. of isopropyl alcohol, and the solution was heated on the steam bath until the ether had evaporated. The resulting solution was filtered and the filtrate placed overnight in the cold room. A bright yellow solid precipitated and was separated by filtration, washed with fresh isopropyl alcohol and dried. The crude product weighed 0.60 g. (43% of theory for 2:1 ratio; 53% for 1:1 ratio.) During an attempted recrystallization of the product from isopropyl alcohol, the material became gummy on contact with the hot solvent. The gum was partially brought into solution by the addition of benzene. The mixture was filtered from 300 mg. of insoluble material. On cooling the filtrate, there was precipitated 0.10 g. of yellow solid product.

Anal. Calcd. for $C_{44}H_{60}N_4O_{10}$ (2:1 ratio): C, 65.65; H, 7.51, N, 6.96. Calcd. for $C_{37}H_{44}N_2O_9$ (1:1 ratio): C, 67.25; H, 6.71; N, 4.24. Calcd. for $C_{37}H_{42}N_2O_8$ (1:1 ratio, repeating unit of polymer product): C, 69.14; H, 6.59; N, 4.36. Found:

C, 67.93, 67.80; H, 6.45, 6.66; N, 4.33, 4.55. The ratios in the parantheses represent the molar ratio of L-lysine methyl ester to gossypol in anil product molecule.

The infrared spectrum (KBr disc) of the product showed medium adsorption at 5.72 μ (ester carbonyl) and strong adsorption at 6.19 μ. The band at 6.19 μ is characteristic of the >CH=N linkage in gossypol anils. The anils from gossypol and the amines listed show adsorption in this region: aniline (6.20 μ), *p*-aminohippuric acid (6.17 μ), β-diethylaminoethylamine (6.20 μ), and glycine methyl ester (6.18 μ). Thus the data support strongly the formation of an anil linkage in the gossypol–lysine methyl ester reaction and the analytical data indicate a product containing one molecule of each.

KNOXVILLE, TENN.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Preparation of Substituted Cyclopropanes Containing Aldehyde and Ketone Groups

DONALD T. WARNER

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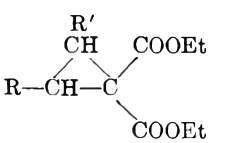
The reaction of acrolein with ethyl bromomalonate in the presence of a molar quantity of sodium ethoxide produces diethyl 2-formylcyclopropane-1,1-dicarboxylate as the main product. Similar reactions of ethyl bromomalonate with crotonaldehyde and methyl vinyl ketone also produce the corresponding substituted cyclopropane compounds. These compounds show the characteristic absorption bands for cyclopropanes in the infrared and near infrared regions of the spectrum.

In a previous publication,[1] the reaction of acrolein with ethyl bromomalonate was described briefly. In the presence of a molar quantity of sodium ethoxide, the reaction product was an aldehyde which contained no bromine. At that time, the reaction product was presumed to be 4,4-dicarbethoxy-3-butenal, resulting from the elimination of hydrogen bromide after the 1,4-addition of bromomalonate to acrolein. The facile hydrogenation of the product to γ,γ-dicarbethoxybutyraldehyde was presented as evidence for the proposed structure.

In a subsequent discussion of this reaction with Professor M. S. Newman, he suggested that the observed dehydrohalogenation might also lead to a cyclopropane structure. If this ring were formed in the acrolein-bromomalonate reaction, the resulting product would be diethyl 2-formylcyclopropane-1,1-dicarboxylate (I) instead of the previously proposed 4,4-dicarbethoxy-3-butenal. The recent disclosure of a cyclopropane ring in the amino acid, hypoglycin,[2a-f] and other natural products has suggested the desirability of preparing certain cyclopropane compounds with aldehydo substituents as intermediates for the probable synthesis of such products. We have therefore prepared additional quantities of the acrolein-bromomalonate intermediate and examined it for the presence of a cyclopropane structure such as I by all of the available methods.



I. R = CHO, R′ = H
II. R = CH_3CO, R′ = H
III. R = CHO, R′ = CH_3

As an initial investigation of the compound, samples were submitted for spectral analysis. The infrared spectrum showed strong absorption maxima at 1002–1015 cm.$^{-1}$, 856 cm.$^{-1}$, and a very definite C—H stretching band at 3070 cm.$^{-1}$ All of these features have been assigned to the cyclopropane ring in the infrared region.[3a-d] The compound was also examined in the near infrared in accordance with the recent observations of Washburn and Mahoney,[3d] and it showed absorptions at about 1.65 μ (6061 cm.$^{-1}$) and 2.25 μ (4444 cm.$^{-1}$) characteristic of cyclopropanes. Although the recent study of Allen and his co-workers[4] would indicate that the assignment of structure for probable cyclopropane compounds on the sole basis of infrared spectral data can be hazardous, in this instance the ultraviolet spectrum also showed the absence of a conjugated carbon-carbon double bond which would be present in 4,4-dicarbethoxy-3-butenal. In view of the rather limited number of possibilities for the present compound, the spectral evidence strongly

(1) D. T. Warner and O. A. Moe, *J. Am. Chem. Soc.*, **70**, 3470 (1948). This reaction is also the subject matter of U. S. Patent 2,540,054, Jan. 30, 1951.

(2) (a) S. Wilkinson, *Chem. & Ind. (London)*, 7 (1958). (b) C. V. Holt and W. Leppla, *Angew. Chem.*, **70**, 25 (1958). (c) J. A. Carbon, W. B. Martin, and L. R. Swett, *J. Am. Chem. Soc.*, **80**, 1002, (1958). (d) R. S. DeRopp, J. C. Van Meter, E. C. DeRenzo, K. W. McKerns, C. Pidacks, P. H. Bell, E. F. Ullman, S. R. Safir, W. J. Fanshawe, and S. B. Davis, *J. Am. Chem. Soc.*, **80**, 1004 (1958). (e) E. V. Ellington, C. H. Hassell, and J. R. Plimmer, *Chem. & Ind. (London)*, 329 (1958). (f) H. V. Anderson, J. L. Johnson, J. W. Nelson, E. C. Olson, M. E. Speeter, and J. J. Vavra, *Chem. & Ind. (London)*, 330 (1958).

(3) (a) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, N. Y., 1954, pp. 27–8. (b) S. E. Wimberley and S. C. Bunce, *Anal. Chem.*, 24, 623 (1952). (c) G. W. King, R. T. Armstrong, and L. Harris, *J. Am. Chem. Soc.*, **58**, 1580 (1936). (d) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958).

(4) C. F. H. Allen, T. J. Davis, W. J. Humphlett, and D. W. Stewart, *J. Org. Chem.*, 22, 1291 (1957).

suggests that the product is I instead of the previously proposed butenal.

Additional chemical evidence for the structure I has now been obtained from hydrogenation experiments. The hydrogenation of the acrolein-bromomalonate product under mild conditions to produce γ,γ-dicarbethoxybutyraldehyde, which we previously reported in support of the alternate 4,4-dicarbethoxy-3-butenal structure,[1] is also consistent with a product containing a cyclopropane ring on the basis of recent observations with such rings having certain activating substituents. Burroughs[5] has shown that 1-amino-1-carboxy-cyclopropane is readily hydrogenated to a mixture of α-amino-*n*-butyric acid and α-aminoisobutyric acid. Similarly Kierstad and his co-workers[6] have reduced diethyl 2-vinylcyclopropane-1,1-dicarboxylate and obtained a 70% yield of *n*-butylmalonate together with a second product which was not positively identified. The early work of Kohler and Conant[7] also indicated that the cyclopropane ring in certain compounds can be readily opened with nascent hydrogen. These results are in marked contrast with the relative stability to hydrogenation of the cyclopropane ring in vinylcyclopropane[8] and 2-ethylcyclopropane-1,1-dicarboxylic acid.[6] In the present investigation, the catalytic hydrogenation of the acrolein-bromomalonate product has been repeated; and at least two products have been identified in the reduction mixture. These two components were separated as their 2,4-dinitrophenylhydrazones, which melted at 75–76° and 122–123° respectively. The product melting at 75–76° was the derivative of γ,γ-dicarbethoxybutyraldehyde.[1] The derivative melting at 122–123° was identical with an authentic sample of the 2,4-dinitrophenylhydrazone of β,β-dicarbethoxybutyraldehyde by mixed melting point, analyses, and infrared spectrum. This aldehyde was synthesized by the ozonolysis of diethyl methylallylmalonate. The production of these two isomeric aldehydes by the catalytic reduction of the acrolein-bromomalonate product can be readily explained only on the basis of a cyclopropane ring. In consideration of this chemical evidence, together with the infrared and ultraviolet spectra interpretations, our previous formulation of this product as 4,4-dicarbethoxy-3-butenal was erroneous; and the alternate structure, diethyl 2-formylcyclopropane-1,1-dicarboxylate (I), is now preferred.

To obtain additional information on the probable preparation of substituted cyclopropanes from diethyl bromomalonate, the reaction with methyl vinyl ketone has been attempted. In this example, it will be apparent that if the 1,4-addition of methyl vinyl ketone to bromomalonate is a presumed reaction intermediate, the subsequent dehydrohalogenation could proceed in two ways to yield an acetyl cyclopropane structure or a cyclopentanone ring. However, the reaction product, obtained in 75–80% yield, shows only the previously observed cyclopropane bands.[3a-d] There was no evidence for the alternate cyclopentanone structure in the infrared spectra of the product or its derivative. This preferred formation of the cyclopropane compound, diethyl 2-acetylcyclopropane-1,1-dicarboxylate (II), in this instance is not without precedence, although the mild conditions of the ring formation are perhaps unusual. Wilzbach and his co-workers,[9] showed that 4,4-bis(chloromethyl)-2-pentanone was converted in 95% yield to 1-acetyl-2-methyl-2-chloromethylcyclopropane. More recently Hart and Curtis[10] have reported the preparation of dicyclopropyl ketone from the corresponding bis(γ-chloropropyl) ketone and of *n*-propyl cyclopropyl ketone from *n*-propyl-γ-chloropropyl ketone[11] by treatment with alkali. These workers also prepared 2-ethyl-cyclopentanone,[11] and showed that its infrared spectrum differed in many respects from the spectrum of *n*-propyl cyclopropyl ketone.

The reaction of crotonaldehyde with diethyl bromomalonate in the presence of a molar quantity of sodium ethoxide also proceeded with the formation of a substituted cyclopropane structure. In this instance, the C—H stretching absorption at about 3030–3100 cm.$^{-1}$ (3.23–3.32 μ) was not clearly distinguishable. On the basis of the conclusions of Allen and his co-workers[4] this would be anticipated for the proposed structure, diethyl 3-methyl-2-formylcyclopropane-1,1-dicarboxylate (III), since the C—H stretching band presumably is prominent only in cyclopropanes having at least one unsubstituted methylene group. A second higher boiling component was isolated from the crotonaldehyde-bromomalonate reaction mixture, and the infrared spectrum of this component also indicated the presence of a cyclopropane ring. Aldehyde carbonyl was absent, but small amounts of hydroxyl group (infrared) and bromine (elemental analysis) were present as impurities. In spite of several distillations and an additional treatment with sodium ethoxide (which did form a small amount of additional sodium bromide), the purest fraction still contained about 0.8% bromine. The analyses corresponded reasonably well with an empirical formula $C_{18}H_{26}O_9$, which could be ascribed to the formation of diethyl 3-methyl-2-(1,2-epoxy-2,2-dicarbethoxyethyl) cyclopropane-1,1-dicarboxylate (IV) from

(5) L. F. Burroughs, *Nature*, **179**, 360 (1957).
(6) R. W. Kierstad, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610 (1952).
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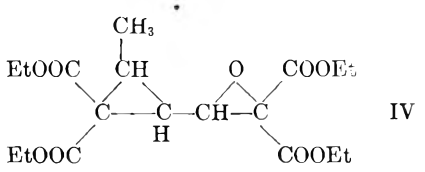
(8) R. Van Volkenburg, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **71**, 172 (1949).
(9) K. E. Wilzbach, F. R. Mayo, and R. Van Meter, *J. Am. Chem. Soc.*, **70**, 4069 (1948).
(10) H. Hart and O. E. Curtis, Jr., *J. Am. Chem. Soc.* **78**, 112 (1956).
(11) H. Hart and O. E. Curtis, Jr., *J. Am. Chem. Soc.* **79**, 931 (1957).



IV

III and diethyl bromomalonate by a Darzen's type condensation. Here the infrared data were of little utility in confirming the presence of an epoxide ring, since the C—H stretching absorption suggested by Henbest and his co-workers[12] to distinguish epoxides is understandably in the same region as the C—H stretching band due to cyclopropanes. The nuclear magnetic resonance spectra of the compounds III and IV were also determined. The spectrum of III clearly showed the two hydrogens on the cyclopropane ring and the single hydrogen of the aldehyde group. The spectrum of IV also showed the two hydrogens of the cyclopropane ring, and a single hydrogen attached to an ether-linked carbon atom. By comparing areas, about 0.85 equivalent of this latter type of hydrogen was present for eight methylene hydrogens (contributed by the four ethyl ester groups). Although the hydroxyl hydrogen of the bromohydrin impurity could not be detected in the open regions of the N.M.R. spectra, the infrared spectra of IV had indicated a small quantity of hydroxyl, estimated at about 0.10 equivalent. This could account for the fact that the hydrogen on the ether-linked carbon atom was about 0.85 equivalent instead of the expected one equivalent for the pure compound. The N.M.R. spectra of III and IV are therefore in agreement with the proposed formulas. The structure IV would be difficult to resolve by chemical methods for the susceptibility to breakdown of either the epoxide or cyclopropane rings with acid or base is an uncertainty which would make chemical identification difficult.

EXPERIMENTAL

Diethyl 2-formylcyclopropane-1,1-dicarboxylate, (I). Ethyl bromomalonate (239 g., 1 mole) was dissolved in 200 ml. of absolute ethanol, and the solution was cooled to about 5° in an ice bath. Freshly distilled acrolein (58.15 g., 1.04 moles) and a solution of sodium ethoxide (from 23.0 g. of sodium and 500 ml. of absolute ethanol) were added simultaneously with stirring and cooling (5°) at such relative rates that the acrolein addition was complete in about 30 min. and the sodium ethoxide addition was complete in 4¾ hr. The reaction mixture was refrigerated overnight, acidified with about 1.8 ml. of glacial acetic acid, and then poured into 1.1 l. of benzene. The precipitated sodium bromide was removed by centrifugation and washed with benzene. The supernatant liquid and benzene washings were combined and concentrated *in vacuo* to an oily liquid. This liquid was dissolved in 550 ml. of benzene, and some additional sodium bromide was removed by filtration. The filtrate was washed with three 100-ml. portions of 10% sodium sulfate solution and then with 100 ml. of water. The combined aqueous layers were extracted with 100 ml. of benzene, and this extract and the main benzene solution were combined and dried with 150 g. of anhydrous sodium sulfate. The benzene was removed *in vacuo*, and the resulting light yellow sirup was distilled through a Claisen distilling head. Approximately 150 g. (70%) of distillate was collected at 80–110°/0.13–0.26 mm. Redistillation using a small Vigreux column yielded 105 g. (49%) of purified I boiling at 84–90°/0.01–0.03 mm. A center cut (88–90°/0.01 mm.) was taken for analyses; $n_D^{25°}$, 1.4509.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.06; H, 6.59. Found: C, 56.25; H, 6.70. Ultraviolet: No maxima at 210 mμ. Infrared: 3070 cm.$^{-1}$ (3.25 μ), 1015–1002 cm.$^{-1}$, 856 cm.$^{-1}$, cyclopropane bands. Near infrared: 6061 cm.$^{-1}$ (1.67 μ) and 4444 cm.$^{-1}$ (2.25 μ), cyclopropane, Ref. (3d).

The 2,4-dinitrophenylhydrazone of the aldehyde was prepared, and melted at 141.7–142.7°. (Given for acroleinbromomalonate reaction product,[1] m.p. 141.5–142.5°). This derivative showed an infrared absorption band at 1023 cm.$^{-1}$ assignable to cyclopropane. Ultraviolet: max. 359 mμ (a_M 23,600), for nonconjugated 2,4-dinitrophenylhydrazones.

Diethyl 2-acetylcyclopropane-1,1-dicarboxylate, (II). This compound was prepared by essentially the same procedure described for Compound I. From 239 g. (1 mole) of ethyl bromomalonate, 72 g. (1.03 moles) of freshly distilled methyl vinyl ketone and 23.2 g. of sodium, there was obtained 177 g. (77%) of crude II, b.p. 70–83°/0.1–0.08 mm. The product was redistilled through a short Vigreux column to yield 127.3 g. of II at 90.5–92.5°/0.08–0.05 mm. A center fraction, $n_D^{25°}$ 1.4486, was analyzed.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.9; H, 7.70. Found: C, 58.17; H, 7.20. Infrared[13]: cyclopropane; 3075 cm.$^{-1}$ (3.23 μ), 1023 cm.$^{-1}$, and 855 cm.$^{-1}$. Near Infrared: 6061 cm.$^{-1}$ (1.65 μ) and 4444 cm.$^{-1}$ (2.25 μ), see Ref. (3d).

The 2,4-dinitrophenylhydrazone was prepared from 1.98 g. (0.01 mole) of 2,4-dinitrophenylhydrazine and 2.5 g. (0.011 mole) of II. The product weighed 3.64 g. (89%, based on 0.01 mole) and melted at 139.5–141.5°. An analytical sample was prepared by two recrystallizations from ethanol, m.p. 142–142.8°.

Anal. Calcd. for $C_{17}H_{20}O_8N_4$: C, 50.0; H, 4.94; N, 13.72. Found: C, 50.08; H, 4.68; N, 13.59. Infrared spectra: cyclopropane; 1020 cm.$^{-1}$

Diethyl 3-methyl-2-formylcyclopropane-1,1-dicarboxylate, (III). The reaction of 239 g. (1.0 mole) of ethyl bromomalonate and 72 g. (1.03 moles) of freshly distilled crotonaldehyde was carried out essentially as described for Compound I. Crude III (136 g., 57%) was collected at 79–111°/0.12–0.3 mm. Upon redistillation through a short Vigreux column, 101 g. (44%) of III was collected at 83–93°/0.02–0.03 mm. A center fraction (90–92°/0.024 mm., $n_D^{25°}$ 1.4500) was analyzed.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.9; H, 7.07. Found: C, 57.15; H, 6.85. Infrared spectra: cyclopropane, 1015 cm.$^{-1}$ 856 cm.$^{-1}$. N.M.R. spectra[14]: ring methyl, doublet centered at 162 c.p.s.; ester methyls, triplets centered at 155 and 157 c.p.s.; ester methylenes, quartets centered at 38 and 41 c.p.s.; cyclopropane hydrogens, many lines lying between

(12) H. B. Henbest, G. D. Meakins, B. Nicholls, and K. J. Taylor, *J. Chem. Soc.*, 1459 (1957).

(13) The recent work of E. R. Nelson, M. Maienthal, L. A. Lane, and A. A. Benderley, *J. Am. Chem. Soc.*, **79**, 3467 (1957) suggests that the characteristic region for cyclopropane absorption should be broadened to 1000–1040 cm.$^{-1}$ from the previous limits of 1000–1020 cm.$^{-1}$ indicated in Ref. (2a). It is interesting to note that Allen[5] concluded acetyl cyclopropane itself shows no characteristic absorption in the 1000–1020 cm.$^{-1}$ region whereas II shows a strong band.

(14) The N.M.R. spectra were measured with a Varian 4300–2 spectrometer at 40 mc. The spectra were calibrated against water in a precision external annular cell (Wilmad Glass Co., Landisville, N. J.) using the audio frequency side-band technique of J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

96 and 128 c.p.s.; aldehyde hydrogen, doublet centered at −161 c.p.s.

Compound III was converted to the 2,4-dinitrophenylhydrazone in 86% yield, m.p. 143.3–145°. An analytical sample, prepared by two recrystallizations from ethanol, melted at 147–147.5°.

Anal. Calcd. for $C_{17}H_{20}O_8N_4$: C, 50.0; H, 4.94; N, 13.72. Found: C, 50.25; H, 5.17; N, 13.48. Infrared spectra: cyclopropane, 1020 cm.$^{-1}$

After the distillation of crude III, the residue in the distilling flask was subjected to further distillation. Although there was some decomposition in the early stages of the fractionation, 40.8 g. of product was collected at about 154–172°/0.4 mm. Upon redistillation through a small heated Vigreux column, 17.3 g. of product was collected at 153–162°/0.1 mm. A center fraction was analyzed, but the analyses indicated small quantities of bromine in the product. Consequently, the fraction was dissolved in 50 ml. of alcohol and treated with sufficient sodium ethoxide to make the solution alkaline to wet litmus. After refrigerating the reaction mixture overnight, the excess sodium ethoxide was neutralized with glacial acetic acid and the alcohol was removed *in vacuo*. The residual oil was dissolved in 100 ml. of benzene, washed with water, and then the benzene was removed *in vacuo*. The residue was distilled through a short Vigreux column and about 13 g. of distillate was collected at 153–165°/0.1 mm. This material was again distilled using a semimicro Vigreux column. The two fractions collected at 156–157°/0.08 mm. (2.89 g., n_D^{25} 1.4574) and 157°/0.08 mm. (2.37 g., n_D^{25} 1.4576) were probably impure diethyl 3-methyl-2-(1,2-epoxy-2,2-dicarbethoxyethyl) cyclopropane-1,1-dicarboxylate (IV).

Anal. Calcd. for $C_{18}H_{26}O_9$: C, 55.95; H, 6.78; O, 37.27. Found: C, 55.07, 55.02; H, 6.48, 6.63; O, 35.42. (Br, 0.81). Infrared: 1020, 855 cm.$^{-1}$ (cyclopropane), aldehyde carbonyl absent. N.M.R. spectra: ring methyl, doublet centered at 161 c.p.s.; ester methyls, triplets centered at 151 and 153 c.p.s.; cyclopropane hydrogens, many lines lying between 105 and 136 c.p.s.; hydrogen on epoxide ring carbon, doublet centered at 75 c.p.s.; ester methylene, many quartets centered at about 37 c.p.s.

Catalytic reduction of I. (*A*) *Identification of γ,γ-dicarbethoxybutyraldehyde*, V. This reduction was carried out essentially by the procedure described previously[1] employing 6.2 g. of I and 0.6 g. of 5% palladium-on-charcoal. The 2,4-dinitrophenylhydrazone of V was obtained directly from the reduction medium as orange crystals melting at 64–67°. Two recrystallizations from absolute ethanol yielded the purified product melting at 75–76°. (Given[1] for derivative of γ,γ-dicarbethoxybutyraldehyde, m.p. 75–76°.)

(*B*) *Identification of β,β-dicarbethoxybutyraldehyde*, VI. A solution of 21.4 g. (0.1 mole) of I in 100 ml. of absolute ethanol was mixed with 0.4 g. of 5% palladium-on-charcoal, and the reduction was carried out at room temperature with an initial pressure of about 30 p.s.i. of hydrogen. Using the lower catalyst ratio (compared with Procedure *A*, above) the reduction was initially quite rapid, then continued at a slow rate so that the hydrogen uptake was about 75% complete in 27 hr. The catalyst was removed by filtration, and a sample of the filtrate was converted to the 2,4-dinitrophenylhydrazone. The derivative was a mixture of orange rod-like crystals and yellow fluffy needles, melting over a range between 80–102°. The remaining filtrate was further hydrogenated with an additional 0.8 g. of 5% palladium-on-charcoal at about 35 p.s.i. initial hydrogen pressure until the hydrogen uptake was nearly theoretical. The catalyst was filtered, the solvent was removed *in vacuo*, and the yellow oil was distilled. About 11.1 g. (55%) of distillate was collected at 87–95°/0.15 mm. Fractional distillation yielded two center fractions boiling at 84–86°/0.08 mm. (1.57 g., n_D^{25} 1.4328) and 86–88°/0.08 mm. (2.85 g., n_D^{25} 1.4336). Analyses of these fractions corresponded fairly well with a structure containing the aldehyde group as the diethyl acetal. The product is probably a mixture of at least two isomeric aldehyde acetals which would result from the hydrogenation of the cyclopropane ring.

Anal. Calcd. for $C_{14}H_{26}O_6$ (—CHO present as diethyl acetal): C, 57.92; H, 9.03. Found: C, 58.24, 58.62; H, 8.34, 8.74.

The fraction boiling at 86–88°/0.08 mm. (2.03 g.) was reacted with 1.5 g. of 2,4-dinitrophenylhydrazine to form about 1.3 g. of derivative melting at 107–117°. Upon recrystallization from ethanol and cooling slowly to room temperature, a first crop of crystals was obtained which melted at about 140° with shrinking at about 120° (mixed m.p. showed this was probably an impure derivative of I). The filtrate was warmed on the steam bath and then diluted with water to incipient turbidity. Upon cooling, the remaining product separated as stout needle clusters, m.p. 115.7–118.5°. Three recrystallizations raised the melting point to 122–123°.

Anal. Calcd. for $C_{16}H_{20}O_8N_4$: C, 48.46; H, 5.06; N, 14.14. Found: C, 48.55; H, 4.95; N, 14.15.

Synthesis of VI *from diethyl methylallylmalonate.* A solution of sodium ethoxide in absolute ethanol (100 ml.) was prepared from 2.3 g. (0.1 mole) of sodium, and 17.4 g. (0.1 mole) of diethyl methylmalonate was added. The light yellow solution was heated to reflux with stirring and 13 g. (0.108 mole) of allyl bromide was added in 15 min. The reaction mixture was refluxed for 17 hr. After cooling, the sodium bromide was filtered, and the filtrate was concentrated to remove ethanol. The crude product was dissolved in benzene (130 ml.), washed with three 30-ml. portions of water, and the benzene was removed *in vacuo*. Distillation of the crude product through a small Vigreux column gave 11.6 g. of diethyl methylallylmalonate, b.p. 84–90°/2.5 mm. n_D^{25} 1.4290.

An ethanol solution (70 ml.) of 10.7 g. of diethyl methylallylmalonate was cooled to 0° and ozone (0.38 millimoles/minute) was passed through the solution until the required quantity of ozone had reacted. The reaction mixture was diluted to 200 ml. with ethanol, cooled to 0°, and hydrogenated (initial pressure, 43 p.s.i.) in the presence of 1 g. of 5% palladium-on-charcoal. The catalytic decomposition of the ozonide was complete in about 10 min., and no further hydrogen uptake was observed during an additional 20 min. The catalyst was filtered, and the colorless filtrate was concentrated *in vacuo* to a sirupy liquid. The liquid was distilled, and about 7.7 g. (70%) of β,β-dicarbethoxybutyraldehyde was collected at 74–82°/0.10–0.17 mm. A center fraction (3.06 g., b.p. 75–77°/0.13 mm.) was used for derivative formation.

The 2,4-dinitrophenylhydrazone of V was prepared from the distilled aldehyde, and melted at 118.5–120°. An analytical sample prepared by 3 recrystallizations from ethanol melted at 124–124.5°. A mixed melting point with the derivative obtained from the catalytic reduction of I (m.p. 122–123°) was 123–124°.

Anal. Calcd. for $C_{16}H_{20}O_8N_4$: C, 48.46; H, 5.06; N, 14.14. Found: C, 48.79; H, 5.26; N, 14.17.

Acknowledgment. We wish to thank Mr. W. A. Struck and the members of his staff for the microanalyses, Dr. J. L. Johnson and his staff and Mr. M. Grostic for the determination and interpretation of the infrared and ultraviolet spectra, and Dr. G. Slomp for the N.M.R. analyses and interpretations.

KALAMAZOO, MICH.

[Contribution from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare]

The Three-Dimensional Structures of the Cocaines. II. Racemic Allococaine and Racemic Allopseudococaine

STEPHEN P. FINDLAY

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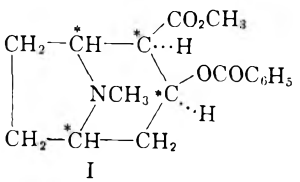
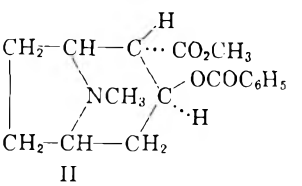
Catalytic hydrogenation of racemic 2-carbomethoxy-tropinone in acetic acid yields racemic alloecgonine methyl ester, which can be transformed to the racemates of alloecgonine, allococaine, allopseudoecgonine, allopseudoecgonine methyl ester, and allopseudococaine. Some limitations of a generalization concerning the course of the catalytic hydrogenation of cyclic ketones as it applies to certain keto derivatives of the tropane and morphine alkaloids are noted. The three-dimensional structures of the new cocaines are tentatively assigned. The possible utility of molecular rotation data in ascertaining the absolute configuration of transformation products of the 2-carbomethoxy derivatives of both tropinone and *N*-methylgranatonine is indicated. Some other possible methods of synthesizing the new cocaine isomers and the drawbacks thereof are mentioned.

Having established the molecular structure of the naturally occurring and medicinally important alkaloid, *l*-cocaine (I)[1] Willstätter and his collaborators remarked that three other stereoisomers having the same sequence of atomic linkages should exist.[1,2,3] Of these he and his associates obtained, both by the transformation of *l*-cocaine and also by total synthesis, one other stereoisomer, pseudococaine (II).[4,5] Although they recorded



I

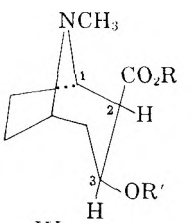


II

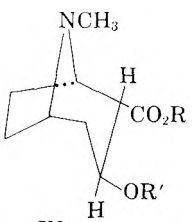
the availability of a third,[4] neither of the two remaining cocaine stereoisomers had been isolated when the problem was abandoned some thirty-five years ago.

The isolation of the four possible modifications at that time, while it would have substantiated their predictions based on the fundamental structural theory of organic chemistry, would have left unanswered the related and equally important question as to the steric or three-dimensional relationship of the functional groups in each of them. Although Willstätter had, to be sure, not overlooked this problem, stereochemistry was at that time in too rudimentary a state to permit a certain conclusion; and his opinion concerning the relation of cocaine to pseudococaine[2] has indeed recently been disproved.[6]

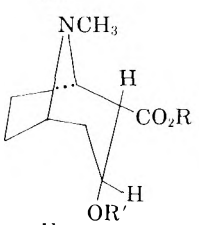
The maturation of stereochemistry which has occurred meanwhile makes possible now the determination of such questions in natural products generally, and, relative to the cocaine problem, has allowed the unequivocal assignment of three-dimensional structures to the known isomers, cocaine and pseudococaine (III and IV, respectively, $R=CH_3$, $R'=COC_6H_5$).[6-9] By the process of elimination the two unknown isomers must be represented by the structures, V and VI ($R=CH_3$, $R'=COC_6H_5$ in both); and this information permits a more rational approach to their selective synthesis.



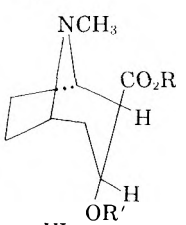
III



IV



V



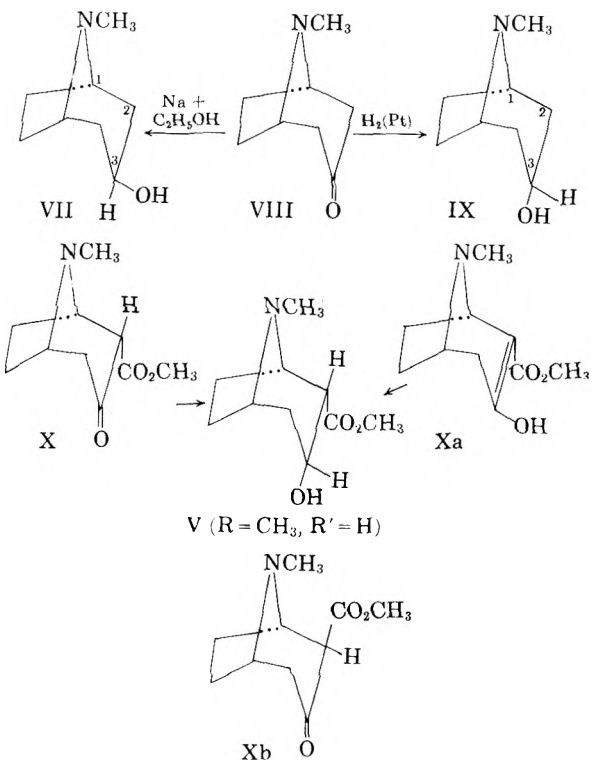
VI

The isolation of these two unknown cocaines would be noteworthy as completing one of the classical topics of alkaloid chemistry. It would also afford ready access to potentially valuable derivatives of the medicinal, atropine; and indeed

(1) R. Willstätter and W. Müller, *Ber.*, **31**, 2655 (1898).
(2) R. Willstätter and M. Bommer, *Ann.*, **422**, 15 (1921).
(3) R. Willstätter and A. Bode, *Ann.*, **326**, 42 (1903).
(4) R. Willstätter, O. Wolfes, and R. Mäder, *Ann.*, **434**, 111 (1923); *Cf.*, E. Merck, German Patent 389,359.
(5) *Cf.*, (a) A. Einhorn and A. Marquardt, *Ber.*, **23**, 468 (1890); (b) C. Liebermann and F. Giesel, *Ber.*, **23**, 508 (1890).
(6) S. P. Findlay, *J. Am. Chem. Soc.*, **75**, 4624 (1953); **76**, 2855 (1954).
(7) S. P. Findlay, *J. Am. Chem. Soc.*, **75**, 1033 (1953).
(8) G. Fodor, *Nature*, **170**, 278 (1952); G. Fodor and Ö. Kovács, *J. Chem. Soc.*, 724 (1953).
(9) According to E. Hardegger and H. Ott these structural formulae rather than their mirror images represent the absolute three-dimensional likeness of the naturally occurring alkaloid and its derivatives [*Helv. Chim. Acta*, **38**, 312 (1955)].

there are recorded few, if any, examples of tropines bearing substituents at the C_2-position.

The three-dimensional structures of the related substances, pseudotropine (VII) and tropine (IX), have also been established.[10] Reduced with sodium and alcohol, sodium amalgam, or sodium and moist ether, the ketone, tropinone (VIII), affords pseudotropine (VII)[11]; and on catalytic reduction this ketone yields the isomeric amino alcohol, tropine (IX).[12,13] These transformations are, among the tropane alkaloids, remarkably stereospecific, no evidence of the formation of more than one isomer having been found in either the sodium and alcohol[11] or the catalytic reduction of tropinone[12,13] (see experimental section). By the action of sodium amalgam on the 2-carbomethoxy derivative of this ketone, both ecgonine and pseudoecgonine (III and IV, respectively, R = R′ = H)[2-4] result in which compounds the C_3-hydroxyl group thus created has the same steric relation to the nitrogen bridge[6-8] as the similarly produced C_3-hydroxyl group of pseudotropine.[11] Hence, the catalytic hydrogenation of the keto tautomer (X) of this substance would be an obvious way of attempting the synthesis of the unknown isomers (V and VI); and indeed, as described in more detail hereinafter, this process, applied to the keto ester, converts it in excellent yield to alloecgonine methyl ester (V, R=CH_3, R′=H).[9]



Since, unlike tropinone, 2-carbomethoxytropinone exists largely as the enol (Xa)[14] in solutions most favorable to its catalytic hydrogenation, an adequate explanation of the steric outcome of this process must take cognizance of the possibility that an enolic rather than a carbon-oxygen double bond is reduced. The results of the reduction of some basic ketones carried out in connection with this investigation together with information of a similar kind drawn from the chemistry of the morphine alkaloids permits one to account satisfactorily for the product obtained, regardless of the tautomeric form actually reduced.

According to the nomenclature now customary for specifying the location of ring substituents,[15] the C_3-oxygen is *equatorial* in molecules having the structures, III, IV, and VII, and *axial* in the structures, V, VI, and IX. As a rule, the reduction of ketones by means of such reagents as sodium and alcohol affords predominantly the *equatorial* configuration of the hydroxyl group,[15] and the well nigh exclusive formation of pseudotropine (VII) (see experimental section) and the equally one-sided production of ecgonine and pseudoecgonine[4] by similar methods apparently provides additional corroboration of this generalization.

In general the catalytic hydrogenation of both hindered and unhindered cyclic ketones in strongly acidic media is rapid and affords the *axial* configuration of the hydroxyl group formed, while in basic and in neutral media this process is slow and leads to the *axial* configuration only when the ketone is strongly hindered.[15] In this investigation the platinum-catalyzed hydrogenation of tropinone which is not notably hindered was observed to occur at the same rate in alcohol as in aqueous acetic acid, and in both instances the product appeared to consist entirely of tropine (IX) (which has the *axial* configuration of the C_3-hydroxyl group). It was observed also that in aqueous hydrochloric acid the platinum-catalyzed hydrogenation of dihydrocodeinone (XI) proceeds quite slowly and gives only a mixture of products from which no pure component could be isolated, while in the relatively weakly acidic medium, aqueous acetic acid, this process took place about ten times more rapidly and yields largely dihydrocodeine (XII).[16] Finally, it has been reported that 8-hydroxydihydrocodeinone (XIV) is reduced much more rapidly in alcohol than in aqueous hydrochloric acid and to the same alcohol, presumably

(10) (a) G. Fodor and K. Nádor, *Nature*, 169, 462 (1952); (b) *J. Chem. Soc.*, 721 (1953); (c) L. F. Fieser and A. Nickon, *J. Am. Chem. Soc.*, 74, 5566 (1952).

(11) R. Willstätter, *Ber.*, 29, 936 (1896).

(12) J. van de Kamp and M. Sletzinger, *Chem. Abstr.*, 39, 2080 (1945).

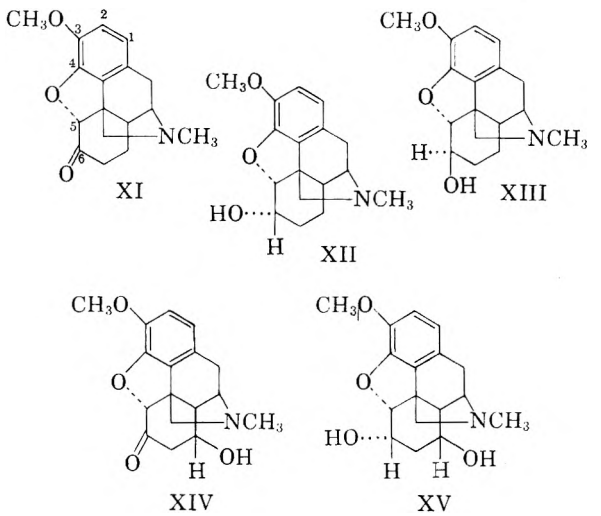
(13) L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, 68, 1608 (1946).

(14) S. P. Findlay, *J. Org. Chem.*, 22, 1385 (1957).

(15) For an informative discussion of ring conformations and the appertaining nomenclature, consult D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(16) In basic media (pyridine) dihydrocodeinone is also readily hydrogenated to dihydrocodeine. K. Goto and T. Arai, *Ann.*, 547, 194 (1941).

8-hydroxydihydrocodeine (XV).[17] Quite evidently the foregoing generalization, of undeniable usefulness among most alicyclic compounds, fails in its application to such complex basic ketones as tropinone and dihydrocodeinone; the cause of this failure suggested below has the double advantage of accounting satisfactorily for the catalytic hydrogenation of 2-carbomethoxytropinone, whatever the tautomeric form in which it is reduced, and of indicating the nature of the exceptions to this rule which may be anticipated.[18]



Possibly what may be referred to as *steric accommodation* between the catalyst and the molecule to be reduced (particularly those molecules containing two or more basic atoms), in conjunction with a coordinating power of metallic catalysts for basic atoms like nitrogen and oxygen, outweighs in importance the tendency of a ring to assume a particular conformation and hence to yield a particular configuration of an attached substituent. Many organic compounds, such as certain of the terpenes and sterols, have molecular structures that are essentially flat and, furthermore, contain no nitrogen which is accessible from only one side of the molecule. In such instances, interaction between either side of the molecule and the catalyst is relatively probable; therefore, ring conformation may be decisive in determining the configuration of the substituent produced by the catalytic hydrogenation. On the other hand, among bridged ring compounds such as the complex morphine alkaloids and the bicyclic terpenes of the camphor type, one side of the molecule is much more convenient to the catalyst than any other—*i.e.*, steric accommodation and/or coordinating power become factors to be considered in the steric course of the hydrogenation of ketones. If these two factors exceed the conformational one in importance, any adherence of such bridged ring compounds to the foregoing generalization arises from the fortuitous circumstance that in the examples so far studied these three influences have usually acted in concert. Only by an examination of instances in which these influences operate in opposing directions can one form some estimate of their relative importance and thus predict intelligently the probable steric course of such hydrogenations generally.

The catalytic hydrogenation of camphor (XVI) and of dihydrocodeinone indicate the possible results of such an examination. In acetic acid the platinum-catalyzed hydrogenation of camphor results in isoborneol (XVII)[19,20] in which the hydroxyl group is equatorial.[15] From X-ray crystallographic studies it appears that Ring C of morphine and many of its derivatives may have the boat or semi-boat conformation.[21,22] Hence, the platinum-catalyzed hydrogenation in acidic media of dihydrocodeinone (XI) should, according to the foregoing generalization, convert this ketone largely to dihydroisocodeine (XIII) in which the C_6-hydroxyl would have the axial configuration for the boat conformation.[22] Such an outcome is, however, contrary to that expected from considerations of coordinating tendencies and of steric accommodation, which generally produce among the morphine alkaloids a C_6-hydroxyl group *trans* to the nitrogen bridge;[23] as noted above, dihydrocodeine (XII) having presumably an equatorial C_6-hydroxyl

(17) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **73**, 4001 (1951).

(18) The supposition that catalytic hydrogenation of unsymmetrical cyclic ketones in acidic media (which leads to the alcoholic groups with the *axial* configuration) is rapid[15] appears to be based on the usually lesser thermodynamic stability of an alcohol with an *axial* hydroxyl group relative to the epimeric alcohol in which this group is *equatorial*. Hence, assuming the rate of formation of the latter to be the same in acidic as in basic and in neutral media, the predominant production of the former in acidic media must be due to a marked favouring by acid of the hydrogenation mechanism whereby the former is produced. It is nevertheless conceivable that the *axial* configuration might predominate under such conditions by the reverse process—namely, the inhibition by strong acid of the hydrogenation mechanism whereby the *equatorial* configuration is formed; it has been pointed out that, in at least one or two instances (coprostanone and possibly 2-methylcyclohexanone), the rate of platinum-catalyzed formation of the alcohol having the *axial* configuration of the hydroxyl group in strongly acid media is slower than the rate of formation of the *equatorial* epimer in neutral media (S. P. Findlay, Archives of The Chemical Society, Paper 8/1044).

(19) G. Vavon and P. Peignier, *Compt. rend.*, **181**, 183 (1925).

(20) M. Lipp, E. Oeckinghaus, and C. L. Conze, *Ber.*, **74**, 6 (1941).

(21) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955).

(22) K. W. Bentley and H. M. E. Cardwell, *J. Chem. Soc.*, 3252 (1955).

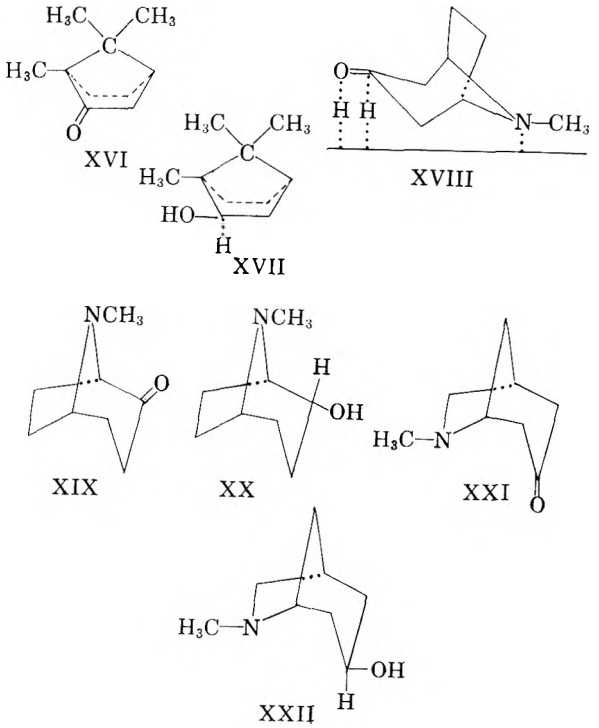
(23) A consideration of the steric factor in the catalytic hydrogenation of morphine C_6-ketones enabled Fieser to predict correctly the configuration of the C_6-hydroxyl so produced in this class of compounds. L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Third Ed., Reinhold Publishing Corporation, New York, 1949, pp. 24–25 [Cf., H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1951); *J. Am. Chem. Soc.*, **74**, 2630 (1952)].

group (*trans*, however, to the nitrogen bridge) is in fact produced.[24]

That coordinating power and steric accommodation are highly significant in other, similar types of catalytic hydrogenation makes itself evident from the reduction of the ethylenic and enolic double bonds of the complex alkaloid, thebaine. The numerous products thus obtained[25-27] result from the addition of one, two, or three molecules of hydrogen to the side of the molecule bearing the nitrogen bridge;[28,29] no such products arising from addition to the other side appear ever to have been found.[25]

Among the tropane alkaloids, tropinone constitutes another example wherein these factors may either coöperate or conflict. Because in this instance an acidic medium (which favors the formation of the *axial* configuration) obviously reinforces the effects of coordination and of steric fit, the conversion of tropinone (VIII) in acetic acid to tropine (IX) by catalytic hydrogen is not surprising. That the substitution of alcohol as solvent—which puts the conformational factor in opposition—has no appreciable influence either on the rate of reduction or on the configurational outcome indicates that for this molecule, as for dihydrocodeinone, the steric and coordination factors predominate and hence bring about the addition of hydrogen somewhat as illustrated by the structure, XVIII, regardless of the relative acidity of the solvent. If so, this process applied to the isomeric and isosteric substances, tropanone-2 (XIX and its mirror image) and isotropinone (XXI and its mirror image), may afford substantial quantities of tropanol-2 (XX and its mirror image) and isopseudotropine (XXII and its mirror image), respectively, wherein the newly created hydroxyl groups are equatorial, the relative acidity of the solvent notwithstanding.

Hydrogenated in the keto form, 2-carbomethoxytropinone should, as already noted, resemble tropinone in yielding the tropine configuration of the C_3-hydroxyl group. If it is hydrogenated in the enol form, the conformational factor is eliminated; steric accommodation and coordination power, operating by analogy with the catalytic reduction of the enolic double bond of thebaine to neopine methyl ether[27] and to tetrahydrothebaine[25,26]



should produce the tropine configuration also. Hence, the conversion of this β-keto ester to alloecgonine methyl ester (V, R=CH_3, R=H) appears to harmonize very well with pertinent available information concerning such processes.

The platinum-catalyzed hydrogenation of racemic 2-carbomethoxytropinone (X or Xa and its antipode) in aqueous acetic acid gives the β-hydroxy amino ester, racemic alloecgonine methyl ester (V and its antipode, R=CH_3, R′=H) in high yield (*ca.* 80%). As described in the experimental section this process was attempted under a variety of conditions. Of particular note are the observations that methanol and benzene are poor or unsatisfactory solvents for the hydrogenation and that hydrogen chloride markedly retards the reduction.[30]

Racemic alloecgonine methyl ester, the only reduction product found, can be readily isolated and purified as its acetate. The free ester, $C_{10}H_{17}NO_3$, which melts at 81.5–83.5°, resembles the long known methyl esters of ecgonine and pseudoecgonine in physical and chemical properties. Sublimation or distillation *in vacuo* except at low temperatures causes a pronounced decrease in its melting point; and, when hydrolyzed, it affords racemic allopseudoecgonine (VI and its antipode, R=R′=H), $C_9H_{15}NO_3$, melting at 243°, in about the same quantity as racemic alloecgonine (V and its antipode, R=R′=H), $C_9H_{15}NO_3$, melting at 241°. The former amino acid gives upon Fischer esterification the expected C_2-epimer, racemic

(24) If, as suggested,[21] the C_6-hydroxyl group of dihydrocodeine and its near relatives is equatorial, the retarding influence of hydrochloric acid on the catalytic process leading to these substances is explicable.[18]

(25) C. Schöpf and L. Winterhalder, *Ann.*, **452**, 232 (1927).

(26) L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).

(27) L. F. Small, *J. Org. Chem.*, **20**, 953 (1955).

(28) G. Stork, *The Alkaloids*, R. H. F. Manske and H. L. Holmes, Eds., Vol. II, Academic Press, New York, 1952, pp. 175 and 199.

(29) *Cf.*, K. W. Bentley, *The Chemistry of the Morphine Alkaloids*, Oxford at the Clarendon Press, London, 1954, pp. 197–203.

(30) Aqueous hydrochloric acid appears to be quite satisfactory as a medium for hydrogenating 3-carbomethoxy-1,2,6-trimethylpiperidone-4. C. Mannich, *Arch. Pharm.*, **272**, 323 (1934).

allopseudoecgonine methyl ester (VI and its antipode, R=CH_3, R′=H), $C_{10}H_{17}NO_3$, which melts at 80°.

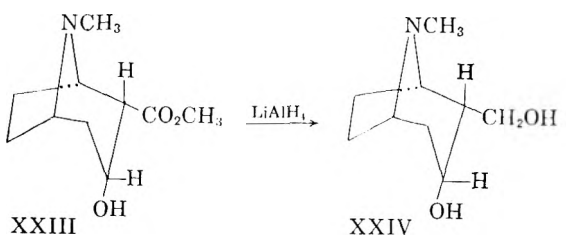
Although the melting points of the two new ecgonine methyl esters lie close together, mixtures of the two melt much lower; and their distinctive salts and infrared spectra leave no doubt concerning their non-identity. Likewise, a mixture of racemic alloecgonine and the allopseudo isomer melts much lower than either component, and their hydrochlorides (melting at 231–233° and at 213° respectively) and differing capacity for hydrate formation make their dissimilarity indubitable.

From the large-scale reduction of racemic 2-carbomethoxytropinone with sodium amalgam, Willstätter and his collaborators obtained, besides racemic ecgonine and racemic pseudoecgonine, a small quantity of a third substance, which he called the 'drittes racemisches Ekgonin'.[4] This melted at 229° (corr.) and afforded a hydrochloride melting at 231°. Assuming the reliability of the data noted above, one may reasonably infer that their hydrochloride was pure or nearly pure racemic alloecgonine hydrochloride and that their free 'drittes racemisches Ekgonin', because of the ready epimerization of alloecgonine methyl ester, contained both the allo and allopseudo ecgonines.

The three-dimensional structures assigned above to the allo and allopseudo series derive primarily from the reactivities of the methyl esters toward methyl iodide. The variety of products got from the reaction of ecgonine methyl ester and this alkiodide[4,6] arises from the *trans* relation of the C_2-hydrogen and the nitrogen atom, Hofmann Degradation being thus possible by the relatively facile *trans* elimination process and further promoted by the electrophilic C_2-carbomethoxy group.[6] Only the expected methiodide results from the combination of methyl iodide with pseudoecgonine methyl ester[4,6] in which the C_2-hydrogen is in the *cis*-position relative to the nitrogen atom. Racemic alloecgonine methyl ester yields readily a pure methiodide, $C_{11}H_{20}INO_3$, melting at 196–197°, both from methanol and from acetone, while the allopseudo isomer affords, under the same circumstances, a mixture of products from methanol from which no methiodide was obtained and only a poorly defined methiodide from acetone. One may conclude tentatively that allopseudoecgonine methyl ester and its derivatives have the ecgonine methyl ester configuration of C_2 in which the hydrogen and carbomethoxy groups are attached *trans* and *cis*, respectively, to the nitrogen atom, while the pseudo and the allo series are alike in having the C_2-hydrogen and -carbomethoxy groups attached *cis* and *trans*, respectively, to the nitrogen atom.[31] The spatial location of the C_3-hydroxyl having been ascertained above and the configurational relation of the optically active 2-carbomethoxytropinones to *l*-cocaine having been established,[14] the three-dimensional structures assigned throughout this discussion follow.

Since the C_3-hydroxyl groups of the two new ecgonine methyl esters have the *axial* configuration and are otherwise hindered, a greater resistance to benzoylation might be anticipated; benzoyl chloride in pyridine, which was the most effective technique employed, did give a low yield (*ca.* 40%) of racemic allococaine, $C_{17}H_{21}NO_4$ (m.p. 82–84°), and hardly more than a trace of racemic allopseudococaine, $C_{17}H_{21}NO_4$ (m.p. 93–95°). As methyl benzoate was liberated during the benzoylation of both esters in noticeable degree, the pyridine-catalyzed decomposition of the new cocaines contributes to the difficulty of realizing a satisfactory yield. This propensity to transesterification is such that the pure bases appear to autocatalyze their decomposition, the odorless crystals of each of the new racemic cocaines gradually changing to a brown oil and emitting the unmistakable aroma of methyl benzoate. The physical and chemical properties of the new racemic cocaines do not depart noticeably from those of the known isomers. Some impression of the similarities and differences between them may be obtained from Table I.

The extensibility of the foregoing procedures to the acquisition of the optically active antipodes of the allo and allopseudo series was established in the ready conversion of *d*- and *l*-(2-carbomethoxytropinone) to the corresponding optically active alloecgonine methyl esters. No evidence of racemization or other unexpected phenomena like that reported by Mannich[30] was noticed. In methanol *d*-alloecgonine methyl ester is weakly dextrorotatory (α_D^{20} +0.15 ±0.03) and affords a strongly laevorotatory ecgonine (α_D^{20}. *ca* −47° in water). Reduced with lithium aluminum hydride in tetrahydrofuran this ester (XXIII) was converted to a substance, presumably alloecgoninol (XXIV), C_9-



XXIII XXIV

(31) Evidence of an indirect character supports this conclusion. If 2-carbomethoxytropinone is hydrogenated in the enol form,[14] hydrogen should add, for reasons already given, in a *cis* manner from the side having the nitrogen bridge creating the structure, V (R=CH_3, R′=H); if in the keto form, of the two possible and interchangeable configurations at C_2 (X and Xb), that (X) in which the carbomethoxy group is *trans* to the nitrogen bridge and, presumably, *equatorial*, appears to be the stabler one, and this would be frozen by the reduction of the keto group.

Also, racemic allopseudoecgonine combines with methanolic methyl iodide, the corresponding methyl ester resulting [*Cf.*, ref. 6; also F. G. Novy, *Am. Chem. J.*, 10, 145 (1888)].

TABLE I

MELTING POINTS OF THE RACEMIC COCAINES AND SOME OF THEIR DERIVATIVES

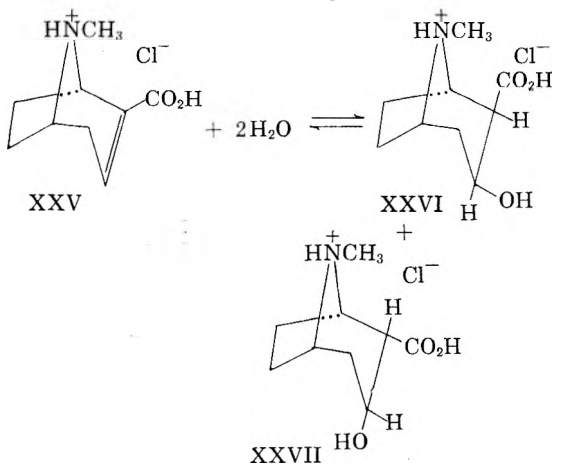
Cocaine Modifications	Racemic Cocaine		Derived Racemic Ecgonine Methyl Ester		Derived Racemic Ecgonine	
Naturally occurring	79–80°[4]		Liq.[4]		212°[4]	
hydrochloride		187°[4]		195°[4]		247°[4]
Pseudo	81.5°[3]		128°[3]		251°[3]	
hydrochloride		205.5°[3]		—		193–194°[3]
Allo	82–84°[32]		81.5–83.5°[32]		241°[32]	
hydrochloride		201.5°[32]		—		233°[32]
Allopseudo	93–95°[32]		80°[32]		243°[32]	
hydrochloride		—		192°[32]		213°[32]

$H_{17}NO_2$, melting at 201.5–202.8°, which was also optically active (α_D^{20} −6.3, in water).

The foregoing synthetic scheme is simple and unambiguous; and, were it not for the benzoylating reaction which can no doubt be improved, the overall yields would be high. Moreover, as it leads to both antipodes of each of the new cocaines, it constitutes a complete solution of the problem, while a scheme based on the transformation of *l*-cocaine can afford but one antipode of each. Several approaches to a limited solution of the latter kind were considered, but investigation showed them to be unpromising. For example, the oxidation of the methyl esters of ecgonine and pseudoecgonine to *d*-(2-carbomethyoxytropinone) in substantial quantity proved impracticable;[14] while an S_{N2} displacement reaction involving the tosyl derivatives of these esters might allow the desired inversion of the configuration at C_3, the preparation of the requisite tosylates is difficult.[33]

(32) See experimental section.

(33) The mutarotation of salts of anhydroecgonine (XXV) in aqueous solution (A. W. K. de Jong, *Rec. trav. chim.*, **42**, 996–7 (1923)), which is no doubt due to hydration of the α,β-ethylenic linkage, suggests another avenue of access. This phenomenon which, among simple aliphatic compounds, has been studied extensively by Lucas and his collaborators [see, *e.g.*, D. Pressman and H. J. Lucas, *J. Am. Chem. Soc.*, 64, 1953 (1942)] now finds exemplification among the α,β-unsaturated ketones derived from morphine[17] [U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957)]. An equilibrium involving ecgonine (XXVI) and alloecgonine (XXVII) in the salt form is thus quite conceivable:

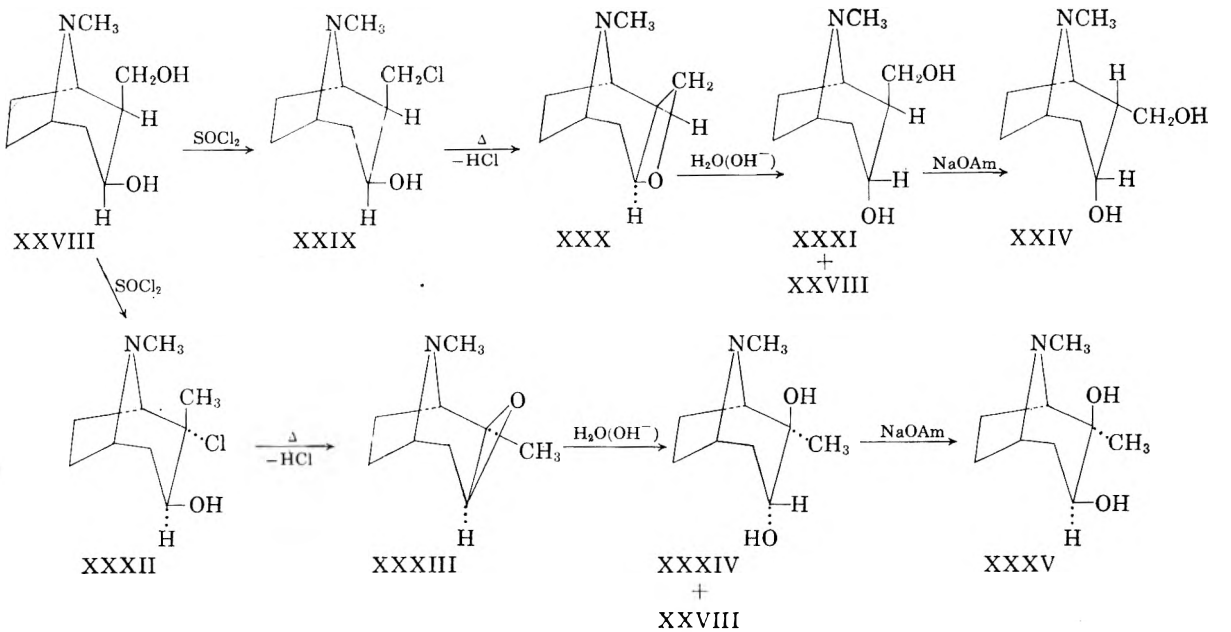


Still another variation of this kind of attack, which has been attempted elsewhere,[34] involves the use of ecgoninol (XXVIII), the lithium aluminum hydride reduction product of cocaine. Thionyl chloride is said to convert this diol to the chlorohydrin (XXIX) which heat transforms to an ether, possibly XXX.[34] By the action of hydroxide the ether reverts in part to ecgoninol (XXVIII) and gives in part a new isomeric diol to which the structure, XXXI, is assigned[34]; this is isomerized with sodium amylate to a product which, if the preceding part of the scheme is correctly represented, should be alloecgoninol (XXIV). However, the reported melting points of this substance and its hydrochloride differ appreciably from those of the alloecgoninol and its hydrochloride described above. In view of the reduction of cocaine to ecgoninol with lithium aluminum hydride in the expected manner,[8] the similar reduction of alloecgonine methyl ester permits no alternative to the structure, XXIV, for the product so obtained in this investigation. It is therefore reasonable to suppose that the foregoing chlorohydrin is a rearrangement product and that an alternative sequence, perhaps XXVIII→XXXII→XXXIII→XXXIV→XXXV, is the correct one. The selective oxidation of alloecgoninol and of allopseudoecgoninol would give optically active alloecgonine and allopseudoecgonine, respectively,[34] which could, of course, be transformed to the hitherto unknown cocaines in the manner indicated above. The successful oxidation in this manner of the two diols obtained by the foregoing reaction sequence has apparently not yet been realized.[35]

Although the rotatory powers of *l*-cocaine and its derivatives have not been measured in a uniform manner, the chemical literature contains enough usable data of this kind to warrant the conclusion,

(34) Ö. Kovács, I. Weisz, P. Zoller, and G. Fodor, *Helv. Chim. Acta*, **39**, 99 (1956).

(35) It has recently been reported also (K. Zeile and W. Schulz, *Chem. Ber.*, 89, 678 (1956)) that a third racemic cocaine, $C_{17}H_{21}NO_4 \cdot {}^1/_2H_2O$, m.p. 156–157°, is obtainable by converting Willstätter's 'drittes racemisches Ekgonin' to the corresponding methyl ester, $C_{10}H_{17}NO_3 \cdot {}^1/_2H_2O$, m.p. 203.5°, and benzoylating this. No information concerning the purity of the starting material, the removability of the hydrated water, the properties of appropriate derivatives, or the three-dimensional structure was furnished.



suggested earlier,[14] that the simpler derivatives of the naturally occurring base have a molar rotation more positive (or less negative) than that of the corresponding salts (Table II), and *vice versa* for the derivatives of the unnatural or antipodal base. Among the pseudo derivatives some exceptions to the rule occur, but for asymmetric derivatives of such compounds as 2-carbomethoxytropinone and 2-carbomethoxy-*N*-methylgranatonine the determination of the sign of this difference for several closely related base-salt pairs is sufficient to decide the absolute configuration or three-dimensional structure of the substance in question.

The synthesis of the racemic forms of allococaine and allopseudococaine together with the ready accessibility of *d*- and *l*-alloecgonine methyl ester reduce the preparation of the optically active isomers of the allo and allopseudo series as yet unknown to a routine laboratory assignment; together with confirmatory evidence for the three-dimensional structures tentatively proposed herein, this preparation will complete a chapter of classical alkaloid chemistry begun seventy-five years ago.

EXPERIMENTAL[37]

Materials. The racemic and optically active forms of 2-carbomethoxytropinone employed herein were obtained as described elsewhere.[14] The platinum oxide came from one batch and was a product of the American Platinum Works.

The catalytic hydrogenation of racemic 2-carbomethoxytropinone. In a typical experiment anhydrous racemic 2-carbomethoxy tropinone (9.00 g., 0.0456 mole), dissolved in glacial acetic acid (195 ml.) and water (30 ml.), and platinum oxide (0.75 g.) were shaken with hydrogen at 1.3 atmospheres for 48 hr., at the end of which period the consumption [1100 ml. (S.T.P.), 108%] of gas had nearly ceased. The catalyst-free solution was concentrated *in vacuo* on a warm water bath to a viscous, nearly colourless gum which was treated cautiously with water (15 ml.) and saturated aqueous potassium carbonate (50 ml.), the resulting white mixture then being extracted with ether (4 × 100 ml.). Unreduced keto ester was removed by washing with saturated aqueous potassium carbonate (20 ml.) mixed with 3*N* aqueous potassium hydroxide (4 ml.), the potassium salt separating in a yellow solution between the ethereal and the colourless aqueous phases (omission of this step did not noticeably interfere with the isolation of the pure reduction product). Concentration of the dried (sodium sulfate) extracts on a water bath (*ca.* 50°), first at atmospheric pressure and then *in vacuo*, afforded a nearly colourless viscous oil which crystallized when seeded with racemic alloecgonine methyl ester: 8.9 g. (98%). As the ester is always impure at this stage, the oil was as a rule taken up at once in acetone (25 ml.) and ether (50 ml.) and the solution treated with glacial acetic acid (2.55 ml.) in ether (20 ml.). Left for several hours, the yellowish solution deposited white crystalline warts of the *hydroacetate* which were collected: 7.5 g. (64%), m.p. 108–110°. By concentrating the mother liquors *in vacuo* and taking up the residue in a little acetone and ether, a second (*ca.* 1.5 g.) and a small third crop of the salt were also obtained, the total yield of acetate in several such experiments varying between 77 and 83%. Dissolved in water (50 ml.), treated with saturated aqueous potassium carbonate (50 ml.), and processed as above described for the crude ester, the acetate (9.15 g.) yielded colourless *racemic alloecgonine methyl ester* as a thick oil which crystallized spontaneously on keeping: 6.6 g. (94%), m.p. 81.5–83.5°.

Conducted in the foregoing manner, the rate of catalytic hydrogenation of racemic 2-carbomethoxytropinone was in three identical preparations remarkably constant, even at the beginning when it is most rapid. Furthermore, the scale of operations scarcely affects either the rate or the yield. Several variations of this method were also tried with the same hydrogenation apparatus and gas pressure. The use of glacial acetic acid as solvent did not appreciably alter the rate. As expected, the rate was approximately proportional to the relative quantity of catalyst employed. In methanol the rate was about half that in aqueous acetic acid and in benzene it was very low: in these experiments the reduction product was not isolated. In either methanol or glacial acetic acid the hydrogenation of 2-carbomethoxytropinone

(36) C. Lieberman, *Ber.*, 21, 2342 (1888).

(37) The melting points recorded herein are corrected and were observed in boro-silicate glass capillaries. Unless noted otherwise, rotations are for solutions in absolute methanol.

TABLE II

MOLECULAR ROTATION DIFFERENCES OF BASE-SALT PAIRS AMONG THE COCAINE ALKALOIDS

	Solvent	$[\alpha]_D^{20}$	$[M]_D^{20}$	$\Delta[M]_D^{20}$
l-Cocaine	Methanol	-29.9^{32}	− 9,060	+13,400
Hydrochloride	Methanol	-66.4^{32}	−22,500	
Ecgonine	Water	-45.5^{36}	− 8,420	+2,100
Hydrochloride	Water	-47.4^{36}	−10,500	
Pseudoecgonine	Water	$+22.7^{6}$	+ 4,200	−400
Hydrochloride	Water	$+21^{6}$	+ 4,600	
Ecgonine methyl ester	Methanol	-12.3^{6}	− 2,450	+9,350
Hydrochloride	Methanol	-50^{6}	−11,800	
Pseudoecgonine methyl ester	Water	$+22.8^{6}$	+ 4,540	−990
Hydrochloride	Water	$+23.4^{6}$	+ 5,530	
Anhydroecgonine	Water	-84.6^{33}	−14,100	+800
Hydrochloride	Water	-73.5^{33}	−14,900	
d-(2-Carbomethoxytropinone)	Water	$+36.7^{14}$	+ 7,230	+5,680
Ammonium ion	Water	$+7.83^{14}$	+ 1,550	
Pseudoecgoninol	Water	$+58.3^{8}$	+10,000	+400
Hydrochloride	Water	$+46.3^{8}$	+ 9,600	
Alloecgoninol	Water	-6.3^{32}	− 1,080	+550
Hydrochloride	Water	-5.9^{32}	− 1,230	
d-Alloecgonine methyl ester	Methanol	$+0.15^{32}$	+ 29	+524
Hydrochloride	Methanol	-2.1^{32}	− 495	

hydrochloride was extremely slow. The optically active forms of the keto ester as the bitartrate were readily reduced in aqueous solution, but the yield of alloecgonine methyl ester was much inferior to that obtained when aqueous acetic acid was used. Ruthenium on charcoal, which is advertised as a powerful catalyst for reducing keto groups, had little or no activity in this reaction either in benzene, in methanol or in aqueous acetic acid. Also, rhodium (5% on alumina) had no hydrogenating activity for solutions of the keto ester in methanol.

The catalytic hydrogenation of tropinone in alcohol and in aqueous acetic acid. Tropinone (1.40 g., 0.0100 mole), dissolved in 95% alcohol (37 ml.), was mixed with platinum oxide (0.12 g.) and shaken with hydrogen (at *ca.* 1.3 atm.). After 6 hr. the uptake of hydrogen had become negligible, the total consumption being then 233 ml. (S.T.P.) (104%). The catalyst-free, colourless solution, which had originally been brownish, was mixed with picric acid (2.30 g., 0.0100 mole) in hot alcohol (30 ml.). *Tropine picrate* separated at once and was filtered from the cold solution: 3.1 g., m.p. 295°.[11] An additional quantity (0.6 g., m.p. 293°) was isolated from the mother liquors, the total yield of tropine thus being quantitative.

Exact repetition of the foregoing experiment in aqueous acetic acid (32 ml. of glacial acetic acid and 5 ml. of water) gave similar results. The plot of gas consumption as a function of time was colinear with that of the previous preparation for the first 150 minutes, and after 5.5 hr. the total uptake amounted to 105% of the theoretical. Concentrated *in vacuo*, the catalyst-free solution yielded a nearly colourless oil which was mixed with water (10 ml.) and saturated aqueous potassium carbonate (20 ml.). Extraction of the liberated bases with ether (5 × 25 ml.) and removal of the solvent from the dried (Na_2SO_4) extracts furnished a colourless liquid which could not be induced to crystallize by seeding either with tropine or with pseudotropine.

The base was heated briefly at 100° with potassium hydroxide (1.0 g.) in water (11 ml.), which caused the formation of a black product also obtainable by similarly treating tropinone. After mixing with some potassium carbonate sesquihydrate, the base was recovered by ether extraction as before: 1.25 g., which crystallized when seeded with tropine. Recrystallized from ligroin it melted at 54–62°. The base was then converted entirely to the picrate as described above: 3.0 g. (81%), m.p. 293–295°.

Pseudotropine. Tropinone (10.0 g.) was reduced with sodium and alcohol according to the directions of Willstätter.[11] The reduction mixture was mixed with water (100 ml.), the liberated alcohol removed *in vacuo*, and the residue extracted with ether (6 × 100 ml.). The dried (K_2CO_3) extracts furnished a brown oil which readily crystallized with the evolution of considerable heat. This was freed of brown gummy by-products by sublimation *in vacuo:* 9.3 g. (93%). The product was further purified by dissolving the sublimate in benzene (12 ml.) and adding hot ligroin (60–71°) (16 ml.): white prisms, m.p. 106–108°. In three such experiments the yields of pure product were 78, 80, and 82%.

The brown residue from the sublimation which partially crystallizes on keeping gave, upon chromatographing on alumina, as the only crystalline component, a small additional quantity of pseudotropine, m.p. 108–109.5°; methiodide, m.p. 323° (dec.).

The catalytic hydrogenation of dihydrocodeinone. (a) *In hydrochloric acid.* Dihydrocodeinone (3.00 g., 0.0100 mole), m.p. 196–198.5°, dissolved in 3.1*N* hydrochloric acid (13.2 ml.) and water (16.8 ml.) was shaken with platinum oxide (0.10 g.) and hydrogen *ca.* at 1.3 atmospheres for 36 hr. (uptake: *ca.* 170 ml., S.T.P.). The old catalyst was then replaced with fresh and the shaking continued for a like interval. The total uptake of hydrogen by the base was about 350 ml. (S.T.P.) (78% of the theoretical quantity for the consumption of 2 equivalents). The catalyst-free solution contained much free phenolic material as indicated by a strongly positive diazosulfanilic acid reaction. Treated with some sodium hydrosulfite and made basic with potassium bicarbonate, the mixture liberated an oily mixture extractable with chloroform. The recovered oil (3.05 g.) did not crystallize on long keeping; and, when treated with picric acid, gave a liquid picrate which only partially crystallized and could not readily be resolved into its component salts.

(b) *In aqueous acetic acid.* Dihydrocodeinone (3.00 g., 0.0100 mole), m.p. 196–198.5°, dissolved in a mixture of glacial acetic acid (32 ml.) and water (7.0 ml.), was shaken with platinum oxide (0.12 g.) and hydrogen as before. At the beginning the uptake of gas was quite rapid, and after 3 hr. it had nearly ceased: 232 ml. (S.T.P.) (103% of the theory for 1 equivalent). The catalyst-free solution gave a negative diazosulfanilic acid response. Recovered as noted above for tropine in this solvent except that chloroform (3 × 25 ml.) was used, the amber gum did not crystallize on

keeping. Dissolved in ethyl acetate containing a little water, it gave no crystals on scratching, but largely crystallized when seeded with authentic dihydrocodeine hydrate: 2.3 g. (73%).

Racemic alloecgonine methyl ester hydroacetate. Prepared as described above, this salt was purified from acetone-ether from which it separated as aggregates of stout prisms, m.p. 110–110.5°. It is extremely soluble in most polar solvents, and even small quantities of acetic acid greatly retard both the inception and the rate of its crystallization.

Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16. Found: C, 55.66; H, 8.20.

Racemic alloecgonine methyl ester. Isolated from the hydroacetate as described above for the hydrogenation mixture, the oily pure ester crystallized spontaneously and slowly to a white cake. It was recrystallized both from acetone and from ligroin (60–71°) and separated from the former as irregular crystals and parallelopipeda and from the latter as striated square tablets, m.p. 81.5–83.5°. It is quite soluble even in the cold in most polar and non-polar solvents. When evaporatively distilled or sublimed *in vacuo* at higher temperatures, the ester appeared to be partially epimerized as indicated by a decline of the melting point to as low as 70–73°.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.44; H, 8.82.

The pure ester (0.060 g.) in methanol was mixed with picric acid (0.040 g.) in methanol and heated with enough more solvent to complete solution; shiny yellow flakes, m.p. *ca.* 185°, separated. Recrystallized from methanol, the *picrate* melted at 194–197°, then crystallized partially as the temperature was raised and remelted completely at 203.5°. Recrystallized again, this salt melted at 195–196° (softening at 193°). By lowering the bath temperature to 185° the salt solidified completely and then remelted only at 203–203.5°.

Anal. Calcd. for $C_{16}H_{20}N_4O_{10}$: N, 13.08; Found: N, 13.11.

The neutral oxalate was prepared in methanol-ether and purified from methanol. It dissolved rather slowly in methanol from which it separated readily only after seeding: warts of feathery, slender prisms, the melting point of which appeared to depend somewhat on the rate of heating but usually occurred about 200.5°.

Anal. Calcd. for $C_{22}H_{36}N_2O_{16}$: C, 54.08; H, 7.43. Found: C, 53.84, 53.77; H, 7.31, 7.46.

The *hydrochloride* was not obtained crystalline either from methanol or from methanol-ether.

Racemic alloecgonine. Hydrolyzed in the same manner as pseudoecgonine methyl ester,[6] racemic alloecgonine methyl ester afforded a white crystalline residue which was contaminated with a purplish impurity when the starting material had not been freed of small amounts of unhydrogenated 2-carbomethoxytropinone. Leaching the dried hydrolysis product with small amounts of absolute alcohol removed one of its two principal components. The remainder (m.p. *ca.* 235°) was then evaporated at room temperature with the stoichiometric amount of hydrochloric acid and the recovered salt recrystallized from absolute alcohol from which it is readily purified: colourless crystals of *alloecgonine hydrochloride*, m.p. 231.5–233.5°. The hydrochloride of Willstätter's 'drittes racemisches Ekgonin' is reported to melt at 231°.[4]

Anal. Calcd. for $C_9H_{16}ClNO_3$: C, 48.76; H, 7.28. Found: C, 49.02; H, 7.18.

The hydrochloride (0.27 g.) in water solution (10 ml.) was shaken with silver carbonate (0.4 g.), the mixture filtered, excess silver removed with hydrogen sulfide, and the Ag_2S-free solution evaporated to dryness *in vacuo*. The residue dissolved readily in hot absolute alcohol and the solution suddenly deposited a fine crystalline precipitate: m.p. 239°. This material, presumably the anhydrous modification, is much less soluble in hot absolute alcohol, requires about 300 times its own weight of this solvent for complete solution and, until dissolved, imparts a noticeable opalescence to the hot mixture. Concentration of such a solution to incipient turbidity and cooling afforded racemic alloecgonine as a finely divided precipitate melting at 237° (dec.). After recrystallization from 95% alcohol it melted at 241.5° (dec.); it separated from alcohol (*ca.* 90%) as lustrous, thin plates, melting at 240–241° (dec.).

Anal. Calcd. for $C_9H_{15}NO_3 \cdot 1H_2O$: C, 53.18; H, 8.43. Found: C, 52.90; H, 8.24.

Drying 5 hr. at 100° *in vacuo alto* removed about half the water of crystallization, and drying 9.5 hr. at 117° *in vacuo alto* removed all of it. Recovered from aqueous solution it did not melt below 125° and thus appeared to be different from Willstätter's 'drittes racemisches Ekgonin' which, as the hydrate, was reported to melt at 110°, and in the anhydrous condition at 229° (cor.).[4]

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.35; H, 7.75. Found: C, 58.17; H, 8.02.

Racemic Allopseudoecgonine. From the hot absolute alcoholic leaching of racemic alloecgonine (described above), needles melting at 241° separated as the solution cooled. These were recrystallized to constant melting point from absolute alcohol for analysis: feathery needles, m.p. 243° (dec.).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.35; H, 7.75. Found: C, 58.14; H, 7.95.

This isomer appeared not to crystallize with water. The hydrochloride, obtained by evaporating a solution of the amino acid in the equivalent amount of hydrochloric acid, was purified readily from absolute alcohol: m.p. 213°.

Anal. Calcd. for $C_9H_{16}ClNO_3$: C, 48.76; H, 7.28; Cl, 16.00. Found: C, 48.64; H, 7.33; Cl, 15.86.

Racemic allopseudoecgonine methyl ester. Allopseudoecgonine hydrochloride (1.45 g.) was dissolved in absolute methanol (75 ml.) containing dry hydrogen chloride (6.2 g.); the mixture, protected from moisture, refluxed 4 hr. The solvent was removed *in vacuo*, the residue treated with saturated aqueous potassium carbonate (20 ml.) and water (10 ml.), and the resulting mixture extracted with ether (3 × 100 ml.). Recovered from the dried (Na_2SO_4) extracts in the same manner as the epimeric ester, the colourless oil obtained crystallized almost at once: 0.9 g. After one recrystallization from ligroin (60–71°) these crystals (0.85 g.) melted at 79–80° and after a second at 80–80.5°. This material consisting of small, colourless, short prisms was sublimed about 60°/1 mm. for analysis. The melting point of its mixture with the racemic *allo* isomer was 60–70°.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.03; H, 8.61; N, 7.05.

The ester (0.100 g.) and oxalic acid dihydrate (0.0317 g.) were dissolved in methanol (≈0.2 ml.). No crystals were obtained either by keeping the solution or after mixing it with an equal additional quantity of oxalic acid.

The ester (0.10 g.) and picric acid (0.12 g.) were mixed in acetone. No crystals separated. Removal of the solvent left a gum which gradually solidified. Recrystallized from acetone to constant melting point (2×), the *picrate* was obtained as yellow, feathery tufts of minute, slender prisms melting at 135–136.3°.

Anal. Calcd. for $C_{16}H_{20}N_4O_{10}$: C, 44.86; H, 4.71; N, 13.08. Found: C, 44.80; H, 4.72; N, 12.57, 12.74.

As a by-product of the action of benzoyl chloride on the ester in pyridine, *allopseudoecgonine methyl ester hydrochloride* was obtained as a salt insoluble in pyridine. This was recrystallized to constant melting point (2×) by dissolving in methanol and adding ether: irregular, stout prisms m.p. 191.5–192°.

Anal. Calcd. for $C_{10}H_{18}ClNO_3$: C, 50.95; H, 7.70. Found: C, 50.60, 50.76; H, 7.57, 7.53.

Racemic allococaine. To a stirred mixture of racemic alloecgonine methyl ester (4.0 g., 0.0200 mole) in dry pyridine (10 ml.) at 0° was added benzoyl chloride (1.0 ml.). The mixture which reddened at once was kept 15 minutes at 0° and then mixed with more chloride (1.5 ml.). Originally transparent orange red, the benzoylation mixture gradually

acquired a brownish red opacity. After 12 hr. at room temperature, the mixture contained a few crystals and after two days had become semi-solid. The mixture, which smelled strongly of methyl benzoate, was rubbed with methanol-ether (10 ml. of each) and the solid material was collected at the pump and recrystallized from methanol to constant melting point: 1.2 g., m.p. 201.5° of *allococaine hydrochloride*, consisting of aggregates of minute prisms.

Anal. Calcd. for $C_{17}H_{21}NO_4 \cdot HCl$: C, 60.08; H, 6.53; Cl, 10.43. Found: C, 59.88; H, 6.57; Cl, 10.37.

The mother liquors from the purification of the hydrochloride furnished additional alkaloid through basification, extraction, and conversion to the neutral oxalate described below: 1.1 g.

The pyridine mother liquors were concentrated *in vacuo*, treated with water and potassium carbonate, and extracted with ether which removed both allococaine and unreacted alloecgonine methyl ester. These were separable by taking advantage of the much greater solubility of the latter in weakly alkaline aqueous solutions: *ca.* 0.6 g. of each ester. The total yield of the cocaine isolated as the hydrochloride and the binoxalate was about 40%.

The feasibility of benzoylation by the Schotten-Baumann method, by Willstätter's method utilizing benzoic anhydride in benzene[4], by the action of benzoyl chloride in inert neutral solvents, by benzoyl chloride alone, and by transesterification with methyl benzoate was examined. None of these methods appears to give results as satisfactory as benzoyl chloride in pyridine.

Recovered from the pure hydrochloride or the pure binoxalate by basification and ether extraction in the usual manner, *racemic allococaine* was obtained as an initially brownish oil which readily crystallized. It could conveniently be recrystallized from ligroin from which it separated as striated, square tablets melting at 82–84°. During several weeks this alkaloid gradually melts to a viscous brown oil with a liberation of methyl benzoate.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.30; H, 6.85.

Prepared in and purified from methanol, the *binoxalate* was obtained as long, slender prisms melting at 177.5–178.5°.

Anal. Calcd. for $C_{17}H_{21}NO_4 \cdot H_2C_2O_4$: C, 58.01; H, 5.89. Found: C, 57.88; H, 5.67.

Its *picrate* was prepared in and purified from methanol: stellate clusters of short, slender prisms, m.p. 178.5–180°.

Anal. Calcd. for $C_{23}H_{24}N_4O_{11}$: C, 51.88; H, 4.54. For $C_{23}H_{24}N_4O_{11} \cdot {}^1/_2CH_3OH$: C, 51.46; H, 4.78. Found: C, 51.42, 51.38; H, 4.41, 4.49.

Prepared in methanol (0.35 ml.) from the base (0.30 g.) and L-tartaric acid, the L-bitartrate separated as dense warts, m.p. 144–148°. Recrystallized from methanol, the crystals obtained melted at 145.5–148°. The degree of resolution was not investigated.

Anal. Calcd. for $C_{21}H_{27}NO_{10}$: C, 55.62; H, 6.00. Found: C, 55.16, 55.22; H, 6.09, 6.13.

The dibenzoyl-L-bitartrate was obtained by mixing the base (0.30 g.) with the acid monohydrate (0.37 g.) in methanol. The salt which precipitated was recrystallized three times from methanol, the melting point being raised successively: 161° to 166° to 168–168.5°. The degree of resolution thus effected was not determined.

Anal. Calcd. for $C_{35}H_{35}NO_{12}$: C, 63.53; H, 5.33. Found: C, 63.68; H, 5.34.

Racemic Allopseudococaine. Racemic allopseudoecgonine methyl ester (0.50 g.) was treated at 0° with a solution (1.4 ml.) made by diluting benzoyl chloride (2.0 ml.) to 10.0 ml. with pyridine. This mixture was stirred at 0° for 30 minutes and kept overnight at room temperature. Removal of the solvent *in vacuo* left a reddish semi-solid (having an odor reminiscent of methyl benzoate), which was mixed with methanol-ether and a crystalline precipitate, *allopseudoecgonine methyl ester hydrochloride* (see above), filtered off. The filtrate was concentrated *in vacuo*, the residue mixed with aqueous sodium bicarbonate, and the liberated oily bases extracted with ether. From the dried ether extracts was recovered a small quantity of greenish brown oil which was induced to crystallize by scratching at dry ice temperature. By several recrystallizations from ligroin (60–71°) and manual separation of the crystals from gummy impurities, pure racemic allopseudococaine was obtained: colorless, irregularly shaped crystals melting at 92.5–98.4° and, after grinding, at 93–95°. Like the allo isomer, these crystals liquefy slowly on standing and acquire the aroma of methyl benzoate.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.45; H, 6.70.

The *picrate* was prepared in and purified from methanol: m.p. 161–162°.

Anal. Calcd. for $C_{23}H_{24}N_4O_{11}$: C, 51.88; H, 4.54. Found: C, 51.61; H, 4.10.

A comparison of the reactivities of alloecgonine methyl ester and allopseudoecgonine methyl ester toward methyl iodide. Methyl iodide (15 ml.) was diluted to 100 ml. with absolute methanol and racemic alloecgonine methyl ester (0.20 g.), m.p. 81–83°, dissolved in some of this solution (0.50 ml.). Kept at 0° overnight the mixture deposited a compact mass of crystals, and an additional quantity was obtained by adding ether to the mother liquor: m.p. 198°. Recrystallized from methanol the first crop of *alloecgonine methyl ester methiodide* gave colorless crystals melting at 196–197°.

Anal. Calcd. for $C_{11}H_{20}INO_3$: C, 38.72; H, 5.91; I, 37.2. Found: C, 38.88; H, 5.69; I, 37.0.

Treated in exactly the same way allopseudoecgonine methyl ester, m.p. 80°, gave no crystalline precipitate even after 44 hr. By diluting with ether to near turbidity and scratching, crystals were obtained: m.p. 175–177°. After one recrystallization from methanol these melted at 208–209°; after two, at 212°. The analysis of this material indicated that it was still impure (*Anal.* Found: C, 40.36; H, 6.14; I, 41.7).

Dissolved in acetone (1.0 ml.) and treated with methyl iodide (0.20 ml.) at 0°, alloecgonine methyl ester (0.185 g.), m.p. 81–83°, gave almost immediately a crystalline precipitate melting at 198° and at 196–197° after mixing with the preparation obtained from methanol.

When allopseudoecgonine methyl ester (0.20 g.), m.p 80°, dissolved in acetone (1.0 ml.) was mixed at 0° with methyl iodide (0.20 ml.) and the solution allowed to warm, crystals soon precipitated. Two different samples from this preparation melted at 160–165° and 164–167°. After one recrystallization from methanol the product melted at 166–167°; after two, at 164–165°. Although apparently inhomogeneous, it has the composition of *allopseudoecgonine methyl ester methiodide.*

Anal. Calcd. for $C_{11}H_{20}INO_3$: C, 38.72; H, 5.91; I, 37.2 Found: C, 38.33; H, 5.77; I, 37.26.

The reaction of allopseudoecgonine with methyl iodide. Allopseudoecgonine (0.20 g.), m.p. 243°, was dissolved in hot methanol (10 ml.), the solution cooled somewhat, and methyl iodide (Mallinckrodt A.R., 2.5, ml.) added. The mixture was refluxed for 3 hr. and the volatile solvents removed *in vacuo*. The residual gum gradually crystallized 0.22 g., m.p. 165.5–170°. The crystals, which are extremely soluble in methanol, were recrystallized by dissolving them in a small amount of this solvent and keeping the solution at 0°: colourless crystals, m.p. 182.5–185 (*Anal.* Found C, 40.83; H, 5.83). This may largely be the methyl betaine hydriodide which like the pseudo isomer[6] seemingly loses hydrogen iodide readily.

The mother liquors from the crystallization were concentrated *in vacuo* to a gum which was taken up in aqueous potassium carbonate and the resulting solution extracted with ether. The oily base (0.030 g.), recovered in the usual manner from the extracts, did not crystallize when seeded with racemic alloecgonine methyl ester (m.p. 81–83°), but did so immediately when treated with a trace of racemic allopseudoecgonine methyl ester.

d-Alloecgonine methyl ester. Hydrogenated in a manner essentially the same as for the racemic modification, *d*-(2-carbomethoxytropinone) yielded the *d*-antipode of *alloecgonine methyl ester*.[14] Hydrogenated in aqueous acetic acid as the bitartrate salt,[14] the β-keto ester gave a yield (67%) of pure acetate lower than was obtained from the racemic β-keto ester, and this salt in water alone gave a lower yield still. The remainder of the hydrogenation product appeared to be non-crystalline. Recovered from the pure hydroacetate as indicated above for the racemic isomer, the *d*-ester was recrystallized from ligroin (60–71°): stout, colourless prisms, m.p 79–82.3°, $[\alpha]_D^{20}$ +0.15° ± 0.03 (C, 2).

Prepared from the stoichiometric amount of methanolic hydrogen chloride and recrystallized from methanol-ether the *hydrochloride* was isolated as colourless, hygroscopic, hexagonal, and irregularly formed stout prisms: α_D^{20} −2.1° (C, 2).[38]

Anal. Calcd. for $C_{10}H_{18}ClNO_3$: C, 50.95; H, 7.70. Found: C, 51.30; H, 7.80.

Prepared in methanol and purified from methanol-ether and from methanol acetone, the *binoxalate*, as small stout prisms, melted at 164–165°. It was dried *in vacuo* at room temperature for analysis.

Anal. Calcd. for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62. Found: C, 49.87; H, 6.63.

The picrate was prepared in and recrystallized from methanol: m.p. 199–201°.

Anal. Calcd. for $C_{16}H_{20}N_4O_{10}$: C, 44.86; H, 4.71. Found: C, 44.81; H, 4.58.

l-Alloecgonine methyl ester. Likewise prepared from *l*-(1-carbomethoxytropinone), the *l*-antipode crystallized from ligroin (60–71°) as stout rectangular prisms, m.p. 78–81°, which *in vacuo alto* at low temperature gave a sublimate of stout prisms melting at 79.5–81.8°, α_D^{20} −0.11° ± 0.03 (C, 2).

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.18; H, 8.67.

Hydrolysis of d-alloecgonine methyl ester. The ester (5.0 g.) dissolved in water (15 ml.) was heated at 70° until the *p*H of the solution had been reduced to 8. Evaporation of the solution at low temperature afforded a colourless syrup which when kept *in vacuo* over potassium hydroxide largely crystallized. Taken up in hot absolute alcohol (10 ml.) the syrup gave colourless stout prisms which separated during several hours: m.p. 214–216°. Repeated recrystallization from absolute alcohol furnished a pure or nearly pure substance isomeric with *l*-ecgonine: m.p. 221.5–222° (dec.), α_D^{20} −47.4° (C, 2, water).[39]

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.35; H, 7.75. Found: C, 58.48; H, 8.13.

Lithium aluminum hydride reduction of d-alloecgonine methyl ester. Lithium aluminum hydride (*ca.* 50 mg. altogether) was added in small portions to purified tetrahydrofuran (15 ml.) until effervescence ceased and then a further quantity (0.60 g.). To the gently refluxing solution of the reducing agent another of *d*-alloecgonine methyl ester (1.0 g.) in tetrahydrofuran (10 ml.) was admitted dropwise. After boiling the mixture 1 hr., the excess reducing agent was decomposed with methyl acetate. The mixture was successively treated with 3*N* aqueous sulfuric acid, tartaric acid (2.0 g.), and potassium carbonate, and the whole continuously was extracted with chloroform for 3 days. Removal of the chloroform gave a light brown oil (0.3 g.) which was readily purified from methanol: colourless, triangularly shaped crystals, m.p. 201.5–202.8°, α_D^{20} −6.3° (C, 1, water).

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.12; H, 10.01. Found: C, 63.45; H, 10.09.

Treated with the stoichiometric amount of methanolic hydrogen chloride the base was converted to the hydrochloride, which was recrystallized from methanol-ether: minute, stout prisms, m.p. 236.5–238°, α_D^{20} −5.9° (C, 1, water).[38]

Anal. Calcd. for $C_9H_{18}ClNO_2$: C, 52.04; H, 8.73. Found: C, 51.78; H, 8.86.

The foregoing is presumably what has been called 2α-hydroxymethyl-3α-tropanol for which the melting point and that of its hydrochloride are reported to be 165–166° and 172°, respectively.[34] An isomeric substance, said to be 2β-hydroxymethyl-3α-tropanol (XXXI), has been reported to melt at 139–140° and its hydrochloride at 258–260°.[34]

Infrared measurements. All measurements were made with a Perkin-Elmer Model 21 double beam spectrometer with sodium chloride optics. In carbon tetrachloride solution the methyl ester of ecgonine, of pseudoecgonine, of racemic alloecgonine, and of racemic allopseudoecgonine each had unmistakable bands in the regions both of hydroxyl group absorption and of carbomethoxy group absorption. For the foregoing esters, respectively, these had the following locations: 2.83μ and 5.79μ, 2.79μ and 5.80μ, 2.83μ and 5.81μ, and 2.76μ and 5.75μ.

Miscellaneous rotations. An apparently pure sample of cocaine [α_D^{20} −15.9 (C, 4, chloroform),[38] [reported −15.9 (C, 4, chloroform[39])] was found to have in methanol α_D^{20} −29.9° (C, 1)[37] and −31.0° (C, 2).[38] Mallinckrodt cocaine hydrochloride in methanol was found to have α_D^{20} −66.4° (C, 1)[38] and −65.6° (C, 2).[38]

Ecgonine methyl ester which had originally n_D^{19} 1.4886[6] and α_D^{20} −12.3° (C, 2)[6] had, after keeping in the dark in a desiccator over $CaCl_2$ in excess of four years, acquired a brownish colouration. This was removed by evaporative distillation at 95°/1 mm. The distillate appeared to be pure: n_D^{20} 1.4887, α_D^{20} −12.75° (C, 5, methanol).

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(38) Rotation determined by Mrs. Evelyn G. Peake of this Institute.

(39) I. Heilbron, *Dictionary of Organic Compounds*, Rev. Ed., Vol. I, Eyre and Spottiswood, London, 1953, p. 594.

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

Effect of *N*-Alkyl on Formation of Quinolones from *N*-Alkylbenzoylacetanilides[1]

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N-Alkylbenzoylacetanilides cyclize to *N*-alkyl-4-phenyl-2-quinolones with sulfuric acid when the alkyl is primary, but not when it is secondary. Failure to cyclize probably results from steric inhibition of =N—Ar conjugation, an interpretation supported by ultraviolet properties of related *N*-alkyl-*p*-nitroacetanilides.

Experiments undertaken to develop a new synthesis of 4-phenylquinoline showed that *N*-methylacetanilide could be acylated with ethyl benzoate in presence of sodium ethoxide, but in low yield. The product, *N*-methylbenzoylacetanilide, reacted with concentrated sulfuric acid to form 1-methyl-4-phenyl-2-quinolone, which was converted into 4-phenylquinoline by standard methods.

When *N*-iso-propylacetanilide was treated with ethyl benzoate and sodium ethoxide, *N-iso*-propylbenzoylacetanilide was formed in good yield. Surprisingly, however, the latter compound was recovered unchanged when it was treated with sulfuric acid.

The object of the present work was to determine why the cyclization failed. It has been found that the class of alkyl group in an *N*-alkylbenzoylacetanilide affects reactivity towards sulfuric acid. When the alkyl is primary (methyl, ethyl, *n*-propyl, *n*-butyl, and *iso*-butyl), the corresponding *N*-alkylquinolone is formed. When it is secondary (*iso*-propyl, *sec*-butyl), no cyclization takes place. When it is tertiary (butyl), it is lost, and unsubstituted 4-phenylquinolone is formed. These qualitative results were substantiated by kinetic studies (Table I).

In order to account for the results, it may be assumed that the protonated carbonyl group attacks the benzene ring only when the nitrogen atom can furnish electrons to the *ortho* position (I). When a bulky *N*-alkyl is present, the ring is hindered from being coplanar with the nitrogen valences (II), a double bond cannot form, and cyclization does not occur.

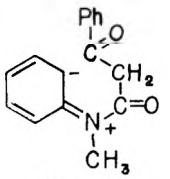
(1) From the Ph.D. Thesis of J. W. Britain, August 1950.

TABLE I

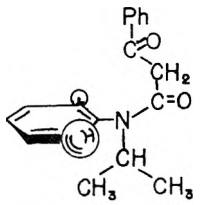
KINETICS OF CYCLIZATION OF *N*-ALKYLBENZOYLACETANILIDES

Alkyl	Temp., °C.	Time, Min.	Prods.[a] g.	Completion %	Acetophenone %	10^4K[b] $sec.^{-1}$
CH_3[c]	60.1	33	4.53	40.1	<1	2.60
	75.3	19.5	4.54	58.8	<1	7.59
	76.2	30	4.36	75.5	<1	7.83
	77.5	32	4.68	81.1	<1	7.78
	88.2	30	4.30	99.3	<1	27.60
C_2H_5[d]	63.2	30	0.90[e]	19.9	2.9	1.23
	74.9	15	4.35	23.7	10.3	3.01
	74.8	30	4.66	41.1	11.2	2.94
	88.7	30	4.35	80.5	<1	9.09
n-C_3H_7[f]	63.3	30	0.89[e]	15.3	4.3	0.92
	75.2	15	3.81[g]	18.7	12.9	2.30
	75.2	30	4.54	36.5	14.3	2.52
	88.9	30	4.42	78.4	<1	8.53
i-C_3H_7	74.8	16	0.95[e]	<1	7.0	<0.10
	74.5	30	0.95[e]	<1	4.6	<0.05
	88.3	30	4.44	4.0	6.7	0.23
n-C_4H_9[h]	63.5	30	0.87[e]	16.6	<1	1.01
	75.1	16	0.90[e]	19.2	<1	2.22
	74.8	30	0.84[e]	32.6	9.9	2.19
	89.6	30	4.39	82.8	<1	9.79
i-C_4H_9[i]	62.4	30	0.93[e]	10.0	26.5	0.59
	75.5	15	0.87[e]	17.4	21.1	2.13
	74.5	30	0.85[e]	29.2	22.2	1.93
	88.8	30	2.47[j]	73.2	5.3	7.32
s-C_4H_9	74.8	15	4.35	<1	1.6	0.11
	74.7	30	4.77	0.6	3.3	0.03

[a] From 5 g. of anilide, unless otherwise noted. [b] $k = [2.303/(t_2 - t_1)] \log C_1/C_2$. [c] H‡ = 19.3 cal., ΔS‡ = −19.7 e.u. [d] H‡ = 18.5 cal., ΔS‡ = −23.9 e.u. [e] From 1 g. of anilide. [f] H‡ = 20.1 cal., ΔS‡ = −19.6 e.u. [g] From 4 g. of anilide. [h] H‡ = 20.1 cal., ΔS‡ = −19.6 e.u. [i] H‡ = 22.5 cal., ΔS‡ = −13.0 e.u. [j] From 3 g. of anilide.

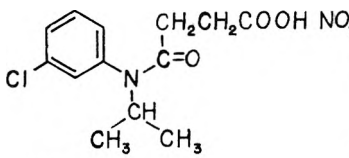


I

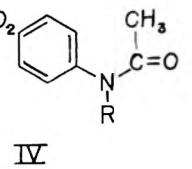


II

If the barrier to phenyl rotation were high enough, it would be possible to resolve a properly substituted analog of II. But *m*-chloro-*N*-*iso*-propylsuccinanilic acid (III) formed a homogeneous crystalline salt with cinchonidine, and the acid regenerated from this salt was optically inactive.



III



IV

Support for the suggestion of a structure like II, however, was found in a comparison of the ultraviolet spectra of *N*-*iso*-propyl-*p*-nitroacetanilide (IV) and other nitro compounds (Table II). It is apparent that the bulky *iso*-propyl group completely inhibits amide-nitro conjugation, indicating hindrance to coplanarity. It is thus probable that a similar effect prevents ring closure in *N*-*sec*-alkylbenzoylacetanilides.

TABLE II

SPECTRA OF *p*-SUBSTITUTED NITROBENZENES

Substituent	λ_{max}	ϵ	Reference
H—	268	$7.8 \cdot 10^3$	Doub and Vanderbelt, *J. Am. Chem. Soc.*, 69, 2714 (1947).
CH_3—	285	$9 \cdot 10^3$	*Ibid.*
CH_3NAc	288	$1.1 \cdot 10^4$	Present work.
C_2H_5NAc	285		Masaki, *Bull. Chem. Soc. Japan*, 7, 313 (1932).
$(CH_3)_2CHNAc$	265	$7 \cdot 10^3$	Present work.

EXPERIMENTAL

N-Methylbenzoylacetanilide. (a). A suspension of sodium ethoxide from 2.3 g. of powdered sodium and 7 ml. of alcohol in 50 ml. of toluene was treated with 15 g. of ethyl benzoate and 15 g. of *N*-methylacetanilide. The mixture was heated for 90 min. under a 20-cm. Vigreux column at such a rate that the temperature at the top of the column was 78–83°, 14.5 ml. of distillate being collected. The mixture was then neutralized with acetic acid and steam distilled, removing toluene and 3.3 g. of methylaniline. The residue was taken up in ether and shaken with 40 ml. of 15% sodium hydroxide. The crystalline sodium salt was removed and decomposed with dilute hydrochloric acid giving 6.6 g. (26%) of colorless prisms m.p. 97–98° (from alcohol).

(b). A mixture of 96 g. of ethyl benzoylacetate, 53.5 g. of *N*-methylaniline and 100 ml. of xylene was heated for 2 hr. in a bath at 170° under a Vigreux column, about 20 ml. of distillate being collected. To complete the reaction, it was found necessary to heat for an additional 20 hr. at 140°, and then for some time at 190–200° while the remaining volatile material was allowed to distill. Crystallization from ligroin gave 85 g. (67%) of crude product, m.p. 94–97°, and recrystallization from alcohol gave the pure anilide, m.p. 97–98°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.9; H, 5.93. Found: C, 76.0; H, 6.14.

The ultraviolet spectrum in alcohol had absorption peaks at 240 and 300 mμ (ϵ = 12,200 and 6,700). With alcoholic ferric chloride, the anilide gave a red-purple color. When 0.5 g. of it was dissolved in 5 ml. of cold acetic acid and treated with 0.2 g. of sodium nitrite in a little water, it was converted into *α-oximino-N-methylbenzoylacetanilide,* fine white needles from alcohol, m.p. 183–185°.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.1; H, 5.00. Found: C, 67.8; H, 4.97.

N-Ethylbenzoylacetanilide was obtained in 56% yield from 96 g. of ethyl benzoylacetate and 60 g. of *N*-ethylaniline in hot xylene; m.p. 73–75°; λ_{max}^{EtOH}, 243 (11,900), 297 (7,200).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.41; N, 5.24. Found: C, 76.8, 76.6; H, 6.76, 6.57; N, 5.26.

N-n-Propylbenzoylacetanilide was obtained in 30% yield from 64 g. of ethyl benzoylacetate and 45 g. of *N*-*n*-propylaniline; m.p. 94–95°; λ_{max}^{EtOH}, 243 (11,500), 300 (7,000).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.81. Found: C, 76.9; H, 7.13.

N-iso-Propylbenzoylacetanilide, from sodium ethoxide, ethyl benzoate, and *N-iso*-propylacetanilide in toluene in 75% yield or from ethyl benzoylacetate and *iso*-propylaniline in hot xylene in fair yield, formed coarse needles from alcohol, m.p. 91–92°; λ_{max}^{EtOH}, 245 (11,000), 295 (6,300).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.81; N, 4.98. Found: C, 77.0, 77.2; H, 7.03, 6.81; N, 4.95.

The *copper salt* formed yellow-green prisms from toluene m.p. 235–237°.

Anal. Calcd. for $C_{36}H_{35}N_2O_4Cu$: Cu, 10.2. Found: Cu, 10.2.

The α-oximino derivative formed faintly yellow needles from alcohol that sintered at 200° and decomposed at 208–211°.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.7; H, 5.85. Found: C, 69.6; H, 5.81.

N-n-Butylbenzoylacetanilide, colorless prisms from ligroin and then alcohol, was obtained in 15% yield from 96 g. of ethylbenzoylacetate and 75 g. of *n*-butylaniline in hot xylene; m.p. 71–73°; λ_{max}^{EtOH}, 245 (12,000), 300 (7,000).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.2; H, 7.17; N, 4.75. Found: C, 77.5; H, 7.43; N, 5.10.

N-iso-Butylbenzoylacetanilide was obtained in 47% yield from 37 g. of ethylbenzoylacetate and 28 g. of *iso*-butylaniline[2] in hot xylene; colorless prisms from ether, m.p. 96–98°; λ_{max}^{EtOH}, 240 (12,000), 300 (8,500).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.2; H, 7.17. Found: C, 77.5; H, 7.32.

N-sec-Butylbenzoylacetanilide was obtained in 73% yield from 200 g. of ethyl benzoylacetate and 160 g. of *sec*-butylaniline in hot xylene; colorless crystals from ether, m.p. 68–70°; λ_{max}^{EtOH}, 242 (11,300), 297 (7,500).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.2; H, 7.17. Found: C, 77.5; H, 7.34.

N-tert-Butylbenzoylacetanilide was obtained in 19% yield from 7.5 g. of ethylbenzoylacetate and 5.7 g. of tert-butyl-

(2) *iso*-Butylaniline was purified through its hydrochloride, colorless plates from alcohol, m.p. 205–207°; $C_{10}H_{16}ClN$ requires C, 64.7; H, 8.69; found: C, 64.7, 64.8; H, 8.86, 8.53.

aniline[3] in hot xylene; colorless prisms from ether, m.p. 94–96°; λ_{max}^{EtOH}, 235 (10,000), 300 (7,800).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.2; H, 7.17. Found: C, 77.3; H, 7.33.

When 0.2 g. of this anilide was heated at 75° for 30 min. with 1 ml. of concentrated sulfuric acid, there was obtained 0.13 g. of 4-phenyl-2-quinolone.

1-Methyl-4-phenyl-2-quinolone. A mixture of 7 g. of *N*-methylbenzoylacetanilide and 20 ml. of concentrated sulfuric acid was heated at 100° for 1 hr. and then poured on ice. The precipitate was washed with dilute sodium carbonate, dried (6.2 g., m.p. 93–120°), and crystallized from dilute alcohol, giving colorless needles (3.6 g., 55%), m.p. 141–142°; λ_{max}^{EtOH}, 230 (37,500), 280 (5,900), 340 (5,500). The quinoline gave no color with ferric chloride.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.0; H, 5.56. Found: C, 81.0; H, 5.76.

1-Ethyl-4-phenyl-2-quinolone, yield 71%, had m.p. 98–99°; λ_{max}^{EtOH}, 230 (40,000), 280 (7,500), 335 (6,200).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.9; H, 6.07. Found: C, 82.0, 81.5; H, 6.40, 6.19.

1-n-Propyl-4-phenyl-2-quinolone, crude yield 94%, had to be freed of impurity that gave a purple ferric chloride test by chromatography over alumina using ether and ligroin. The pure substance, yield 83%, had m.p. 73–74°; λ_{max}^{EtOH}, 230 (39,000), 280 (7,500), 335 (6,500).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.1; H, 6.51. Found: C, 82.0; H, 6.67.

1-n-Butyl-4-phenyl-2-quinolone, crude yield 87%, yield after chromatography 40%, had m.p. 71–72°; λ_{max}^{EtOH}, 230 (40,000), 280 (6,000), 335 (5,500).

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.3; H, 6.90. Found: C, 82.3; H, 7.15.

1-iso-Butyl-4-phenyl-2-quinolone, crude yield 68%, yield after recrystallization from ether 35%, had m.p. 83–84°; λ_{max}^{EtOH}, 235 (42,500), 280 (7,500), 335 (6,000).

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.3; H, 6.90. Found: C, 82.6; H, 7.07.

After treatment with sulfuric acid at 100°, the remaining anilides were unchanged: *iso*-propyl-, recovery 96%, *sec*-butyl-, recovery 85%.

Kinetic experiments (*see Table I*). A quantity (usually 5 g.) of *N*-alkylbenzoylacetanilide was stirred rapidly into four parts (ml./g.) of 96% sulfuric acid which had been brought to temperature. After the desired time, the reaction was stopped by stirring the mixture into ice, and the precipitate was taken up in ether. The ether solution was washed with bicarbonate and evaporated, and a portion of the weighed residue was diluted to a definite volume with alcohol. Analyses of the products were made using a Beckmann spectrophotometer, by comparing the observed ultra violet spectra with those of the pure components. The method used was similar to the one recently described by Dewar and Urch,[4] in which complete curves, rather than isolated points, were combined to reproduce the observed one. The odor of acetophenone was apparent in some of the reaction mixtures, and this compound was identified by isolation, λ_{max}^{EtOH}, 240 (13,000), 280 (1,000), and as its dinitrophenylhydrazone. Since quantitative studies indicated that acetophenone was formed in erratic fashion, it is probable that it was formed after the reaction mixtures were quenched. Since the quinolones containing *N-iso*-propyl- and *N-sec*-butyl groups were not formed in insoluble amount, it was assumed that their spectra would be an average of the nearly identical spectra of the 1-*n*-alkylquinolones.

m-Chloro-N-iso-propylaniline. A mixture of 95 g. of *iso*-propyl bromide and 200 g. of *m*-chloroaniline was heated under reflux until the temperature of the mixture had reached 150°. The mixture was then cooled and shaken with 300 ml. of 15% sodium hydroxide and the amine was separated and shaken with a solution of 150 g. of zinc chloride in 150 ml. of water. Excess zinc chloride solution was then decanted, and the remaining cheesy mass was extracted with 4 × 200 ml. of 30–60° ligroin. Distillation gave 111 g. of colorless product, b.p. 109–111° at 11 mm.

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.6; H, 7.00. Found: C, 63.7; H, 7.08.

m-Chloro-N-iso-propylsuccinanilic acid. A mixture of 16 g. of amine with 9.7 g. of succinic anhydride heated for 3 hr. at 105° gave 23.4 g. of product, colorless needles from dilute acetic acid, m.p. 132–134°.

Anal. Calcd. for $C_{13}H_{16}ClNO_3$: C, 58.0; H, 5.95. Found: C, 58.4; H, 5.99.

The *cinchonidine salt* separated in cotton-like needles in a yield of 50% when a solution of 2.5 g. of the acid and 2.5 g. of cinchonidine in 25 ml. of hot ethyl acetate was treated with 30 ml. of 30–60° ligroin and kept at room temperature for a week. It had $[\alpha]_D^{25}$ −60° ($CHCl_3$, C = 3).

Anal. Calcd. for $C_{13}H_{16}ClNO_3 + C_{19}H_{22}N_2O$: C, 68.2; H, 6.81. Found: C, 68.0; H, 7.02.

The acid was regenerated at below 10° and examined within 3.5 min., but neither the crystalline cinchonidine salt nor the material remaining in the mother liquor furnished an active product.

N-iso-Propyl-p-nitroacetanilide. A solution of 25 g. of *N-iso*-propylacetanilide in 50 ml. of concentrated sulfuric acid was stirred at 15° and treated dropwise with 10 ml. of nitric acid (1.42) in 10 ml. of sulfuric acid. After 10 min., the mixture was poured on ice; the resulting oil crystallized when it was rubbed with a little ether. Fractional crystallization from ethyl acetate gave 12.2 g. of a mixture, m.p. 60–69°, which was discarded, and 7.9 g. of pure product, nearly colorless needles, m.p. 103–104°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.35. Found: C, 59.9; H, 6.38.

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(3) *tert*-Butylaniline was prepared by Hickenbottom's method [*J. Chem. Soc.*, 946 (1933)] and purified by fractional crystallization of its *picrate*, yellow crystals from benzene and then alcohol, m.p. 184–185° ($C_6H_{18}N_4O_7$ requires: C, 50.8; H, 4.76; N, 14.8; found: C, 51.0; H, 4.98; N, 14.98); yield, 5.75 g. of pure amine from 500 g. of *tert*-butyl iodide.

(4) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957).

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Preparation of the 2′-, 3′- and 4′-Chloro- and Bromo-2,4-dihydroxydiphenylmethanes[1]

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Received June 8, 1959

The preparation of the 2′-, 3′- and 4′-chloro- and bromo-2,4-dihydroxydiphenylmethanes has been carried out. Certain derivatives have also been prepared.

It is well-known that resorcinol and several of its alkyl derivatives, especially hexylresorcinol, show a remarkable improvement in germicidal action over the corresponding phenols. Klarmann[2] has shown that by the introduction of the benzyl group into the resorcinol nucleus a compound of high germicidal activity coupled with low toxicity could be obtained. Germicidal potency is also known to be increased in phenols and their alkyl derivatives by the introduction of a halogen into the nucleus. Florestano[3] has reported the testing against tubercle bacilli of a number of diphenylmethane derivatives, more than half of which contained halogen.

As part of a program in these laboratories in the synthesis of halogenated phenols and their evaluation as possible antitubercular agents, the synthesis of the 2′-, 3′- and 4′-chloro- and 2′-, 3′- and 4′-bromo-2,4-dihydroxydiphenylmethanes was undertaken. Of these compounds, two have been reported previously. Klarmann and von Wowern[4] synthesized both the 4′-chloro and 4′-bromo isomers from resorcinol and the corresponding benzonitriles by the Hoesch synthesis, the benzophenones thus obtained being converted to the diphenylmethanes by a Clemmensen reduction. These workers also prepared the 4′-chloroisomer by the Friedel-Crafts alkylation of resorcinol with *p*-chlorobenzyl chloride. The Friedel-Crafts method seemed most suitable for our work. Consequently, the compounds prepared in the course of this work were made by the latter method, using essentially the procedure of Klarmann and von Wowern. These compounds are assigned the accompanying formula since substitution in resorcinol is in the 4 position; that is, ortho to one hydroxyl group and para to the other.

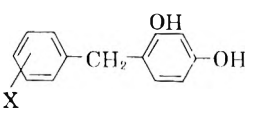


Table I shows the chloro- and bromo-dihydroxydiphenylmethanes and their derivatives prepared in the course of this work, together with pertinent physical properties and analytical data relating thereto. The 2′-, 3′- and 4′-chloro isomers were prepared satisfactorily by alkylating resorcinol with the *o*-, *m*-, and *p*-chlorobenzyl chlorides in nitrobenzene solvent. The 2′-, 3′- and 4′-bromo isomers were likewise made from the *o*-, *m*-, and *p*-bromobenzyl chlorides prepared earlier in this laboratory.[5] However, an irregularity in the melting point of the 3′-bromo isomer and our inability to raise the melting point of our 4′-bromo isomer from 92.5–93.5° to the 96° reported by Klarmann and von Wowern[4] led us to question the purity of the preparations from the bromobenzyl chlorides. As the bromobenzyl chlorides prepared by the peroxide catalyzed chlorination of the bromotoluenes with sulfuryl chloride[5] might possibly have contained traces of chlorobenzyl chlorides, the condensations with resorcinol were repeated using the bromobenzyl bromides instead of the bromobenzyl chlorides. The 2′-bromo isomer obtained from the *o*-bromobenzyl bromide possessed a slightly higher melting point (113.5–114.2° compared to 109.5–111°) than the preparation from *o*-bromobenzyl chloride; however, the melting points of the 3′- and 4′-bromo-2,4-dihydroxydiphenylmethanes prepared from either the bromobenzyl chlorides or the bromobenzyl bromides were the same.

Further attempts to purify the 3′-bromo isomer, m.p. 59–66°, involved the preparation and hydrolysis of the dibenzoate. The latter, melting sharply at 95.5–96° and possessing the correct analysis, yielded on hydrolysis the 3′-bromo isomer which again melted at 59–66°. After storing over mineral oil *in vacuo* for several days, some of the crystals were observed to melt on a block at 60–64°, whereas the remainder melted at 75–77°. After melting at 125° and cooling until crystallization, their melting point was again 59–60.5° and 77–79°. This behavior is apparently due to polymorphism. Another example of apparent polymorphism was observed with the 4′-chloro isomer. When the melting point was determined on a melting point block, some crystals were observed to melt at 76–78°, others at

(1) The material concerning the bromo-2,4-dihydroxydiphenylmethanes was abstracted from the M.S. Thesis of Richard C. Nametz, 1950. (a) Present address, Michigan Chemical Corporation, St. Louis, Michigan.

(2) E. Klarmann, *J. Am. Chem. Soc.*, 48, 791 (1926).

(3) H. J. Florestano, *J. Pharmacol. Exp. Therap.*, 96, 238 (1949).

(4) E. Klarmann and J. von Wowern, *J. Am. Chem. Soc.*, 51, 605 (1929).

(5) G. L. Goerner and R. C. Nametz, *J. Am. Chem. Soc.*, 73, 2940 (1951).

TABLE I

BROMO- AND CHLORO-2,4-DIHYDROXYDIPHENYLMETHANES

Isomer	Yield, %	B.P., °C. (mm.)	M.P., °C.	Br, %[a]	Dibenzoate M.P.	Dibenzoate Br, %[b]	Di-*p*-bromobenzoate M.P.	Di-*p*-bromobenzoate Br, %[c]
2′-Br	37[d]	202–215 (2)	109.5–111[e]	28.69	87.5–88.5	16.60	115.5–116.6	37.11
	30.5[d]	195–228 (2)						
	27.5[f]	211–212 (3)	113.5–114.2[g]					
3′-Br	36[d]	205–215 (2)	59–66.5[e,h]	28.47	95.5–96	16.69	153.5–154.5[i]	37.15
	21.5[d]	190–229 (2)						
	6[f]	190–210 (1)	59–64[h]					
4′-Br	38.5[d]	200–219 (2)	92.5–93.5[j,k]	28.48	101–102	16.37	154–155[i]	37.03
	40[d]	200–227 (5)						
	34[f]	200–218 (3)	92.5–94[e]					
2′-Cl	27.5[l]	190–200 (~1)	100–101[m]	15.62[n,o]	71–71.5[p]	8.37[n,q]	117–118[r]	20.93[n,s]
3′-Cl	20.5[l]	212–247 (3)	73–74[u]	14.59[n,o]	97.5–98[p]	8.06[n,q]	150–151[p]	20.79[n,s]
4′-Cl	27.[t]	200–205 (~1)	76–78 and	[v]	114–115[p]	8.00[n,q]	139[p]	21.45[n,s]
	61[t]	193–210 (~1)	83–84[g]					

[a] Calcd. for $C_{13}H_{11}BrO_2$: Br, 28.62. [b] Calcd. for $C_{27}H_{19}BrO_4$: Br, 16.40. [c] Calcd. for $C_{27}H_{17}Br_3O_4$: Br, 37.16. [d] Yield of crude product obtained by distillation. Based on bromobenzyl chloride. [e] Recrystallized from toluene. [f] Yield of crude product based on bromobenzyl bromide. [g] Recrystallized from water. [h] See Discussion and Experimental. Polymorphic crystalline forms melt at 59–60.5° and 77–79°. [i] Mixed melting point for the di-*p*-bromobenzoates of 3′-Br and 4′-Br isomers was 135–145°. [j] Recrystallized from 1:1 ligroin-xylene. [k] Klarmann and von Wowern (ref. 4) reported m.p. 96°. [l] Yield purified product based on chlorobenzyl chloride. [m] Extracted with Skelly Solve and recrystallized from xylene. [n] Chlorine analyses by Micro-Tech Laboratories, Skokie, Ill. [o] Calcd. for $C_{13}H_{11}ClO_2$: Cl, 15.12. [p] Recrystallized from ethanol. [q] Calcd. for $C_{27}H_{19}ClO_4$: Cl, 8.01. [r] Recrystallized first from ethanol then methanol. [s] Calcd. for $C_{27}H_{17}Cl_3O_4$: Cl, 20.80. [t] Yield of crude product based on chlorobenzyl chloride. [u] Recrystallized from water after prior extraction with ligroin. [v] Klarmann and von Wowern (ref. 4) reported m.p. 80.4°.

83–84°. When the oil from the low melting form was scratched while still on the block above its melting point, or when it was seeded with the higher melting form, it resolidified and again melted at 83–84°. Previously melted material remelted at 83–84°.

The chloro- and bromo-2,4-dihydroxydiphenylmethanes are solids which distil, usually with superheating, at 200 to 220° at 2 mm. as light yellow, viscous oils which crystallize slowly on prolonged standing or on scratching or stirring. Their solubility in oxygenated solvents, especially alcohols and esters, is so great that recovery is virtually impossible. They are insoluble in the common aliphatic hydrocarbon solvents, but can be recrystallized with difficulty from toluene, xylene-ligroin, carbon tetrachloride and large volumes of water. Although the pure solids are relatively stable, their solutions oxidize easily and the removal of traces of color is very difficult.

Attempts were made to prepare five different types of derivatives from the bromo isomers. Of these only the dibenzoates and di-*p*-bromobenzoates were satisfactory. The diacetates were apparently oils, the *p*-tosylates failed to form, and the diaryloxyacetic acids were obtained in insufficient quantities for purification and subsequent analysis. The chloro isomers formed both the dibenzoates and the di-*p*-chlorobenzoates. However, the latter could not be made entirely satisfactorily using *p*-chlorobenzoyl chloride and pyridine in the customary manner. Under these conditions the predominant product was *p*-chlorobenzoic acid anhydride. A preparation for the latter from the acid chloride and pyridine is described in *Organic Syntheses*.[6] Heating *p*-chlorobenzoyl chloride directly with the chloro isomers above 130° easily produced in excellent yield the *p*-chlorobenzoates, uncontaminated with the acid anhydride.

All of the chloro and bromo isomers were submitted for testing for antitubercular activity.[7] All were very toxic but were without activity against tuberculosis. All except the 2′-bromo isomer were submitted to the Cancer Chemotherapy Section of the National Institutes of Health for testing in the cancer screening program. None possessed activity when tested against the S-180, Ca-755 and L-1210 tumor systems.

EXPERIMENTAL

Materials used. The *bromobenzyl chlorides* and *bromobenzyl bromides* were prepared from the bromotoluenes as described previously,[5] the former by the peroxide-catalyzed chlorination with sulfuryl chloride[8] and the latter by bromination in bright light. The physical properties of the benzyl halides are listed in a prior communication.[5]

o-Chlorobenzyl chloride was Eastman white label grade. *m-Chlorobenzyl chloride*, prepared by the chlorination of *m*-chlorotoluene with sulfuryl chloride and benzoyl peroxide,[8]

(6) C. F. H. Allen, C. J. Kibler, D. M. McLachlin and C. V. Wilson, *Org. Syntheses*, **26**, 1 (1946).

(7) We wish to express our thanks to Eli Lilly and Company, Indianapolis, Indiana, and to the Michigan Department of Health, Lansing, Michigan, for carrying out these tests.

(8) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 2142 (1939).

distilled at 98° (14 mm.), n_D^{20} 1.5563–1.5576, reported b.p. 104° (17 mm.).[9] *p-Chlorobenzyl chloride* was redistilled Eastman practical grade, b.p. 100.5–101° (15 mm.), reported b.p. 94–96° (14 mm.).[10]

p-Bromobenzoyl chloride, obtained in 82% yield from *p*-bromobenzoic acid and phosphorus pentachloride, distilled at 220–225°. *p-Chlorobenzoyl chloride*, obtained by treating the acid with thionyl chloride, distilled at 107–108° (17 mm.).

The *chloro- and bromo-2,4-dihydroxydiphenylmethanes* were all obtained by the same general procedure. Typically, *4'-bromo-2,4-dihydroxydiphenylmethane* was prepared from 70 g. (0.636 mole) resorcinol, 64.7 g. (0.31 mole) *p*-bromobenzyl chloride and 50 g. (0.378 mole) anhydrous aluminum chloride in nitrobenzene solvent (400 g.) by the procedure of Klarmann and von Wowern.[4] Distillation of the resulting heavy red oil from an Allihn flask, the column of which was wrapped with asbestos tape and heated by a nichrome wire winding, gave 33.7 g. (38.4%) of a light colored viscous oil distilling at 200–219° (2 mm.). After standing several days or after repeated stirring the crude product solidified. Recrystallization from 1:1 ligroin-xylene gave colored needles of m.p. 90–92°. A product of slight gray color, m.p. 92.5–93.5°, was obtained after treatment with charcoal and repeated recrystallization from ligroin-xylene.

Derivatives. The *dibenzoates* and the *di-p-bromobenzoates* were made in the customary manner[11] by heating the dihydroxy compound and the appropriate acid chloride in pyridine. Attempts to prepare the *di-p-chlorobenzoates* of the 2'-chloro and 3'-chloro isomers in a similar fashion yielded small amounts of the impure derivative plus large quantities of a difficulty soluble crystalline material, m.p. 194–197°, which was identified as *p*-chlorobenzoic acid anhydride. The desired derivatives could be purified only with considerable difficulty because of their like solubility with the acid anhydride. Larger quantities of an initially purer di-*p*-chlorobenzoate could be made more conveniently by heating the dihydroxy compound with about 2.5 times its weight of *p*-chlorobenzoyl chloride at temperatures approximating 130° for about 4 hr.[12] The solid which resulted on cooling was broken up and dissolved in ether and the acidic materials were extracted with sodium bicarbonate solution. After evaporation of the ether, the residual solid or oil was dissolved in ethanol and permitted to crystallize. Recrystallization was from ethanol.

The *aryloxydiacetic acid* of the 3'-bromo isomer resulted in minute amounts when the 3'-bromo isomer was heated for one hour with chloroacetic acid in the presence of base.[13] The resulting solid, after crystallization from aqueous acetic acid melted at 172.5–174°. This derivative was not further investigated.

The attempted *purification* of the *3'-bromo isomer* consisted of: converting a sample, consisting of flat plates of m.p. 59–66°, into the dibenzoate, which melted at 95.5–96° after recrystallization from ethanol and which possessed the analysis shown in Table I; hydrolysis of 3 g. of the dibenzoate by refluxing it for one hour with 5 g. of potassium hydroxide in 25 ml. of diethylene glycol and 8 ml. of water; and isolating the liberated dihydroxy compound. The latter was accomplished by cooling and acidifying the alkaline diethylene glycol solution. The solid was separated and dissolved in ether and the acidic materials removed by extraction into sodium bicarbonate solution. Evaporation of the ether left a red oil which, after solution in toluene, yielded crystals of the 3'-bromo isomer of m.p. 59–66°, even after repeated recrystallization.

Bromine determination was carried out by the method of Lemp and Broderson.[14]

EAST LANSING, MICH.

(9) G. M. Bennet and B. Jones, *J. Chem. Soc.*, 1818 (1935).

(10) E. H. Huntress, *Organic Chlorine Compounds*, John Wiley and Sons, Inc., New York, 1948, p. 44.

(11) R. L. Shriner, R. C. Fuson and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th Ed., John Wiley and Sons, Inc., New York, 1956, p. 212.

(12) R. C. Huston and K. R. Robinson, *J. Am. Chem. Soc.*, **73**, 2483 (1951).

(13) C. F. Koelsch, *J. Am. Chem. Soc.*, **53**, 304 (1931).

(14) J. F. Lemp and H. J. Broderson, *J. Am. Chem. Soc.*, **39**, 2069 (1917).

[CONTRIBUTION FROM THE CHEMICAL ABSTRACTS SERVICE]

Stereo Numbers: A Short Designation for Stereoisomers[1]

ALFRED FELDMAN

Received May 26, 1959

A new method of designation for stereoisomers is proposed. Its advantage is conciseness.

The practice of designating a stereoisomer by individual reference to its asymmetric centers, as in, *e.g.*, *trans-anti-trans*-perhydrophenanthrene,[2] leads to cumbersome names for compounds containing several asymmetric centers. As a consequence, methods of nomenclature have been elaborated which achieve shorter names. These shorter names, however, were attained at the expense of uniformity in nomenclature, by taking advantage of peculiarities inherent in each particular field of stereochemistry. This fragmentation was aided by the requirement of correlating compounds to a steric prototype (which has become unnecessary since the advent of methods for determining absolute configurations).

Thus, carbohydrate chemists have developed a system of prefixes,[3] each one of which denotes the configuration at several asymmetric carbon atoms (Table I).

Carbohydrates containing more than 4 asymmetric centers can be named by combining the

(1) Paper presented before the 135th ACS meeting, Boston, Mass., April 1959.

(2) R. P. Linstead, *Chem. & Ind. (London)*, **15**, 510 (1937).

(3) Rules of Carbohydrate Nomenclature, *Chem. and Eng. News*, **31**, 1776 (1953).

TABLE I

PREFIXES FOR CARBOHYDRATE STEREOISOMERS[3]

No. of Asymmetric Carbons	Prefixes
2	D- or L-*erythro-*, *threo-*
3	D- or L-*arabino-*, *lyxo-*, *ribo-*, *xylo-*
4	D- or L-*allo-*, *altro-*, *galacto-*, *gluco-*, *gulo-*, *ido-*, *manno-*, *talo-*

prefixes of Table I as, *e.g.*, methyl L-*erythro*-β-D-*galacto* octopyranoside (Fig. 1) which expresses the configuration at seven carbon atoms.

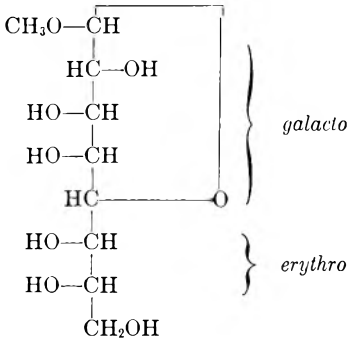


Fig. 1. Methyl L-*erythro*-β-D-*galacto*-octopyranoside

In other methods for carbohydrate nomenclature, the asymmetric positions are designated only by their number. A comma (,)[4] or a fraction bar (/)[5] separates those having a substituent above a plane from those having one below (Fig. 2).

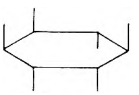
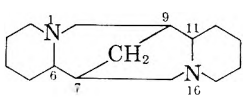


Fig. 2. Maquenne's[6] notation for *dextro*-inositol

Steroid chemists take advantage of the fortuitous circumstance that natural steroids are amazingly similar in their configuration. They implicitly assume this "natural" configuration, designating only those positions that are at variance with it.[6] Thus, in 5β-pregnane, the positions 8β,9α,10β,13β, 14α, and 17β are implied. If the compound differs much from the natural configuration, the system fails to provide short names. Thus, the compound commonly known as lumistane[7] should properly be called 5α,8α,13α,14β,17α,20α,24α-ergostane.

To avoid this, it has been proposed to distinguish between a *lumi-* and an *ergo*-sterol series.[8] Similarly, butyrospermol, the structure of which has recently been elucidated, was described as 9α-eupha-7,24-dien-3β-ol,[9] from the parent name "euphol," a compound with the lanostane skeleton but related to lumistane in its configuration. Such instances of alternative nomenclatures are quite common.

The more the field of stereoisomer nomenclature is subdivided, the more tenaciously trivial prefixes from early times survive, and the more the need arises for a system of general applicability. Several such systems have been proposed recently.[10-12] However, because of their scope, they no longer can take advantage of some inherent peculiarity of a class of compounds in order to obtain short names. Instead, each asymmetric center is mentioned separately.[13] Thus, α-*iso*-sparteine (Fig. 3) is designated by the method of Cahn, Ingold, and Prelog[11] as (1*R*:6*R*:7*S*:9*S*:11*R*:16*R*)-sparteine. No wonder then, that these authors feel compelled to state that a universal system "need not be allowed to disturb any local system in an area in which the latter is preserving good order. But a general system could provide for the unregulated areas; and it could be used to circumvent ambiguities caused by the overlapping of local systems."



(1*R*:6*R*:7*S*:9*S*:11*R*:16*R*)-Sparteine

Fig. 3. α-*iso*-Sparteine, and its name by the universal system of Cahn, Ingold, and Prelog[11]

(4) M. R. Lespiau, *Bull. soc. chim. France* [3], **13**, 105 (1895).

(5) L. Maquenne, *Les Sucres et leurs Principaux Dérivés*, Gauthier-Villars, Paris, 1900, p. 15 *ff*.

(6) International Union of Pure and Applied Chemistry, *Nomenclature of Organic Chemistry 1957*, Butterworths, London, 1958, pp. 73-82.

(7) J. Castells, E. R. H. Jones, G. D. Meakins, and R. W. J. Williams, *J. Chem. Soc.* 1159 (1959).

(8) A. Butenandt and L. Poschmann, *Ber.*, **73B**, 893 (1940).

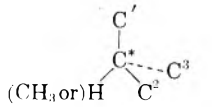
(9) W. Lawrie, W. Hamilton, F. S. Spring, H. S. Watson, *J. Org. Chem.* **21**, 491 (1956).

(10) G. E. McCasland, *A New General System for the Naming of Stereoisomers*, available from Chemical Abstracts, Columbus (Ohio), 1953.

(11) R. S. Cahn, C. K. Ingold, V. Prelog, *Experientia*, **12**, 81 (1956).

(12) A. P. Terentiev and V. M. Potapov, *Tetrahedron*, **1**, 119 (1957).

(13) This author is aware of one other attempt to provide a more general system with short prefixes. In a personal communication, Dr. Charles D. Hurd, of Northwestern University, suggested that carbohydrate configurational prefixes could be adapted readily to designate the steric arrangement of the sequences of asymmetric carbons in steroids. He would adopt the convention that in



H to C^2 to C^3 is clockwise (or +) if viewed from underneath, that the terminal atom of the asymmetric sequence (C*) is held by C′ which is of lower number than C^2 or C^3, and that for the next asymmetric carbon of the sequence C′ becomes C*, and the atom C^2 is attached to the prior ring and C^3 to the succeeding ring. With this convention, pregnane (and related 5β compounds) would have the sequence 5β, 10β, 9α, 8β, 14α, 13β, 17β or D-*arabino*-L-*talo*-; + + + − − + +

the 5α isomer of pregnane, as found in androstane or cholestane, would be − + + − − + + or D-*arabino*-L-*galacto*-.

To overcome the above difficulties, this writer wishes to propose a system by which explicit designations for stereoisomers can be drastically reduced in length, without causing loss of information. This method is not a new nomenclature system, but rather a technique that can be applied to any system of nomenclature, universal or specialized. But in the case of the above-mentioned general designations, the availability of prefixes of trivial proportions may well prove to be the simplification needed to carry one of these designations over into general acceptance.

The system is based on the fact that no more than two symbols are necessary to describe an asymmetric position in a compound. Thus, in the steroids, the Greek letters α and β suffice; in the sugars, the asymmetry can be denoted by drawing substituents to the left or the right of a Fischer projection; etc. Conceivably, stereoisomeric positions could be differentiated by using the symbols 0 and 1.

The advantage of using the latter symbols instead of α and β, D and L, *etc.*, is that the 0's and 1's can be assembled (in the same order in which they occur along a compound's skeleton) to constitute a *binary* (or *dyadic*) number.[14] This can be converted, by table or by routine methods (shown in parts A and B of appendix) into a short *decimal number*.[15] It is proposed to call this number, to be used as a prefix, the "stereo number" of the compound concerned.

For instance, the full configuration of 17-*iso-allo*-pregnane is:

$5\alpha,\ 8\beta,\ 9\alpha,\ 10\beta,\ 13\beta,\ 14\alpha,\ 17\alpha$

In binary notation this is:

0 1 0 1 1 0 0

In decimal notation this is:

44

(*The procedure for this conversion is given in the appendix.*)

Forty-four is thus the stereo number of 17-*iso-allo*-pregnane, which can be written as follows: /44/-pregnane. It is a complete and unequivocal yet utterly concise description of this stereoisomer.

Similarly, the sugar methyl L-*erythro*-β-D-*galacto*-octopyranoside (Fig. 1) can be named, as shown in the appendix C, as methyl /36/-octopyranoside. The compound α-*iso*-sparteine could be named (using the *R* and *S* of Cahn *et al.*, and setting $R=0$ and $S=1$) /12/-Sparteine (see appendix D).

In view of the ability of stereo numbers to fit many nomenclature systems, it might be advisable to prefix them by a symbol denoting the nomenclature used. For instance, in /s44/-pregnane, the "s" might signify that the steroid numbering has been used; in /c12/-sparteine, the "c" will indicate the numbering according to Cahn *et al.* Obviously, some convention must be adopted in this matter before stereo numbers are to be used by authors.

It is worthwhile noting some interesting properties of stereo numbers. Depending upon whether the first asymmetric carbon in a steroid is α or β, its stereo number will be within the lower or upper half of the possible number of stereoisomers.[16] In steroids, as it happens, C-5 is a special case, warranting separate designation. Since this carbon atom is frequently the first asymmetric center, its configuration can be deduced from the stereo number at a glance. (Thus, /44/-pregnane must be an allo (5α) compound because $44 < \frac{128}{2}$.) Again, depending upon whether the last asymmetric carbon is α or β, the stereo number will be even or odd. As it happens in steroids, the positions next to C-5 most likely to vary are C-17 and C-14, both frequent candidates for the asymmetric center with the highest number. (Thus, /44/-pregnane must be a 17-*iso* compound because 44 is an even number.)

Similarly, in sugars, the position that is specifically designated by α or β is frequently the lowest, while the highest position determines whether the compound is D or L. Here too, then, a glance at the stereo number will tell the configuration at these positions. (Thus, methyl /36/-octopyranoside is a L sugar because 36 is even; and it is β because $36 < \frac{128}{2}$.) Octal numbers may prove even more advantageous in this respect.

Finally, it might be pointed out that the stereo numbers of a pair of enantiomorphs will add to 2^n-1, where n is the number of asymmetric carbons in the molecule. This particularity may solve the problem of designating steroid enantiomorphs.[17] (Thus, the enantiomorph of /44/-pregnane is necessarily /83/-pregnane, since $44 + 83 = 127 = 2^7 - 1$.)

All such mathematical niceties notwithstanding, it remains a fact that stereo numbers do not indicate at first glance *all* the steric relations shown by the "extended" prefixes. This could be construed as

(14) A binary notation uses only the digits 0 and 1. Values greater than 1 are expressed by the position of the digits, as in our common (decimal) system. Thus, the binary 10, 100, 1000, 10,000 equal, respectively, 2, 4, 8, 16. This notation was proposed by Leibnitz. It also has been found in actual use among primitive Australian and South American tribes. Because of their use by digital computers, binary numbers have ceased to be a mathematical curiosity.

(15) H. Friedman, of our research department, suggests that the binary numbers be expressed as the corresponding octal numbers. Although somewhat longer than the equivalent decimal numbers, they are even easier to convert, as shown in the appendix E.

(16) The number "s" of possible sterioisomers of a compound containing n asymmetric carbon atoms is given by the equation: $s = 2^n$.

(17) A. Horeau, J. Jacques, J. P. Mathieu, A. Petit, *Bull. soc. chim. France* [5], **22**, 1304 (1955); T. Reichste in *Helv. Chim. Acta*, **40**, 677 (1957).

a serious shortcoming, but it is not. The chemist specifically interested in these relations can revert at will to the extended prefixes. Any annoyance in this respect is more than compensated for, whenever names have merely to be "handled." Stereo numbers combine the convenience of trivial names with the accuracy of the systematic names. Anyone who has been aware of the amount of information lost in the literature because authors assumed too much stereoisomerism known, will appreciate this advantage.

APPENDIX

Stereo numbers can be obtained by using a conversion table.[18] The actual calculations, however, are shown here:

A. To obtain the stereo number corresponding to 17-*iso-allo*-Pregnane (5α,17α-Pregnane):

The full configuration of the compound is:

5α, 8β, 9α, 10β, 13β, 14α, 17α

Step 1. Assign arbitrarily the digits of the binary numbers: $\alpha = 0$ and $\beta = 1$:

0 1 0 1 1 0 0

Step 2. Make a table of the powers of the number two, as shown below (column 1).

Step 3. Write the digits of the binary number so that the lowest (rightmost) binary digit matches the lowest number (which is 1) in the table of powers of 2 (column 2).

Step 4. Multiply each number in column 1 by the corresponding number in column 2, and enter result in column 3.

Step 5. Add column 3; the total is the sought decimal, or *stereo number*.

Column 1		Column 2		Column 3
64	×	0	=	0
32	×	1	=	32
16	×	0	=	0
8	×	1	=	8
4	×	1	=	4
2	×	0	=	0
1	×	0	=	0
				44
				(stereo number)

Thus, /44/-pregnane = 17-*iso-allo*-pregnane.

B. To obtain the configuration of /93/-Cortisol: The above procedure could be reversed, but a simpler method will be illustrated in this example:

Step 1. Draw a horizontal line and write the stereo number above and on the extreme right of the line.

Step 2. Divide this number by two. Write the remainder (0 or 1) below the stereo number, and the result to the left of the stereo number (on the line). Repeat this operation on the result, and continue till numbers are exhausted. The number below the line will be the sought binary number.

1	2	5	11	23	46	93
1	0	1	1	1	0	1

We know that the asymmetric centers in cortisol are located at the positions:

8, 9, 10, 11, 13, 14, 17

Step 3. Align these with the corresponding digits of the binary number:

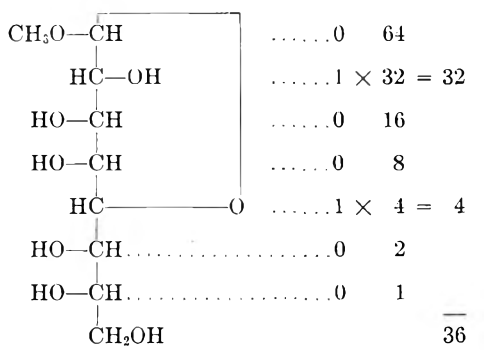
1 0 1 1 1 0 1

Step 4. Set $0 = \alpha$ and $1 = \beta$:

8β, 9α, 10β, 11β, 13β, 14α 17β

which is the configuration sought.

C. To obtain the stereo number for methyl L-*erythro*-β-D-*galacto*-octopyranoside. The convention adopted here is to assign 0 to all substituents to the left of the Fischer projection, and 1 to those on its right:



D. The compound α-*iso*-Sparteine can be named (using the *R* and *S* of Cahn *et al.*, and setting $R = 0$ and $S = 1$) as /12/-Sparteine:

1*R*:6*R*:7*S*:9*S*:11*R*:16*R*
0 0 1 1 0 0
12

E. Octal numbers: Another method of expressing binary numbers in a shorter form is the use of the equivalent octal number. In the octal system numbers run from 0 through 7.

Binary No.	Octal No.	Binary No.	Octal No.
000	0	100	4
001	1	101	5
010	2	110	6
011	3	111	7

(18) Available, *e.g.*, in *Reference Manual, 704 Data Processing System* (appendix C), by International Business Machines Corp.

In the first example, 17-*iso-allo*-Pregnane, the binary number is given as 0 1 0 1 1 0 0. To obtain the equivalent octal number the binary number is broken into groups of three:

0 101 100

and the equivalent octal number is expressed:

0 5 4

Thus, in an octal system the compound becomes [54]-Pregnane.

Translation of an octal number back into its binary equivalent is also very simple. In the second example, the octal number would have been [135]-Cortisol. The binary equivalent is easily written down: 1 3 5

001 011 101

COLUMBUS, OHIO

Notes

A department for short papers of immediate interest.

Selected Phenyl-2-methylhexanes

GORDON L. GOERNER, HERMAN L. MULLER, AND JAMES L. CORBIN

Received March 16, 1959

Of the six possible isomeric alkylbenzenes possessing the 2-methylhexyl group as the alkyl side chain, Francis[1] in his review on the properties of the alkylbenzenes listed two as having been obtained in the pure state. These are 2-phenyl-2-methylhexane, prepared by Huston and coworkers,[2,3] and 2-phenyl-5-methylhexane, prepared by Klages.[4] Two of the four remaining isomers, namely 3-phenyl-2-methylhexane and 3-phenyl-5-methylhexane, were presumably obtained in a ternary mixture with 2-phenyl-5-methylhexane by Huston and Kaye.[3] An examination of the literature since Francis' review has revealed no further reference to the latter two isomers of Huston and Kaye nor any reference to the two remaining unknown isomers, 1-phenyl-5-methylhexane and 1-phenyl-2-methylhexane.

The purpose of the present investigation was to prepare the four "unknown" or unseparated phenyl-2-methylhexanes by unequivocal methods and to determine the physical properties of each. The methods chosen for the preparations are described in the following paragraphs. Each synthesis led in the penultimate step to a ketone which was reduced easily to the desired alkylbenzene[5,6] by the Huang-Minlon modification of the Wolff-Kishner reduction.

1-Phenyl-5-methylhexane was synthesized from malonic ester. The latter was alkylated with isoamyl bromide to give ultimately 5-methylhexanoic acid. The acid chloride of the latter was used in the Friedel-Crafts acylation procedure to yield 5-methylhexanophenone.

The synthesis of 1-phenyl-2-methylhexane was attempted initially in a similar fashion. Diethyl methylmalonate, prepared by the methylation of malonic ester according to the procedure of Organic Syntheses,[7] was alkylated with *n*-butyl bromide to yield 2-methylhexanoic acid. The latter, via the acid chloride and a Friedel-Crafts acylation of benzene, should give the known 2-methylhexanophenone. For this ketone Campbell and co-workers[8] have reported an orange colored 2,4-dinitrophenylhydrazone melting at 74.5–75°. During attempts to establish that the ketone obtained in this work was identical with the ketone of Campbell *et al.*, two 2,4-dinitrophenylhydrazones were isolated. A yellow crystalline one, melting around 78–80°, apparently corresponded to the derivative prepared by the latter workers. The second, crystallizing as thick red needles from acetic acid, melted at 166–168° in comparison to the 2,4-dinitrophenylhydrazone of hexanophenone melting at 168°.[9] It appears, therefore, that the diethyl methylmalonate contained some diethyl malonate and that the hexanophenone came from this source. Pure 2-methylhexanophenone was then made by the excellent one-step synthesis of Campbell *et al.* by alkylating propiophenone on the α-carbon with *n*-butyl bromide in the presence of sodamide.

The synthesis of 3-phenyl-5-methylhexane started with phenylacetonitrile. Alkylation of the latter with isobutyl bromide in the presence of sodium hydride yielded 2-phenyl-4-methylpentanenitrile, which was forced to react with methyl magnesium bromide at elevated temperatures. The resulting mixture of ketone and unreacted nitrile could not be separated completely with the distillation equipment available. A ketone fraction boiling near 118° at 10 mm. and a presumed nitrile fraction boiling approximately 10 degrees higher were obtained. Both fractions showed the characteristic infrared carbonyl absorption at 3.6 to 3.7 microns, and both gave a strong test for nitrogen by the sodium fusion method. This agrees with the observations of Jullien,[10] who found that he also was unable to separate the ketone and nitrile by distillation, but the ketone could be isolated by the hydrolysis of the nitrile with 80% sulfuric acid. In the present work it was decided that the presence of the nitrile would not interfere with the isolation of the alkylbenzene after the Wolff-Kishner reduction. If the nitrile were not hydrolyzed under the conditions of the reduction, the hydrocarbon would boil so much lower (below 100° at 10 mm.) than the nitrile (above 130° at 10 mm.) that separation should offer no difficulty. On the other hand, if the nitrile were hydrolyzed, the resulting acid would stay in the water

(1) A. W. Francis, *Chem. Rev.*, **42**, 107 (1948).
(2) R. C. Huston, W. B. Fox and M. N. Binder, *J. Org. Chem.*, **3**, 251 (1938).
(3) R. C. Huston and I. A. Kaye, *J. Am. Chem. Soc.*, **64**, 1576 (1942).
(4) A. Klages, *Ber.*, **35**, 2645 (1902).
(5) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(6) E. Berliner and F. Berliner, *J. Am. Chem. Soc.*, **72**, 222 (1950).
(7) N. Weiner, *Org. Syntheses*, **Coll. Vol. II**, 279 (1943).
(8) A. D. Campbell, C. L. Carter and S. N. Slater, *J. Chem. Soc.*, 1741 (1948).
(9) D. P. Evans, *J. Chem. Soc.*, 785 (1936).
(10) P. Jullien, *Bull. soc. chim. France*, [5] **3**, 1347 (1936).

layer (as the sodium salt) during the work up of the hydrolysis mixture and hence would be separated from the hydrocarbon fraction. When the reduction was carried out, part of the nitrile was recovered unchanged and part was hydrolyzed to the acid (as sodium salt). No difficulty was encountered in separating the hydrocarbon.

The starting material for the preparation of 3-phenyl-2-methylhexane was again phenylacetonitrile. Alkylation with isopropyl bromide in the presence of sodamide yielded 2-phenyl-3-methylbutanenitrile, which in turn was treated with ethyl Grignard reagent. Unlike the reaction described above, a much purer ketone could be isolated in this case.

As a result of the work described above, two observations concerning methods of preparation of alkylbenzenes can be made. First, alkylbenzenes of the type of 1-phenyl-2-methylhexane (alternatively it might be named 2-benzylhexane) which have a benzyl group attached to an alkyl chain are made very conveniently by the alkylation of propiophenone or other appropriate alkyl phenyl ketone in the presence of sodamide, followed by a modified Wolff-Kishner reduction. Thus alkylbenzene is produced in two steps from the phenyl ketone. Second, phenylacetonitrile or a nuclear-substituted phenylacetonitrile is alkylated to yield an α-alkylphenylacetonitrile, the latter is converted into ketones *via* the Grignard reaction, and the ketones thus obtained are reduced readily by the Wolff-Kishner method. Many alkylbenzenes are thus available in three steps from the appropriate phenylacetonitriles. Pure alkylbenzenes free from rearranged products also are available by either of the methods outlined above. Further work is under way in our laboratories toward the preparation of other pure alkylbenzenes.

EXPERIMENTAL[11]

5-Methylhexanoic acid. From 412.5 g. (2.58 moles) of diethyl malonate, 377.5 g. (2.5 moles) of isoamyl bromide, and sodium ethoxide (from 57.5 g., 2.5 moles of sodium), there was obtained in the usual fashion (essentially as described by Curtius and Sieber[12]) a total of 386 g. (1.67 moles) of diethyl isoamylmalonate distilling at 123–125° (13 mm.), n_D^{25} 1.4229–1.4235, reported b.p. 118–130° (12 mm.),[12] n_D^{20} 1.4255.[13] The foregoing ester was hydrolyzed by refluxing for 5 hr. with 320 g. (5.7 moles) of potassium hydroxide in 320 ml. of water. After the alcohol was distilled off, the aqueous layer was extracted with ether to remove unhydrolyzed ester, and the isoamylmalonic acid was liberated with sulfuric acid. The aqueous acid solution was refluxed for 5 hr. and the oil layer was extracted with benzene. After the low boiling liquids were removed, decarboxylation was completed by heating the resulting oil to about 200° until the evolution of carbon dioxide ceased. Distillation through a 12 in. Vigreux column gave 146 g. (1.12 moles, 44.8% based on sodium) of 5-methylhexanoic acid, b.p. 110–116° (16 mm.), n_D^{25} 1.4202–1.4206, reported[13] b.p. 108–110° (14 mm.), n_D^{19} 1.4209.

5-Methylhexanophenone. To the above 5-methylhexanoic acid was added dropwise 157 g. (a 20% excess) of thionyl chloride. The mixture was refluxed for 2.5 hr. Distillation gave 145 g. (0.977 mole) of acid chloride boiling at 76–82° (34 mm.). The Friedel-Crafts acylation of benzene was carried out essentially as described[5] for a similar acylation by adding a solution of 83 g. (0.56 mole) of the acid chloride in 500 ml. of anhydrous thiophene-free benzene to 115 g. (0.937 mole) of anhydrous aluminum chloride in 150 ml. of benzene. Distillation of the product fraction through the Vigreux column gave 84 g. (0.44 mole, 79%) of ketone boiling at 148–151° (17 mm.), n_D^{25} 1.5050–1.5060, reported[14] b.p. 145–148° (18 mm.), n_D^{26} 1.5067.

1-Phenyl-5-methylhexane. To a solution of 400 ml. of diethylene glycol, 50 g. (0.9 mole) of potassium hydroxide and 50 ml. of 85% hydrazine hydrate[5,6] was added 84 g. (0.44 mole) of the above ketone. The solution was refluxed for an hour, the water and excess hydrazine hydrate were distilled out until the temperature reached 190°, and the solution was then refluxed an additional 3 hr. After the reaction mixture was worked up in the usual way, distillation through a Vigreux column gave the hydrocarbon boiling at 110–115° (mostly 111–112°) at 17 mm. Redistillation from metallic sodium through the Vigreux column gave five fractions. The three middle fractions, b.p. 111–114° (17 mm.), possessed a constant n_D^{20} 1.4850, n_D^{25} 1.4828 and amounted to 55 g. *Fraction 3*, taken as the pure hydrocarbon, had a micro b.p. 238.3° (735 mm.) corr. and d_4^{20} 0.8547, d_4^{25} 0.8509.

Anal. Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44. Found: C, 88.62; H, 11.44.

The diacetamino derivative, prepared by nitrating the alkylbenzene at 50° or above and then proceeding in the usual fashion, had a m.p. 206.5–207° corr. (from ethanol).

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: N, 9.65. Found: N, 9.68.

2-Methylhexanophenone. To a sodamide [prepared from 11.5 g. (0.5 mole) of sodium by the procedure of Hancock and Cope[15]] suspension 67 g. (0.5 mole) of propiophenone was added dropwise with stirring. After 30 min. of stirring, 77 g. (0.56 mole) of *n*-butyl bromide was added dropwise, and the mixture was heated on the steam bath an additional 1.5 hr. and then permitted to stand overnight. The oil layer was washed with 300 ml. of water, the wash water was extracted with benzene, and the combined organic layers were again washed with water. The benzene was removed and the residual oil was fractionated through a 12 in. glass helices packed column at 2 mm. pressure. After a forerun of 12 g. distilling up to 107°, there was obtained a total of 69 g. (0.363 mole, 72.5%) of 2-methylhexanophenone, b.p. 107–110°, n_D^{25} 1.5048–1.5058, reported b.p. 133–138° (15 mm.),[8] 109–110° (3 mm.),[16] n_D^{20} 1.5070.[16] The 2,4-dinitrophenylhydrazone melted at 74.5–76°, reported[8] 74.5–75°.

1-Phenyl-2-methylhexane. Wolff-Kishner reduction of 67 g. (0.35 mole) of the above ketone was carried out by the Huang-Minlon procedure as described above. Fractionation of the product layer through a 12 in. Fenske-type column at 6 mm. gave 39 g. (0.22 mole, 63%) of product distilling at 97–100°, n_D^{25} 1.4833–1.4840. Redistillation from sodium metal through an 8 in. packed column at 10 mm. gave the following: *Fraction 1*, 1.2 g., b.p. 99–101°, n_D^{25} 1.4832; *Fractions 2–6*, 27.7 g., b.p. 101–102.5°, each with constant n_D^{20}

(11) Melting points and boiling points are uncorrected unless otherwise indicated. Analyses by Micro-Tech Laboratories, Skokie, Illinois.

(12) T. Curtius and W. Sieber, *J. prakt. chem.*, [2] **125**, 156 (1930).

(13) I. Heilbron, *Dictionary of Organic Compounds*, Revised Edition, Oxford University Press, New York, 1953, Vol. III, pp. 58 and 61.

(14) W. M. Lauer and M. A. Spielman, *J. Am. Chem. Soc.*, **55**, 4923 (1933).

(15) E. M. Hancock and A. C. Cope, *Org. Syntheses*, **25**, 25 (1945).

(16) T. I. Temnikova, A. K. Petryaeva and S. S. Skorokhodov, *Zhur. Obshchei Khim.*, **25**, 1575 (1955); *Chem. Abstr.*, **50**, 4891 (1956).

1.4852, n_D^{25} 1.4832. *Fraction 4*, taken as the pure alkylbenzene, had micro b.p. 233.5° (735 mm.) corr., and d_4^{20} 0.8558, d_4^{25} 0.8521.

Anal. Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44. Found: C, 88.48; H, 11.36.

The diacetamino derivative (from ethanol) had a m.p. 193–193.8° corr.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: N, 9.65. Found: N, 9.85.

2-Phenyl-4-methylpentanenitrile. To a suspension of 24.4 g. (1.017 moles) of sodium hydride in 200 ml. of anhydrous toluene contained in a 1-l. three-necked flask equipped with a stirrer, condenser, thermometer, dropping funnel, and necessary drying tubes, there was added all at once a mixture of 122 g. (1.043 moles) of phenylacetonitrile and 150 g. (1.095 moles) of pure isobutyl bromide (b.p. 90.5–91°). The reaction flask was heated by a mantle to 65°, at which temperature the reaction started. The mantle was removed and the flask was cooled as necessary by means of a dry ice-cooled kerosene bath in order to keep the reaction from becoming too vigorous. The main vigor of the reaction was spent in 0.5 hr. The reaction mixture was refluxed an additional 5 hr. and permitted to stand over night.

Ethyl alcohol (40 ml.) was cautiously added dropwise, followed by the dropwise addition of water until a total of 200 ml. was added. The oil layer was removed and the water extracted with benzene. The organic phase was washed with dilute acid, water, sodium carbonate solution, and again with water. After filtration through a layer of anhydrous sodium sulfate, the benzene was distilled and the product fractionated through a 12 in. Fenske-type column packed with glass helices. After a forerun of 24 g. consisting largely of recovered phenylacetonitrile, there was obtained 115 g. (0.666 mole, 65.5%) of product distilling at 130–134° (mostly 132–134°) at 10 mm., n_D^{20} 1.4990, n_D^{25} 1.4970, reported b.p. 136–138° (15 mm.)[17] n_D^{25} 1.4978–1.4985.[18]

3-Phenyl-5-methyl-2-hexanone. To an ethereal solution of methyl magnesium bromide [prepared in the usual manner from 50 g. (2.05 moles) of magnesium] there was added in the course of 2 hr. 175.5 g. (1.014 moles) of 2-phenyl-4-methylpentanenitrile. The solution was refluxed for 5 hr., part of the ether was removed and replaced by toluene, and the reflux continued for several hours at 90°. After hydrolysis of the complex and removal of the solvent, the product was fractionated through a 12 in. Fenske column at 10 mm. pressure. Two main fractions were obtained: *Fraction A*, about 95 g., b.p. 115–122°, n_D^{25} 1.4952–1.4968, n_D^{20} 1.4971–1.4988, shown by sodium fusion to contain nitrogen, was mainly the desired ketone. Schultz *et al.*[19] reported a b.p. 119–124° (14 mm.), n_D^{20} 1.4966 for the ketone prepared by the alkylation of methyl benzyl ketone with isobutyl iodide and powdered sodium hydroxide. *Fraction B*, 46 g., b.p. 124–127°, n_D^{25} 1.4982–1.4894, n_D^{20} 1.5000–1.5011, possessing a strong carbonyl absorption at 3.6 μ, was nitrile mixed with the desired ketone. Jullien[10] was also unable to separate the ketone and nitrile.

3-Phenyl-5-methylhexane. All the fractions obtained immediately above were recombined and treated with 110 ml. of 64% hydrazine hydrate in a solution of 110 g. of potassium hydroxide in 500 ml. of diethylene glycol by the modified Wolff-Kishner procedure.[5,6]

Distillation of the hydrocarbon fraction through the 12 in. Fenske column at 10 mm. gave 67.6 g. of material distilling at 76–96° (mostly 88–90°). A light brown residue, n_D^{25} 1.4960, appeared to be starting nitrile. From the alkaline diethylene glycol solution there was obtained 32 g. of crude, brown crystalline 2-phenyl-4-methylpentanoic acid.

Purification of the hydrocarbon fraction was achieved by shaking repeatedly with ice-cold concentrated sulfuric acid, washing with cold water and sodium carbonate solution. After it dried, thiophene free benzene was added and azeotroped off to remove the final traces of water. The hydrocarbon was then fractionated from 1 g. of sodium metal through the 12 in. Fenske column. The following fractions were collected at 10 mm.: *Fraction 1*, 4.6 g., b.p. 72–77°, n_D^{20} 1.4850, isoamylbenzene [proved by b.p. 197–199° at 752 mm. vs. reported[1] b.p. 196° at 760 mm., n_D^{20} 1.4847 and by diacetamino derivative, m.p. 216–217° vs. reported[20] m.p. 215–216°. Probably arose by decarboxylation of sodium 2-phenyl-4-methylpentanoate at the high temperatures of the Wolff-Kishner reduction]; *Fractions 2–3*, 5.6 g., b.p. 77–86°; *Fraction 4*, 3.2 g., b.p. 85–88°, n_D^{20} 1.4835, n_D^{25} 1.4818; *Fractions 5–11*, 45.7 g., b.p. 87.5–88.5°, n_D^{20} 1.4832, n_D^{25} 1.4813, b.p. and refractive index identical for all fractions. *Fraction 7*, selected as the pure hydrocarbon, had micro b.p. 216.6° (733 mm.) corr., and d_4^{20} 0.8539, d_4^{25} 0.8501.

Anal. Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44. Found: C, 88.78; H, 11.45.

The diacetamino derivative (from ethanol) melted at 198.8–199.2° corr.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: N, 9.65. Found: N, 9.61.

2-Phenyl-3-methylbutanenitrile was prepared by the alkylation of phenylacetonitrile (117 g., 1.0 mole) with isopropyl bromide (123 g., 1.0 mole) in a manner identical with that used by Hancock and Cope[15] for the preparation of α-cyclohexylphenylacetonitrile. Distillation through a 12 in. Fenske-type column at 3 mm. gave 127.5 g. (0.8 mole) of the desired nitrile, b.p. 106–119° (mostly 113–119°), n_D^{25} 1.5038–1.5043, reported[21] b.p. 106° (6 mm.), $n_D^{24.5}$ 1.5032.

4-Phenyl-5-methyl-3-hexanone[10] was prepared by adding 127.5 g. (0.8 mole) of the above ketone in 375 ml. of anhydrous toluene to an ethyl magnesium bromide solution (from 44 g., 1.8 moles of magnesium and 218 g., 2.0 moles of ethyl bromide) in 300 ml. of ether. This solution was reflexed for 12 hr. and worked up in the usual fashion. Fractionation through a 12 in. Fenske-type column at 10 mm. gave 65.0 g. (0.342 mole, 43%) of ketone, b.p. 115–125°, n_D^{20} 1.4968–1.4970. Schultz and Bicking[22] reported a b.p. 118–119° (14 mm.), n_D^{25} 1.4943. The above ketone gave a slight test for nitrogen by the sodium fusion method.

3-Phenyl-2-methylhexane was prepared from 65 g. of the above ketone by the modified Wolff-Kishner procedure. Fractionation of the hydrocarbon layer through the 12 in. Fenske column at 10 mm. gave, after a very small forerun, 33.9 g. of product, b.p. 88–91°, n_D^{25} 1.4811–1.4858. After purification by washing with ice cold sulfuric acid, *etc.*, as described before and refractionation at 10 mm. from metallic sodium, the following were obtained: *Fractions 1–2*, 4.3 g., b.p. 87–90.5°, n_D^{25} 1.4860; *Fractions 3–6*, 22.4 g., b.p. 90–91°, n_D^{20} 1.4870–1.4873, n_D^{25} 1.4850–1.4853; *Fraction 7*, 4.3 g., b.p. 89° and falling n_D^{20} 1.4860, n_D^{25} 1.4840. *Fraction 4*, selected as the analytical sample, had a micro b.p. 220.2° (733 mm.) corr., n_D^{20} 1.4872, n_D^{25} 1.4852, d_4^{20} 0.8609, d_4^{25} 0.8571.

Anal. Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44. Found: C, 88.58; H, 11.38.

The diacetamino derivative melted at 222.9–223.3° corr.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: N, 9.65. Found: N, 9.67.

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The Conversion of 5α-Pregnane-3,11,20-trione to 11-Ketoprogesterone

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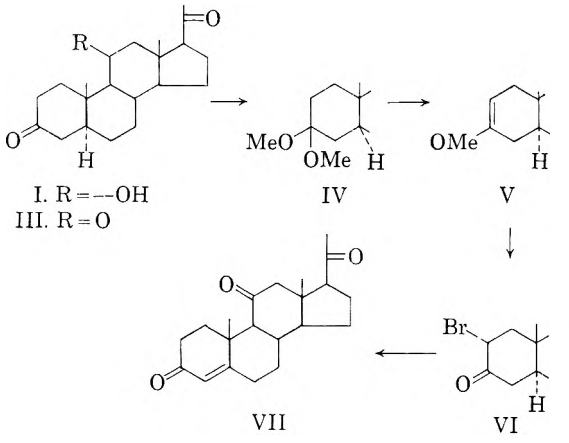
The initial step in one of the early methods for the synthesis of cortisone from 11α-hydroxyprogesterone[1] was the catalytic reduction of the Δ^4-double bond.[2] The reduction of 11α-hydroxyprogesterone gives predominantly the 5β (normal) dihydroisomer, but the 5α (allo) isomer I is isolated in yields up to 30%.[2] 11α-Hydroxy-5α pregnane-3,20 trione (I) may be converted to cortisone acetate *via* 21-acetoxy-17α,21-dihydroxy-5α-pregnane-3,11,20-trione (II) (allo dihydrocortisone acetate). The difficulty of the introduction of the Δ^4-double bond into allo dihydrocortisone acetate is well known.[3]

This note describes the conversion of 11α-hydroxy-5α-pregnane-3,20-dione (I) to the versatile intermediate, 11-ketoprogesterone (VII).[4] 11α-Hydroxy-5α-pregnane-3,20-dione (I) was oxidized with chromic acid to the allo trione III. The 3-methyl ketal was selectively prepared in 44% yield using selenium dioxide in methanol.[5] Pyrolysis of the ketal IV formed the enol ether to which the structure V is assigned. When V was treated with hypobromous acid[6] the 2-bromide VI was formed in almost quantitative yield. The infrared spectrum of VI showed raised carbonyl absorption at 1720 cm.$^{-1}$ as well as the usual carbonyl absorption at 1700 cm.$^{-1}$ The displacement of the carbonyl to the higher frequency is indicative of 2-equatorial or 2α-bromine.[7] Dehydrohalogenation of the 2-bromide using lithium chloride-dimethyl formamide[8] gave 11-ketoprogesterone in 40% yield. Less than 5% yield of the Δ^1-isomer was detected in the crude dehydrohalogenation product.[9]



EXPERIMENTAL[10]

3,3-Dimethoxy-5α-pregnane-11,20-dione (IV). A mixture of 20 g. of 5α-pregnane-3,11,20-trione, 20 g. of selenium dioxide, and 500 ml. of methanol was stirred at room temperature for 2 days. The mixture was filtered and poured into 2 l. of water containing sufficient sodium hydroxide to make the solution alkaline. Extraction of the aqueous mixture with methylene chloride gave a crystalline residue which when recrystallized from methanol yielded 10 g. of IV, m.p. 130–136°. The yield was 43.8%. Several recrystallizations from methanol gave material melting at 148–151°, $[\alpha]_D$ +104° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.61; H, 9.80.

3-Methoxy-5α-2-pregnene-11,20-dione (V). Five g. of IV, m.p. 130–136°, was heated at 220° until bubbling ceased. About 9 min. was required. The cooled melt was crystallized from methanol to give 2.58 g. of V, m.p. 154–156°. The yield was 56.4%. Recrystallization yielded broad melting products of inferior quality. The crude reaction product was therefore not purified but used directly in the next step.

2α-Bromo-5α-pregnane-3,11,20-trione (VI). A solution of 564 mg. of *N*-bromosuccinimide in 30 ml. of *t*-butyl alcohol and 20 ml. of 0.8*N* sulfuric acid was added to a solution of 1.0 g. of enol ether V in 25 ml. of *t*-butyl alcohol. After 2 min. the reaction mixture was poured into water. The crystals were filtered and dried. The yield of VI, m.p. 167–173°, was 1.10 g. (93.4%). Recrystallization from methanol raised the m.p. to 170–172.5°, $[\alpha]_D$ +144° (acetone), λ_{max}^{Nujol} 1720, 1700, 709 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.41; H, 7.13; Br, 19.47, 19.43.

11-Ketoprogesterone (VII). A solution of 1.04 g. of bromide VI, 300 mg. of lithium chloride, and 3 ml. of dimethylformamide was heated under nitrogen at 70–80° for 2 hr. The cooled mixture was diluted with 10 ml. of water and 10 ml. of saturated sodium chloride solution. The crystalline product weighed 810 mg. (97.4%). Recrystallization from methanol afforded 340 mg. (40.8%) of VII, m.p. 164–168°. Pure 11-ketoprogesterone, (260 mg., 31.2%) m.p. 170.5–172.3°, $[\alpha]_D$ +265° ($CHCl_3$), (λ_{max}^{EtOH} 239 mμ, a_M 15,500)

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(9) See J. J. Beerboom and C. J. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954) who reported that dehydrohalogenation of 4α-chlorocholestanone afforded a mixture from which Δ^1- and Δ^4-Cholesten-3-one were isolated in yields of 43 and 31%, respectively.

(10) The author is indebted to W. A. Struck and associates for the elemental analyses, to Mrs. G. S. Fonken for the infrared data, and to L. M. Reineke and associates for paper chromatography analyses.

was obtained by a final recrystallization from methanol. The infrared curve of this material was identical with that of pure 11-ketoprogesterone. Paper chromatography of the crude reaction product showed the presence of less than 5% of 1-dehydro-5α-pregnane-3,11,20-trione.

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N-Vinyltetrazoles

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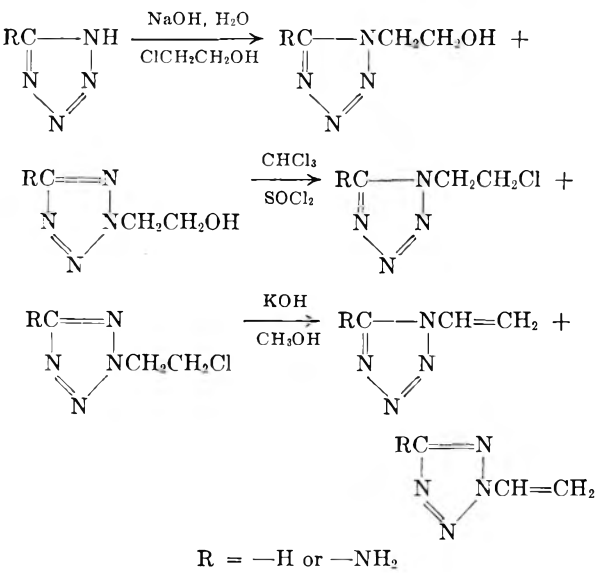
As part of a continuing program on the synthesis of new *N*-alkyl substituted tetrazoles,[1] the syntheses and polymerizations of the *N*-vinyltetrazoles, their 5-amino derivatives, and the *N*-allyltetrazoles were investigated.

The following sequence of reactions was employed for the syntheses of the *N*-vinyltetrazoles:



When tetrazole was employed as the starting material, the sequence of reactions was carried out as indicated and the 1- and 2-vinyltetrazoles were separated by distillation at reduced pressure. With 5-aminotetrazole, it was convenient to separate the isomers by crystallization at the hydroxyethyl stage[1] and convert these to the vinyl derivatives independently.

1- and 2-Allyltetrazoles were readily synthesized in moderate yields by direct alkylation of sodium tetrazole with allyl bromide in refluxing aqueous ethanol solution.

No attempts were made to bring the syntheses of the vinyl derivatives to optimum yields. It is anticipated, however, that vinylation with acetylene[2] would be the preferred approach.

In preliminary polymerization studies, the vinyltetrazoles and the vinyl-5-aminotetrazoles gave only insoluble-infusible homopolymers, regardless of whether solution or emulsion techniques were employed. The possibility of di-vinyl derivatives of tetrazole as impurities appears to be remote since di-*N*-alkylation of the tetrazole ring results in the formation of undistillable tetrazolium salts.[3] The insolubility of the vinyltetrazole polymers must be due either to strong molecular interactions between polymer chains, to ring involvement during free radical propagation, or possibly to involvement of the proton in the 5-position in the case of the 1- and 2-vinyltetrazoles. Limited attempts using chain transfer agents in solution polymerizations were more successful; initially soluble polymers were obtained with 1- and 2-vinyltetrazoles, but re-solution of the freshly precipitated and undried polymers gave solutions which jelled in a short time. The 1- and 2-allyltetrazoles could not be induced to homopolymerize, but would copolymerize with styrene and methyl methacrylate.[4]

Refractive indices and densities were measured and the molar refractivity of the tetrazole ring was calculated for each of the liquid tetrazoles. These data are shown in Table I.

TABLE I

INDICES AND DENSITIES OF LIQUID TETRAZOLES

Tetrazole	n_D^t	D_4^t	M_R Tetrazole Ring
1-Ethyltetrazole[a]	1.4602^{25}	1.12^{25}	12.7
2-Ethyltetrazole[a]	1.4366^{25}	1.07^{25}	12.7
1-Allyltetrazole	1.4854^{20}	1.12^{20}	12.6
2-Allyltetrazole	1.4670^{20}	1.08^{20}	12.7
1-Vinyltetrazole	1.5000^{20}	1.18^{20}	13.1
2-Vinyltetrazole	1.4850^{20}	1.13^{20}	13.4

[a] Synthesized for comparison by the method used for the syntheses of 1- and 2-allyltetrazoles. *Cf.* ref. (9) for physical constants.

EXPERIMENTAL[5]

Tetrazole. Tetrazole was prepared by diazotization of 5-aminotetrazole in the presence of hypophosphorous acid.[6] An improvement was made in the procedure[7] by extracting the tetrazole with ethyl acetate directly from the reaction

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(5) The melting points were determined in capillary tubes and are uncorrected.

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(7) This improvement is a variation of one suggested by James Moffat, University of Louisville, Louisville, Ky.

solution after neutralization to *p*H 3.5. A continuous extraction was used with an efficient stirrer to ensure thorough mixing of the two phases; and an efficient condenser to permit rapid cycling of the ethyl acetate. The yields of high purity tetrazole recovered from the ethyl acetate approached 98%.

1- and 2-(2-Hydroxyethyl)tetrazoles. A suspension of 140 g. (2.0 moles) of tetrazole in 300 ml. of distilled water was neutralized to a phenolphthalein end point with a solution of 82.5 g. (2.0 moles) of 97% sodium hydroxide in 300 ml. of water. The solution of sodium tetrazole was heated to reflux and 201 g. (2.5 moles) of 2-chloroethanol was added from an addition funnel over a 15-min. period. The resulting solution was refluxed for 18 hr. and then concentrated *in vacuo* on a steam bath to a sirupy mixture of products and sodium chloride.

The hydroxyethylated products were extracted from the sodium chloride with one 300-ml. and three 100-ml. portions of boiling acetone. Concentration of the acetone extracts *in vacuo* on a steam bath yielded 236 g. (theory 228 g.) of a mixture of 1- and 2-(2-hydroxyethyl)tetrazoles and other alkylated products. Attempts to separate the mixture by distillation at 1 mm. pressure were unsuccessful due to decomposition.

1- and 2-(2-Chloroethyl)tetrazoles. The mixture of 2-hydroxyethyltetrazoles (236 g.) from the preceeding section was slurried with 250 ml. of chloroform in a 2-liter, 3-necked flask. Thionyl chloride (300 g., 2.5 moles) was added dropwise with stirring while the temperature of the reaction mixture was maintained below 20° by immersing the flask in an ice bath. The cooling bath was then removed and the mixture was allowed to stir at room temperature for 24 hr. The reaction mixture became homogeneous during this time. The mixture was refluxed for 2 hr. to drive off hydrogen chloride and sulfur dioxide and then concentrated to a sirup at reduced pressure on a steam bath. After cooling to 5°, the sirup was treated with 100 g. of crushed ice, with stirring, to decompose thionyl chloride complexed with the tetrazoles. When the exothermic reaction was over, the excess ice was melted by warming the mixture on a steam bath and the chloroethyltetrazoles were extracted with three 100-ml. portions of chloroform. Evaporation of the chloroform solution left 265 g. of 1- and 2-(2-chloroethyl)tetrazoles as a yellow viscous oil. Separation of the isomers was possible at this point by distillation. Distillation of the chloroethyltetrazoles obtained from 3.8 moles of tetrazole yielded 154.3 g. (30.7%) of 2-(2-chloroethyl)tetrazole, b.p. 76° at 1 mm. The 1-(2-chloroethyl)tetrazole was not distilled, but could be using molecular distillation techniques.

1- and 2-Vinyltetrazoles. The 265 g. (*ca.* 2.0 moles) of chloroethyltetrazoles from the preceeding chlorination and 1 g. of hydroquinone were dissolved in 200 ml. of methanol in a 2-liter, 3-necked flask and the solution was heated to reflux.

A solution of 132 g. (2.0 moles) of 85% potassium hydroxide in 500 ml. of methanol was added dropwise with stirring over a 1-hr. period. Precipitation of potassium chloride began immediately. The reaction mixture was maintained at reflux temperature for 30 min. after the addition was complete. The methanol was then distilled at atmospheric pressure; stirring was continued to prevent bumping. After cooling the residue of vinyltetrazoles, water, and potassium chloride to room temperature, the vinyltetrazoles were extracted with three 100-ml. portions of methylene chloride. The methylene chloride solution was dried with anhydrous magnesium sulfate and an additional gram of hydroquinone was added to prevent polymerization. Distillation of the methylene chloride at atmospheric pressure left a residue of 1- and 2-vinyltetrazoles which was distilled at reduced pressure to yield: 38.6 g. (20.1%) of 2-vinyltetrazole, b.p. 66–68° at 60 mm.

Anal. Calcd. for $C_3H_4N_4$: C, 37.49; H, 4.19; N, 58.31. Found: C, 37.62; H, 4.60; N, 57.82.

and 70.6 g. (36.8%) of 1-vinyltetrazole, b.p. 94° at 1 mm.

Anal. Calcd. for $C_3H_4N_4$: C, 37.49; H, 4.19; N, 58.31. Found: C, 37.52; H, 4.42; N, 58.12.

Dehydrohalogenation of 154.3 g. (1.17 moles) of distilled 2-(2-chloroethyl)tetrazole by the same procedure yielded 78.0 g. (70%) of 2-vinyltetrazole. *Caution:* 2-Vinyltetrazole is capable of detonation by cavity impact at a drop height only slightly greater than that required for the detonation of nitroglycerin.[8]

The structure assignment of the lower boiling vinyltetrazole was established by catalytic dehalogenation of the preceeding 2-chloroethyltetrazole.

2-Ethyltetrazole. A mixture of 13.25 g. (0.1 mole) of 2-(2-chloroethyl)tetrazole, b.p. 76° at 1 mm., 13.8 g. (0.1 mole) of potassium carbonate, and 50 ml. of methanol was hydrogenated at 50 p.s.i. with 0.2 g. of 5% platinum-on-charcoal and 1 ml. of aqueous 5% palladium chloride for 18 hr. After filtration to remove solids, the solvent was removed by distillation leaving 9.48 g. of fluid oily residue. Distillation of the residue at reduced pressure yielded 6.42 g. (65.6%) of 2-ethyltetrazole, b.p. 72° at 37 mm. An authentic sample of 2-ethyltetrazole[9] was purified by distillation in the same apparatus, b.p. 72° at 37 mm. Comparison of the two samples using infrared and nuclear magnetic resonance spectroscopy confirmed their identity.

1-(2-Chloroethyl)-5-aminotetrazole. Thionyl chloride (150 ml.) was placed in a 500-ml. flask and cooled to 5° in an ice bath. 1-(2-Hydroxyethyl)-5-aminotetrazole[1] (45.4 g., 0.352 mole) was added portionwise with shaking and cooling to maintain the temperature below 20°. The mixture was then heated to reflux for 4 hr. Hydrogen chloride and sulfur dioxide were evolved and the mixture became homogeneous. The excess thionyl chloride was then removed *in vacuo* on a steam bath and the residue was treated (after cooling to room temperature) with 50 ml. of 95% ethanol to decompose complexed thionyl chloride. When the exothermic reaction had subsided, 50 ml. of water was added and the mixture was stripped to dryness at reduced pressure on a steam bath. The solid residue was dissolved in 250 ml. of boiling water, decolorized with charcoal, and the solution was cooled to 5° overnight. The yield of 1-(2-chloroethyl)-5-aminotetrazole amounted to 39.24 g. (75.7%), m.p. 150–151.5°.

Anal. Calcd. for $C_3H_6N_5Cl$: N, 47.46; Cl, 24.03. Found: N, 47.43; Cl, 24.40.

2-(2-Chloroethyl)-5-aminotetrazole. The chlorination of 78.5 g. (0.069 mole) of 2-(2-hydroxyethyl)-5-aminotetrazole[1] was accomplished in the same manner as that described for the 1-isomer. Recrystallization of the crude final product from benzene yielded 55.4 g. (61.8%) of 2-(2-chloroethyl)-5-aminotetrazole, m.p. 51–52°.

Anal. Calcd. for $C_3H_6N_5Cl$: N, 47.46; Cl, 24.03. Found: N, 47.71; Cl, 24.0.

1-Vinyl-5-aminotetrazole. A solution of 39.79 g. (0.27 mole) of 1-(2-chloroethyl)-5-aminotetrazole and 0.1 g. of hydroquinone in 150 ml. of methanol was heated to reflux. A solution of 18 g. (0.27 mole) of 85% potassium hydroxide in 100 ml. of methanol was then added dropwise with stirring over a period of 30 min. The reaction was refluxed for 1 hr. after the addition was complete and then cooled to 20°. After the precipitated potassium chloride was removed by filtration the solution was evaporated to dryness at reduced pressure on a steam bath. The residue of impure 1-vinyl-5-aminotetrazole was dissolved in a minimum of hot water and cooled, yielding 22.75 g. (0.247 mole) of 1-vinyl-5-aminotetrazole, m.p. 157–158°. An additional 2.30 g. was recovered by concentrating and cooling the mother liquors. The total of 26.05 g. represents an 86.8% yield.

(8) See F. P. Bowden, M. F. R. Culcahy, R. G. Vines, and A. Yoffee, *Proc. Roy. Soc. London*, **188**, 306 (1947) for a detailed discussion of the detonation of liquid explosives by cavity impacts.

(9) E. Oliveri-Mandala and T. Passalaqua, *Gass. Chim. Ital.*, **43**, II, 468 (1913).

Anal. Calcd. for $C_3H_5N_5$: C, 32.42; H, 4.54; N, 63.04. Found: C, 32.7, 32.5; H, 4.50, 4.72; N, 62.86.

Hydrogenation of 2.72 g. (0.098 mole) of 1-vinyl-5-aminotetrazole in glacial acetic acid at 50 p.s.i. using Adams platinum oxide as catalyst gave 2.70 g. (97.7%) of 1-ethyl-5-aminotetrazole, m.p. 149–150.5° after recrystallization from water. A mixture melting point with an authentic sample of 1-ethyl-5-aminotetrazole[10] was not depressed.

2-Vinyl-5-aminotetrazoles. The dehydrohalogenation of 40.47 g. (0.274 mole) of 2-(2-chloroethyl)-5-aminotetrazole was accomplished in the same manner as for the 1-isomer using potassium hydroxide in methanol. After evaporation of the methanol at reduced pressure, the crude product was extracted with three 50-ml. portions of methylene chloride. Distillation of the methylene chloride left 30 g. of oil which on distillation gave 23.39 g. (77.7%) of 2-vinyl-5-aminotetrazole, b.p. 75–77° at 0.8 mm., m.p. 47–49° after recrystallization from carbon tetrachloride. The melting point of a sample was unchanged by sublimation at reduced pressure.

Anal. Calcd. for $C_3H_5N_5$: C, 32.42; H, 4.54; N, 63.04. Found: C, 32.29; H, 4.65; N, 63.05.

1- and 2-Allyltetrazoles. A suspension of 70 g. (1.0 mole) of tetrazole in 400 ml. of 95% ethanol was neutralized to a phenolphthalein end point with a 50% aqueous solution of 41.2 g. (1.0 mole) of 97% sodium hydroxide. The suspension was heated to reflux, 121 g. (1.1 moles) of allyl bromide was added dropwise with stirring over a 10-min. period and the solution was refluxed overnight. The ethanol was then removed by distillation at atmospheric pressure and the residue was extracted with three 100-ml. portions of cold benzene. After drying the solution with anhydrous magnesium sulfate, the benzene was distilled at atmospheric pressure. The residue of mixed 1- and 2-allyltetrazoles was distilled at reduced pressures, yielding 36.3 g. (28.96%) of 2-allyltetrazole, b.p. 80–81° at 20 mm.

Anal. Calcd. for $C_4H_6N_4$: C, 43.62; H, 5.49; N, 50.89. Found: C, 43.51; H, 5.62; N, 51.22.

and 41.52 g. (37.36%) of 1-allyltetrazole, b.p. 101° at 1 mm.

Anal. Calcd. for $C_4H_6N_4$: C, 43.61; H, 5.49; N, 50.89. Found: C, 44.23; H, 5.45; N, 50.71.

1-Vinyl-4-methyl-5-iminotetrazole hydrochloride. 1-Vinyl-5-aminotetrazole (5.55 g., 0.05 mole) and 9.5 g. (0.055 mole) of redistilled methyl benzenesulfonate were mixed and heated on a hot plate in a small beaker. An exothermic reaction occurred when the temperature of the mixture reached about 100° and the beaker was removed from the hot plate. The reaction temperature rose spontaneously to 165°. After cooling, the mixture solidified. The product was dissolved in 50 ml. of methanol and made basic by the addition of 3.62 g. (0.055 mole) of potassium hydroxide in 25 ml. of methanol. The solution was then evaporated to dryness. The free base was extracted from the residue with three 50-ml. portions of chloroform and the insoluble potassium benzenesulfonate discarded. Evaporation of the chloroform solution yielded an oily yellow residue of 1-vinyl-4-methyl-5-iminotetrazole,[11] which was acidified with 5 ml. of concentrated hydrochloric acid. After the water was removed *in vacuo* on a steam bath, the 1-vinyl-4-methyl-5-iminotetrazole hydrochloride was recrystallized twice from 98% 2-propanol, yielding 2.56 g. (31.7%) of product, m.p. 214–215° (dec.).

Anal. Calcd. for $C_4H_8N_5Cl$: C, 29.73; H, 4.99; N, 43.35; Cl, 21.94. Found: C, 29.74; H, 5.73; N, 42.79; Cl, 21.73.

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(10) W. G. Finnegan, R. A. Henry, and Eugene Lieber, *J. Org. Chem.*, 18, 779 (1953).

(11) See R. A. Henry, W. G. Finnegan, and Eugene Lieber, *J. Am. Chem. Soc.*, 76, 2894 (1954) and R. M. Herbst and D. F. Percival, *J. Org. Chem.*, 19, 439 (1954) for proof of structures of analogous compounds.

Lucernic Acid, A New Triterpene from Alfalfa

ARVIN L. LIVINGSTON

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Interest in the possible toxic physiological activity of alfalfa (*Medicago sativa*) saponins in poultry and animal feeds has led to further investigation of these saponins and their aglycones. Recent manuscripts have described the isolation and characterization of medicagenic acid from the "cholesteride" saponins of alfalfa.[1,2] Further examination of the fractions obtained during the isolation of medicagenic diacetate has led to the isolation of a new triterpene, $C_{30}H_{46}O_7$, which is shown to be a trihydroxy, monolactone, monocarboxylic acid.

Characterization studies of this triterpene—now named lucernic acid[3]—demonstrated the presence of 3 easily acylable hydroxyl groups, as shown by the formation of the triacetate (II) at room temperature with pyridine–acetic anhydride. The infrared spectrum (KBr pellet) of II shows bands at 1775, 1730, and 1250 cm.$^{-1}$, corresponding to a 5-membered lactone, acetate, and C—O stretching adsorption. The presence of lactone was confirmed by the consumption of 5 equivalents (3 acetyls, a lactone, and a carboxyl) of alkali during saponification of II with 0.1*N* KOH in methanol; upon neutralization of the salt the lactone ring closed. II gives no color with tetranitromethane in glacial acetic acid or with the Liebermann-Burchard reagent and shows no high terminal ultraviolet adsorption.

Periodic acid oxidation of the methyl ester (III) resulted in the consumption of one equivalent of the reagent, thus demonstrating the existence of a 1,2-glycol moiety in lucernic acid.

Biogenetic relationship of I to triterpenes previously isolated from alfalfa[2,4] might lead one to expect a β-amyrin structure; present information, however, gives only very limited clues as to the location of the functional groups.

Final characterization of I will necessitate correlation with the structure of a known triterpene.

(1) C. Djerassi, D. B. Thomas, A. L. Livingston, and C. Ray Thompson, *J. Am. Chem. Soc.*, 79, 5292 (1957).

(2) E. D. Walter, G. R. Van Atta, C. R. Thompson, and W. D. Maclay, *J. Am. Chem. Soc.*, 76, 2271 (1954).

(3) Taken from the English term, lucerne, a common name for alfalfa.

(4) E. D. Walter, E. M. Bickoff, C. R. Thompson, C. H. Robinson, and C. Djerassi, *J. Am. Chem. Soc.*, 77, 4936 (1955).

EXPERIMENTAL

Lucernic triacetate. Preparation of the saponin,[2] sapogenin, and sapogenin acetate,[1] has been previously described. Purification was accomplished by chromatography of II on 37 times its weight of magnesia-silica gel. Elution of the chromatographic column with benzene-alcohol (95:5) and repeated crystallization from aqueous methanol gave platelets, m.p. 297–299° $[\alpha]_D^{26} = +7.7$ (*c*, 4.9),[5] which showed no high terminal adsorption in the U. V. and gave no color with either tetranitromethane in glacial acetic acid or the Liebermann-Burchard reagent.

λ_{max}^{KBr} 1775, 1730, 1250 cm.$^{-1}$ For analysis it was dried *in vacuo* at 130°.

Anal. Calcd. for $C_{36}H_{52}O_{10}$: C, 67.0; H, 8.1; CH_3CO, 20.0, neutral eq. 644. Found: C, 67.0; H, 8.1; CH_3CO, 20.3, neutral eq. 637.

II was quantitatively saponified with 0.1*N* alkali in methanol.

Anal. Calcd. for 5 equivalents per mole (3 acetyls, 1 carboxyl, and 1 lactone) and the consumption of 0.378 meq. of alkali. Found: 0.388 meq. alkali were consumed.

Methyl lucernate triacetate was prepared by treatment of an etheral solution of II with diazomethane. Recrystallization from aqueous methanol afforded rodlike crystals, m.p. 273–275°; $[\alpha]_D^{25} = -5.9°$ (*c*, 0.5).

$\lambda_{max}^{CCl_4}$ 1774, 1745 cm.$^{-1}$ $\lambda_{max}^{CS_2}$ 1235 cm.$^{-1}$ max

Anal. Calcd. for $C_{37}H_{54}O_{10}$. C, 67.5; H, 8.22; CH_3O, 4.71; CH_3CO, 19.6; mol. wt. 658. Found: C, 67.4; H, 8.32; CH_3O, 4.55; CH_3CO, 19.4; mol. wt. (Rast) 646.

Lucernic acid. Refluxing of II with 0.1*N* KOH in methanol, followed by neutralization, gave amorphous sapogenin. I proved to be almost insoluble in most organic solvents and could not be crystallized. $[\alpha]_D^{25} = +12.4°$ (pyridine) (c, 0.6).

λ_{max}^{KBr} 3155, 1745, 1704 cm.$^{-1}$

Anal. Calcd. for $C_{30}H_{46}O_7$: C, 69.2; H, 8.88. Found: C, 69.2; H, 8.86.

Methyl lucernate. Treatment of a suspension of I with diazomethane in ether gave crystalline III. Recrystallization from aqueous methanol afforded rodlike crystals, m.p. 347–350° $[\alpha]_D^{25} = +25.5°$ (*c*, 0.4).

λ_{max}^{KBr} 1758, 1724 cm.$^{-1}$

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.9; H, 9.02; CH_3O, 5.82. Found: C, 69.9; H, 9.13; CH_3O, 5.71.

Periodic oxidation of methyl lucernate. 50 mg. of III was dissolved in 4 ml. absolute alcohol. To this solution was added 1 ml. of 0.63M H_5IO_6. The solution was left in the dark at room temperature and analyzed periodically by the standard As_2O_3 technique.

Anal. Calcd. for 1 glycol, or consumption of 0.0866 × 10^{-3} moles periodate. Found: 0.0833 × 10^{-3} moles of periodate were consumed.

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(5) All melting points were made on a Kofler block. Unless noted otherwise, rotations were measured in chloroform solution.

Organophosphorus Compounds. V.[1] Dialkyl Phosphorofluoridates

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Received March 24, 1959

Dialkyl phosphorofluoridates were first prepared in 1932 by Lange and Krueger[3] using silver phosphorofluoridate and alkyl iodide. They also observed the high toxicity of the compounds. Schrader[4,5] later elaborated a synthesis using halogen exchange of the corresponding dialkyl phosphorochloridates. McCombie and Saunders[6,7] also worked out this reaction independently. Chapman and Saunders[8] reacted phosphorus oxydichlorofluoride with alcohols to prepare dialkyl phosphorofluoridates.

We found considerable difficulty in the preparation of phosphorus oxydichlorofluoride as the main product, using the Swarts reaction.[9] Therefore, we investigated the use of the more readily available phosphorus oxyfluoride.

Phosphorus oxyfluoride was prepared by the Swarts reaction from phosphorus oxychloride without using antimony pentachloride catalyst with 94% yield (and 5% phosphorus oxydichlorofluoride).

$$POCl_3 + SbF_3 \longrightarrow POF_3 + SbCl_3$$

Similarly phosphorus oxyfluoride can be prepared from phosphorus oxybromide, according to Booth and Seegmiller.[10]

$$POBr_3 + SbF_3 \longrightarrow POF_3 + SbBr_3$$

During the course of our investigation we prepared dimethyl, diethyl, and diisopropyl phosphorofluoridate (DFP) from phosphorus oxyfluoride and the corresponding alcohols.

$$POF_3 + 2\ ROH \longrightarrow (RO)_2\ POF + 2\ HF$$

The HF was removed from the DFP before distillation by neutralization with dry ammonia or was bonded with pyridine.

There have been described the preparation of dialkyl phosphorochloridate under acid free conditions through the chlorination of dialkyl phosphite with *N*-chlorosuccinimide.[11] Previously,[12] we obtained dialkyl phosphorochloridates as acid

(1) Part IV, *Ann.*, **625**, 92 (1959).

(2) Present address: Research Department, Imperial Oil Limited, Sarnia, Ontario, Canada.

(3) W. Lange and G. Krueger, *Ber.*, **65**, 1598 (1932).

(4) G. Schrader, German Patent **767,153**.

(5) BIOS Final Report 714; G. Schrader, *Die Entwicklung neuer Insektizide auf Grundlage organischer Fluor- und Phosphor-Verbindungen*, Verlag Chemie, Weinheim, W. Germany, 1951.

(6) H. McCombie and B. C. Saunders, *Nature*, **157**, 287 (1946).

(7) B. C. Saunders, *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine*. Cambridge University Press, 1957.

(8) N. B. Chapman and B. C. Saunders, *J. Chem. Soc.*, 1010 (1948).

(9) H. S. Booth and F. B. Dutton, *J. Am. Chem. Soc.*, **61**, 2937 (1939).

(10) H. S. Booth and C. G. Seegmiller, *J. Am. Chem. Soc.*, **61**, 3120 (1939).

(11) H. Goldwhite and B. C. Saunders, *J. Chem. Soc.*, 2040 (1955).

(12) G. Olah, A. Pavlath, and G. Hosszang, *Acta Chim. Hung.*, **8**, 41 (1955).

free products from the reaction of sodium alcoholate and phosphorus oxychloride in toluene. Using a similar method dialkyl phosphorofluoridates were also now prepared from phosphorus oxyfluoride and sodium alcoholates.

An advantage of the method described herein is the complete absence of any chlorine containing compounds. Since phosphorus oxyfluoride can be prepared with excellent yield the described method seems to be generally applicable for the preparation of any dialkyl phosphorofluoridates.

EXPERIMENTAL

Phosphorus oxyfluoride. Phosphorus oxychloride, 230 g. (1.5 mole) was placed in a four neck round bottom flask equipped with an efficient sealed mechanical stirrer, a feeder for antimony trifluoride powder, a thermometer, and a distillation column. The flask was then heated to 50°. The column was connected to a water cooled descending condenser and three traps cooled with ice water, dry ice–acetone, and liquid air. Antimony trifluoride 178.7 g. (1 mole) was added during 3 hr. to the reaction mixture while the temperature was maintained at 50–70°. The stirring mixture was then heated for an additional 2 hr. The reaction products distilled into the condenser system.

On redistilling the condensed products 20.5 g. phosphorus oxydichlorofluoride (5% based on SbF_3), b.p. 53° and 98 g. phosphorus oxyfluoride (94% based on SbF_3), b.p. −40° and a trace of phosphorus oxychlorodifluoride, b.p. +3° were obtained.

An analogous reaction, using phosphorus oxybromide was carried out in a similar manner, except that the further 2 hr. heating was carried out at 100°. Phosphorus oxyfluoride, b.p. −40° was again the main product. Phosphorus oxybromodifluoride (b.p. 30°) and phosphorus oxydibromofluoride (b.p. 110°) were also formed as low-yield products.

Dialkyl phosphorofluoridate from phosphorus oxyfluoride with alcohols. Diisopropyl phosphorofluoridate. (a) Absolute ether (250 ml.) was placed in a 500 ml. four neck round bottom flask equipped with a sealed mechanical stirrer, dropping funnel, thermometer, and feeding neck closed with a calcium chloride tube. The flask was cooled in a dry ice–acetone mixture. To the cooled ether solution 26 g. (0.25 mole) of phosphorus oxyfluoride, and then, with continuous stirring and cooling 30 g. (0.5 mole) of isopropyl alcohol were added. After the addition of the isopropyl alcohol was complete, the temperature of the solution was allowed to reach 20° and dry ammonia gas was introduced until the reaction mixture was neutral to litmus. The ammonium fluoride which separated was removed by filtration. The ether was stripped from the system and the product distilled to give 30.8 g. (67%) diisopropyl phosphorofluoridate, b.p. 60–61°/10 mm.

Anal. Calcd. for $C_6H_{14}FO_3P$: F, 10.32. Found: F, 11.0.

(b) A mixture of 60 g. (1 mole) of isopropyl alcohol and 250 ml. of ether was placed in a four-necked round-bottomed flask equipped with a sealed mechanical stirrer, gas inlet tube, dropping funnel, and thermometer. The solution was cooled with a dry ice–acetone mixture and then 52 g. (0.5 mole) of phosphorus oxyfluoride was added with stirring and cooling. The phosphorus oxyfluoride dissolved instantly. Anhydrous pyridine, 79 g. (1 mole) was added to the solution at about −40°. After the addition of the pyridine was complete, the mixture was allowed to reach room temperature about 20° while stirring was continued. When the stirring was stopped, the reaction mixture separated in two phases. The lower pyridine layer was discarded and the upper ethereal layer was distilled. After removing the ether, diisopropyl phosphorofluoridate (84.5 g., 93%) b.p. 60–61°/10 mm. was obtained.

Anal. Found: F, 10.6.

Diethyl phosphorofluoridate was similarly prepared according to method (b). The yield was 89%, b.p. 48–49°/10 mm.

Anal. Calcd. for $C_4H_{10}FO_3P$: F, 12.18. Found F, 12.4.

Dimethyl phosphorofluoridate was also obtained with method (b) in a similar way. Yield 91%, b.p. 58–59°/20 mm.

Anal. Calcd. for $C_2H_6FO_3P$: F, 14.85. Found: F, 14.65.

Dialkyl phosphorofluoridate from phosphorus oxyfluoride with sodium alcoholates. Diisopropyl phosphorofluoridate. In a four neck round bottom flask, equipped as described previously 50 ml. of toluene was added. The flask was cooled in CO_2-acetone and then 26 g. (0.25 mole) phosphorus oxyfluoride was condensed into the cold toluene. To this mixture a sodium isopropylate suspension, prepared by using 11.5 g. (0.5 mole) sodium and 30 g. (0.5 mole) isopropyl alcohol in 200 ml. toluene, was added with efficient stirring and Dry Ice–acetone cooling. Thereafter, the mixture was allowed to reach room temperature with continuous stirring. The separated sodium fluoride was removed by filtration and the filtrate was distilled yielding 27 g. (58%) of diisopropyl phosphorofluoridate, b.p. 82–85°/20 mm.

Anal. Calcd. for $C_6H_{7}FO_3P$: F, 10.32. Found: F, 10.45.

Dimethyl phosphorofluoridate was similarly prepared by the adding the equimolar quantity of sodium methylate as a methanolic solution to the phosphorus oxyfluoride solution. The yield was 77%, b.p. 58–60° at 20 mm.

Anal. Calcd. for $C_2H_6FO_3P$: F, 14.84. Found: 14.6.

Diethyl phosphorofluoride was prepared according to the preparation of dimethyl phosphorofluoridate. In a manner described in the previous example 0.2 mole of sodium ethylate in alcoholic solution was added to 10.4 g. (0.1 mole) phosphorus oxyfluoride also in alcohol with dry ice–acetone cooling. On working up the reaction mixture 12.5 g. (80%) diethyl phosphorofluoridate, b.p. 47–49°/10 mm., was obtained.

Anal. Calcd. for $C_4H_{10}FO_3P$: F, 12.18. Found: F, 12.0.

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Preparation of Pyridinedicarboxylic Acid *N*-Oxides

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Although the pyridinecarboxylic acid *N*-oxides and several substituted pyridinecarboxylic acid *N*-oxides are known[1–7] and were prepared, in most cases, by the usual peracid oxidation of the pyridinecarboxylic acid, none of the corresponding pyridinedicarboxylic acid *N*-oxides are reported.

(1) O. Diels and K. Alder, *Ann.*, **505**, 103 (1933).
(2) O. Diels and H. Pistor, *Ann.*, **530**, 87 (1937).
(3) E. Ghigi, *Ber.*, **75**, 1318 (1942).
(4) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, S133 (1949).
(5) G. R. Clemo and H. Koenig, *J. Chem. Soc.*, S231 (1949).
(6) E. C. Taylor, Jr., and A. J. Crovetti, *J. Org. Chem.*, 19, 1633 (1954).
(7) E. C. Taylor, Jr., and A. J. Crovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956).

Initial attempts to prepare 2,6-pyridinedicarboxylic acid *N*-oxide by peracetic or performic acid oxidation of 2,6-pyridinedicarboxylic acid led to recovery of unreacted dicarboxylic acid, even when large excesses of peracid at elevated temperatures were used.[8] 2,5-Pyridinedicarboxylic acid also was unreactive to *N*-oxide formation by peracetic acid, although a small yield of *N*-oxide was isolated in one experiment when a 40-fold excess of peracid was used at 80–100°. These results might have been anticipated in the light of patents[9] which describe the use of 2,5- and 2,6-pyridinedicarboxylic acids as stabilizers for hydrogen peroxide, persulfuric and peracetic acids, although it was not demonstrated whether the stabilizing action was due to the pyridine diacid or the *N*-oxide.

2,5- and 2,6-Pyridinedicarboxylic acid *N*-oxide were prepared in good yields by oxidizing the sodium salts of the dicarboxylic acid in water–acetic acid solution with peracetic acid. Structures of the *N*-oxides were indicated by analyses and by decarboxylation to the known nicotinic and picolinic acid *N*-oxides. Although excess acetic acid was present, the relatively high dissociation constant[10] of the first carboxylic acid group of the pyridine diacid ensures that the species being oxidized was the mono-salt, probably in equilibrium with the disalt.

The low reactivity of the pyridine diacids toward electrophilic attack on the nitrogen atom is at least in part due to steric hindrance and/or Zwitterion formation, but an additional effect is the accumulation of electron withdrawing substituents on the pyridine nucleus, a phenomenon observed also by Taylor and Crovetti.[7] It is suggested that all the above effects are removed or minimized by oxidizing the diacid as the mono- or disodium salt.

EXPERIMENTAL

2,6-Pyridinedicarboxylic acid, 2,5-pyridinedicarboxylic acid monohydrate and picolinic acid *N*-oxide were obtained from Aldrich Chemical Co.; melting points are uncorrected.

2,6-Pyridinedicarboxylic acid N-oxide. 2,6-Pyridinedicarboxylic acid (5.01 g., 0.03 mole) was dissolved in 45 g. of 6.67% aqueous sodium hydroxide, and to this was added 10 g. of 45% peracetic acid in acetic acid, concurrently with 20 g. 10% aqueous sodium hydroxide. After heating at 60° for 1 hr. an additional 5 g. peracetic acid solution was added and the solution was warmed on the steam bath for 1 hr. The solution was cooled, acidified with conc. HCl, and filtered, and the white crystals were dried to yield 4.0 g. (73% yield) of 2,6-pyridinedicarboxylic acid *N*-oxide, m.p. 155–157°. Mixed m.p.'s with 2,6-pyridinedicarboxylic acid and with picolinic acid *N*-oxide were depressed (146° and 116°, respectively).

Anal. Calcd. for $C_7H_7O_5N$: C, 45.91; H, 2.75; N, 7.65; acid equiv., 91.5. Found: C, 45.54; H, 3.06; N, 7.94; acid equiv., 93.

The decarboxylation of 2,6-pyridinedicarboxylic acid *N*-oxide was accomplished by immersing a test tube containing the *N*-oxide (4.0 g.) in a bath held at 155°; as the contents melted, vigorous gas evolution was observed and the temperature rose to 163°. After 4 min., the test tube was cooled. The resulting solid mass was dissolved in hot methanol and filtered while hot, and the filtrate was allowed to cool. The crystals obtained were recrystallized again from methanol, m.p. and mixed m.p. with authentic picolinic acid *N*-oxide, 153–154°.

2,5-Pyridinedicarboxylic acid N-oxide. Conditions similar to those for oxidation of 2,6-pyridinedicarboxylic acid were used; 15.0 g. of 2,5-pyridinedicarboxylic acid monohydrate gave 14 g. (86%) 2,5-pyridinedicarboxylic *N*-oxide as light tan crystals, m.p. 241–244°, mixed m.p. with starting material, 216–218°.

Anal. Calcd. for $C_7H_5O_5N$: C, 45.91; H, 2.75; N, 7.65; acid equiv. 91.5. Found: C, 46.08; H, 3.20; N, 7.73; acid equiv., 91.9.

The decarboxylation of 2,5-pyridinedicarboxylic acid *N*-oxide was accomplished by heating the above product in ethylene glycol at 150° for 30 min., to give nicotinic acid *N*-oxide, m.p. 246–248° (methanol). Mixed m.p.'s of this product with starting dicarboxylic acid *N*-oxide and with nicotinic acid (m.p. 234°) were depressed (199–208° and 187–230°, respectively). Acid equiv.: calcd. for $C_6H_5O_3N$: 139; found: 143.

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(8) We are indebted to Mr. P. S. Starcher of this department for these observations.

(9) F. P. Greenspan and D. G. MacKellar, U. S. Patent 2,609,391 (Sept. 2, 1952); F. P. Greenspan, U. S. Patent 2,624,655 (Jan. 6, 1953); F. P. Greenspan and D. G. MacKellar, U. S. Patent 2,663,621 (Dec. 22, 1953).

(10) V. D. Canic, *Ber. Chem. Ges. Belgrad*, **20**, 29 (1955), as reported in *Chem. Zentr.* **128**, 381 (1957).

Rearrangement of 4-Amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine in Basic Solution[1]

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Received March 26, 1959

When 4-amino-6-chloro-1-methylpyrazolo(3,4-d)-pyrimidine (I)[4] was refluxed in dilute alkaline solution, the expected 4-amino-6-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (IV) was not obtained. Instead, the isomeric 6-amino-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (II) was formed in 68% yield. The product was identified by comparison of ultraviolet absorption spectra, as well as by the R_f values of authentic samples of both 4-amino-6-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine[4] and 6-amino-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine[4] previously prepared.

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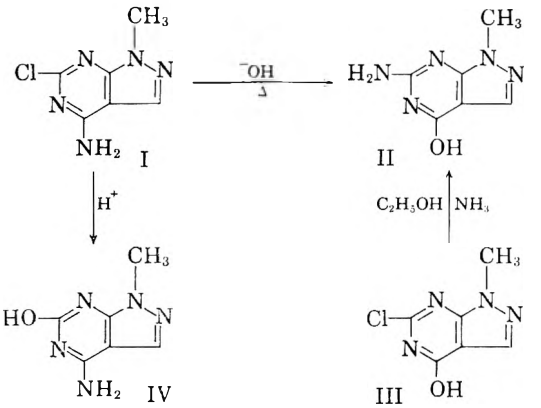
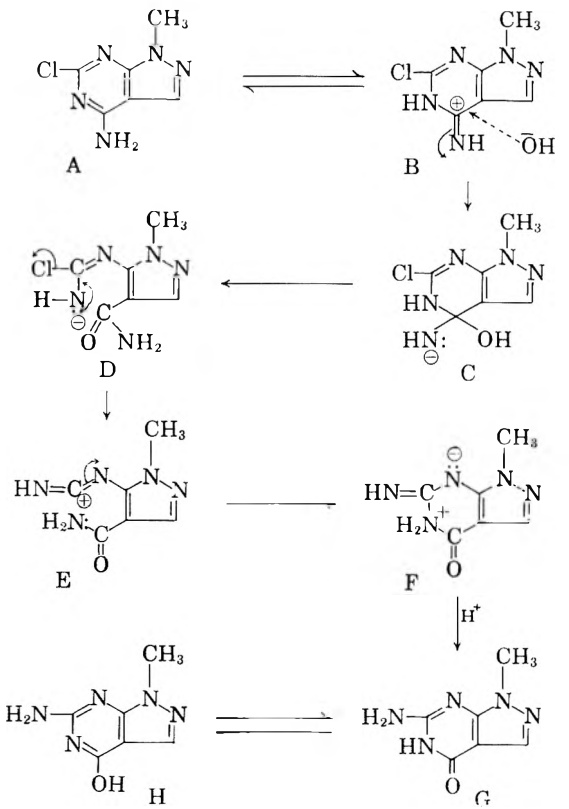
(4) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 852 (1958).



A theoretical mechanism for this rearrangement involves a ring opening followed by ring closure as follows:



This type of rearrangement has previously been noted in the purine series. Fischer[5] observed that 6-amino-2-chloro-7-methylpurine (isomeric to I) rearranged in basic medium to give 7-methylguanine. It is interesting to note that in Fischer's case, although the 7-methyl group exerts a steric interference to the nearby amino group, the rearrangement was not influenced since the initial nucleophilic attack was at the *carbon* atom in the 6 position.

No rearrangement was observed in acid medium. When 4 - amino - 6 - chloro - 1 - methylpyrazolo-(3,4-d)pyrimidine (I) was refluxed in hydrochloric acid, the expected 4-amino-6-hydroxy derivative (IV) was obtained.

(5) E. Fischer, *Ber.*, **31**, 542 (1898).

EXPERIMENTAL

4-Amino-6-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (IV). This compound was prepared from 4-amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine and concentrated hydrochloric acid as previously described.[4] The ultraviolet absorption spectra of this compound at *p*H 1 are 234 mμ (log ε = 4.10) and 251 mμ (log ε = 4.19); at *p*H 11.6, 247 mμ (log ε = 4.28) and 269 mμ (log ε = 4.11). The R_f value of the compound measured at 23° using *n*-propyl alcohol–1% ammonium hydroxide (2:1, volume ratio) is 0.55 (descending method). (Absorption spot was measured on Whatman #1 paper.)

6-Amino-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (II). This compound was prepared from 6-chloro-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine and ethanolic ammonia as indicated in a previous paper.[4] The ultraviolet absorption spectra of this compound at *p*H 1 is 251 mμ (log ε = 4.34); at *p*H 11.6, 267 mμ (log ε = 4.29). The R_f value of the compound measured under the same conditions as for IV is 0.64.

Action of sodium hydroxide on 4-amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine. Five g. of finely powdered 4-amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine was added to 400 ml. of boiling water. To this suspension was added 20 ml. of 30% sodium hydroxide. The mixture was vigorously refluxed for 1 hr. The hot, clear solution was acidified with acetic acid. The white precipitate was filtered and re-dissolved in dilute hydrochloric acid, followed by reprecipitation with ammonium hydroxide. It was recrystallized from dimethyl formamide to give 3.1 g. (68%) of a white solid, m.p. >300°. The R_f value of this compound, measured under the same conditions as for IV, was identical with that of 6-amino-4-hydroxy-1-methylpyrazolo-(3,4-d)pyrimidine (II) prepared by the above procedure. The ultraviolet absorption spectra measured at *p*H 1 and *p*H 11.6 are also identical.

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: (dried at 135° *in vacuo* for 6 hr.) C 43.3; H, 4.5; N, 42.4.

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Amylsodium, Triethyl Amine, Sodium Hydroxide and the Metalation of Cumene[1]

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A previous paper[2] reported that the association of triethyl amine and sodium hydroxide (sodium chloride also was present) with amylsodium changed the polymerization of butadiene from a 1,2- to a

(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) A. A. Morton and F. K. Ward, *J. Org. Chem.*, **24**, 929 (1959).

1,4-process. This effect resembled alfin catalysis[3] where sodium isopropoxide and sodium chloride were associated with allylsodium. These added compounds must affect critically either the sodium reagent or the hydrocarbon, and one way to judge is to test another hydrocarbon in some other reaction. Accordingly, cumene was chosen because it is a key compound; it contains aromatic, primary and tertiary hydrogens, the last being attacked easily by free carbyls. Also, its alkyl group has steric and directive influences. Should the triethyl amine and sodium hydroxide alter the kind of reaction with cumene, their influence might be general —affecting the character of amylsodium itself; but if the type of reaction were unchanged, these compounds could reasonably have had a special influence upon the diene hydrocarbon so that its reaction, but not that of cumene, was changed. The latter proved to be the case.

The experiment began by preparing amylsodium from amyl chloride and sodium.[4] Then successively water (to form sodium hydroxide *in situ*), the amine, and cumene were added. After an alloted time the mixture was carbonated. The carboxylic acids were separated and in some cases were oxidized[5] in order to determine the positions metalated. Control tests in the absence of the hydroxide and of both the hydroxide and amine were made.

The results (Table I) show that the amine and sodium hydroxide reduced the percentage of total carboxylic acids, but that effect is one of degree and would be expected because another paper[6] will show that these compounds accelerate the decomposition of amylsodium. Within experimental error, however, the kind of metalation was unchanged; the distribution of the products at the various positions remained the same.

This behavior contrasts with the numerous tests upon butadiene. Therefore, the influence of the two added compounds can be interpreted as involving in some way the butadiene, so that its manner of chain growth was much less a 1,2-process. That effect might seem remarkable because the amine and the sodium hydroxide should enhance the polarity of the medium and, therefore, should cause more 1,2-polymerization (if any change occurred), that type of chain growth being credited[7] as symbolic for anionic polymerization; but the view adopted in this laboratory has been that these active organosodium salts can function as radical pairs[3,8] and that the added compounds, possibly by complexing with, or orienting of, monomer, can favor 1,4-polymerization.

TABLE I

YIELDS OF CARBOXYLIC ACIDS OBTAINED FROM THE METALATION OF CUMENE BY AMYLSODIUM UNDER A VARIETY OF CONDITIONS

Acids	Amylsodium with: No added compounds	Triethyl amine	Amine and hydroxide[a]
Total carboxyl,[b] %	85	67	16
Distributed as			
Caproic,[c] %	12	10	6
Isophth.,[d] %	29	30	31
Para-bz.,[e] %	52	53	56
Meta-bz.,[f] %	1	3	1

[a] Triethyl amine and sodium hydroxide. [b] The total percentage yield is calculated on the amyl chloride used in making amylsodium. The yield of formic acid, which would arise from decomposition of amylsodium to sodium hydride, is not included in this determination. [c] Caproic acid represents unchanged amylsodium. [d, e] and [f] represent successively 5-isopropylisophthalic acid, *p*-isopropylbenzoic acid and *m*-isopropylbenzoic acid.

This work also adds another example to a long list of fruitless attempts to metalate the isopropyl group with sodium reagents. Monometalation of either cumene[9] or 1,3-diisopropylbenzene[10] took place on the ring. In dimetalations the second sodium atom entered the ring in *m*-cumenylsodium[11] and *p*-isopropylbenzylsodium[11b] rather than replaced the tertiary hydrogen. *p*-Cumenylsodium[11a] resisted further metalation by amylsodium although a parallel reaction with *n*-butylbenzene[11b] showed no difficulty in a lateral attack. 2,6-Diisopropylanisole,[10] where an adjoining methoxy should favor metalation on the alkyl group (it did so when the alkyl group was methyl[12,13]), was metalated instead on the distant para position. 2,4,6-Trimethoxybenzene[12] was cleaved to a phenol instead of being metalated.

This resistance to metalation affects the interpretation of another reaction of cumene, namely, its alkylation with ethylene in the presence of organosodium compounds as promoters. That re-

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(5) D. Bryce-Smith and E. E. Turner, *J. Chem. Soc.*, 861 (1953); D. Bryce-Smith, *J. Chem. Soc.*, 1079 (1954).

(6) A. A. Morton and F. K. Ward, *J. Org. Chem.*, **24**, in press (1959).

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action has been pictured[14] as progressing through the intermediate phenyldimethyl carbanion, $C_6H_5C(CH_3)_2^-$, which adds to ethylene to form a new carbanion, $C_6H_5C(CH_3)_2CH_2CH_2^-$, which, in turn, abstracts a tertiary hydrogen from cumene to maintain the chain, while forming the final hydrocarbon, *t*-amylbenzene. With sodium reagents however, this alkylation should be on the nucleus instead of the tertiary carbon, because the carbanion is on the nucleus. Alkylation of *p*-cymene also should occur at the methyl group, because that position alone is metalated by either sodium[9b] or potassium[15] reagent, yet alkylation occurred at the isopropyl group.[14a] The above mechanism, therefore, can scarcely be correct.

The facts are beautifully accommodated, however, to the view of biradical activity along the lines used to explain alfin catalysis.[3] At first, ethylene coordinates with the cation of the promoter, $Na^+{}^-R$, to give the complex salt, $[C_2H_4{\rightarrow}Na]^+{}^-R$. Next, dissociation to two radicals, Na· and ·R, occurs. Then the carbyl removes the tertiary hydrogen from cumene to give $C_6H_5C(CH_3)_2\cdot$ in a process typical for radicals, while atomic sodium converts the adjacent olefin into an anion-radical, $Na^+{}^-CH_2CH_2\cdot$. Finally, the two radicals unite to form an end salt product, $Na^+{}^-CH_2CH_2$-$(CH_3)_2CC_6H_5$, which serves as the promoter to start the cycle again and to form *t*-amylbenzene. The several steps are closely consecutive or almost simultaneous. In its fine detail the process provides good evidence for radial pair (atomic metal and carbyl)[3,8] activity rather than serves as an example of carbanion chemistry.

EXPERIMENTS

Metalation of cumene. In three experiments amylsodium was prepared in heptane from 1 g. atom of sodium sand and 0.5 mole of amyl chloride in the customary way.[4,12] To one preparation a mole of cumene was added. To a second was added one mole of cumene and 1.5 mole of triethyl amine which previously had been dried over amylsodium. To the third was added 4 ml. (0.22 mole) of water, followed by one mole of triethyl amine and 0.5 mole of cumene. Each mixture was heated quickly to 70° and kept there for 3 hr., with stirring at 10,000 r.p.m. After being cooled to room temperature, the contents were forced into a 4-liter Erlenmeyer flask filled to a quarter of its depth with powdered carbon dioxide. The reaction flask was rinsed twice with 200 ml. of heptane which likewise was carbonated.

The next day 300 ml. of water was added to dissolve the salts. When both layers had cleared the hydrocarbon portion was separated and extracted with 50 ml. of 10% aqueous sodium hydroxide, followed by 50 ml. of water. Next, the combined aqueous layer and extracts were extracted with four 150-ml. portions of ether, after which the aqueous portion was acidified with 50% (by volume) sulfuric acid. A white precipitate which appeared and the solution were extracted with four 150-ml. portions of ether. The ether extract was dried over Drierite, filtered and made up to 500 ml., from which a 5-ml. aliquot was titrated in order to determine the total carboxylic acid.

The ether solution was evaporated to about 50 ml. and 200 ml. of petroleum ether was added. Overnight, 5-isopropylisophthalic acid precipitated. It was washed, dried, weighed and recorded as dimetalated product. After being crystallized from ethanol-water, it was identified by its neutralization equivalent, 107 (calcd. 104), its melting point, 282–285° (lit.[16] 285°), the melting point of its dimethyl ester, 64–65° (lit.[11] 64–65°), and a mixed melting point with an authentic sample.

The petroleum ether decantate was evaporated to one-half its volume and cooled. The first crop of crystals had the correct neutralization equivalent for *p*-isopropylbenzoic acid and melted at 115–117° (lit.[9] 116–118°). Its amide melted at 152–153° (lit.[17] 153°).

The remaining petroleum ether in the mother liquor was evaporated and the acid residue was fractionated to remove caproic acid (b.p. 60°/4 mm.). An aliquot (1.5 g.) from the acid residue was oxidized with chromium trioxide according to the method developed by Bryce-Smith and Turner[6] for determining the amount of *m*-isopropylbenzoic acid and α-phenylisobutyric acid.

The yields calculated from these operations, with appropriate allowances for all samples removed, are recorded in Table I. They show that triethyl amine, and particularly triethyl amine with sodium hydroxide, decreased the amount of metalation of cumene. The loss is accounted for as decomposition of amylsodium,[1,8] although the formic acid was not measured. No product from metalation at the alpha carbon atom was observed.

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Transmetalation of Thiophene by the Ethylsodium-Diethylzinc Complex[1]

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In general, organosodium compounds will transmetalate with hydrocarbons if they can form an organometallic corresponding to a stronger acid. However, Morton and co-workers[3] have shown that this rule is not followed invariably (for example: Amylsodium metalates *t*-butylbenzene predominantly in the *para* position, but in the presence of sodium alcoholates *meta* metalation occurs preferentially). The mechanism of transmetalation is still the subject of discussion.[4] Its elucidation is made more difficult because sodium alkyls are insoluble in hydrocarbon solvents. Steric factors and

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(3) A. A. Morton, Ch. E. Claff, Jr., *J. Org. Chem.*, **21**, 736 (1956); A. A. Morton, Ch. E. Claff, Jr., Fr. W. Collins, *J. Org. Chem.*, **20**, 428 (1955).

(4) R. A. Benkeser, D. J. Foster, D. M. Sauve, J. F. Nobis, *Chem. Revs.*, **57**, 867 (1957).

changes in the polarization of bonds may create surface effects on the insoluble sodium alkyl aggregates which overrule the acidity influence.

A homogeneous system should greatly simplify a study of transmetalation reactions. As the complex formed by ethylsodium and diethylzinc is soluble in benzene,[5] its use as a metalating agent was attempted. For convenience a solution of the complex in diethylzinc was chosen which contained ethyl sodium and diethylzinc in a ratio of 1:1.84 and which could easily be prepared according to Hein.[6]

The complex, dissolved in benzene or 1,2-dimethoxyethane, metalated fluorene but not triphenylmethane at room temperature. Thus, the activity of the complex, relative to the hydrocarbon acidity series,[7] was intermediate between that of ethylsodium and diethylzinc. Complex formation does, therefore, decrease the activity of ethylsodium.

The complex seemed to be stable at room temperature, as a 2% solution in styrene did not give any visible signs of polymerization, which would be indicative of the presence of radicals according to Ziegler.[8] When the solution was warmed to 60°, a red color developed and the styrene was polymerized violently. This is in agreement with the thermal instability of the complex as reported by Wanklyn[5] and by Carothers and Coffman.[9] A transmetalation by the complex was attempted with thiophene which according to Schick and Hartough[10] cannot be metalated by sodium alkyls except in the presence of mercury, although Morton[11] has claimed lately that thiophene can be dimetalated by amylsodium in presence of sodium *t*-amylate.

On addition of the complex to thiophene a clear solution resulted, gas development began, and later two layers formed. After several hours the mixture was carbonated and thiophene-2-carboxylic acid was isolated in a 55% yield. The acidity rule predicted metalation by alkylsodium rather than by the less reactive complex. The separation of the solution into two phases suggested the formation of a compound of the complex with thiophene, which seemed to be responsible for the unexpected course of the reaction.

EXPERIMENTAL

Metalation of Fluorene by the Ethylsodium–Diethylzinc Complex. Fluorene, 0.248 g. (0.00149 mole), was treated with 0.408 g. of the ethylsodium–diethylzinc complex (containing 0.00145 mole NaC_2H_5) in 40 ml. of dry benzene under nitrogen at room temperature. Gas bubbles developed, and the solution became reddish orange. After 30 minutes the reaction mixture was carbonated by pouring into Dry Ice and ether, and worked up to give 0.125 g. (41.2%) of fluorene-9-carboxylic acid, m.p. 221–223°. A mixed melting point with an authentic sample of fluorene-9-carboxylic acid was not depressed.

The result was the same with 1,2-dimethoxyethane as solvent.

Diethylzinc did not affect fluorene under these conditions.

Reaction of the Ethylsodium-Diethylzinc Complex with Styrene. The complex (0.534 g., containing 0.0019 mole NaC_2H_5), dissolved in 20 ml. of freshly distilled styrene and kept under nitrogen at room temperature, gave no indication of reaction after 30 minutes. The flask was then heated to 60–65° with a water bath. At this temperature the solution became dark red and the styrene polymerized violently.

Metalation of Thiophene by the Ethylsodium-Diethylzinc Complex. The complex (2.99 g., containing 0.0106 mole NaC_2H_5) was dissolved in 25 ml. of dry thiophene under nitrogen at room temperature. Gas development was noted. After about 10 minutes a second phase, from which the gas bubbles appeared to originate, separated. After 4 hr. the reaction mixture was carbonated by pouring into Dry Ice and ether. 0.75 g. (55%) of thiophene-2-carboxylic acid was isolated, m.p. 127–128°. No depression of a mixed melting point with an authentic sample of thiophene-2-carboxylic acid was observed.

No reaction was observed between thiophene and diethylzinc under the same conditions.

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Synthesis of 4(5)-Imidazolylacetylcholine and 2-Pyridylacetylcholine

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The isolation from natural sources of β-[4(5)-imidazolyl]-acryloylcholine (murexine)[1,2] as well as the apparent isolation of 4(5)-imidazolylacetylcholine[3] from mammalian brain has led to numerous studies of the pharmacology of these choline esters as well as β-[4(5)-imidazolyl]-propionylcholine (dihydromurexine[4,5]). These compounds are potent ganglionic stimulants and neuromuscular blocking agents.[4] In order to study the pharmacology of

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(5) See references cited in footnote (4).

compounds of this type we have synthesized 4(5)-imidazolylacetylcholine[6] and 2-pyridylacetylcholine. The pharmacology of 2-pyridylacetylcholine was of special interest since β-(2-pyridyl)-propionylcholine had been shown to be the most potent of a series of heterocyclic analogues of murexine and dihydromurexine in causing contraction of the frog rectus abdominus muscle.[7]

The preparation of the intermediate β-bromoethyl esters of 4(5)-imidazoleacetic acid and 2-pyridineacetic acid and their conversion to the corresponding choline esters was similar to the reported syntheses of murexine and dihydromurexine.[7–9]

Details of the pharmacological properties of these compounds have already been published.[4,10–12] In summary, it may be stated that as neuromuscular blocking agents the order of decreasing potency is as follows: dihydromurexine, murexine, 4(5)-imidazolylacetylcholine, and 2-pyridylacetylcholine; while as ganglionic stimulants the order is changed only in that 2-pyridylacetylcholine is more active than 4(5)-imidazolylacetylcholine.

EXPERIMENTAL[13]

4(5)-Imidazoleacetic acid hydrochloride was prepared by the method of Bauer and Tabor[14] modified to avoid any possibility of ester formation. Steam was passed through a boiling solution of 60.4 g. (0.56 moles) of 4(5)-imidazoleacetonitrile[14] and 40.0 g. (1.00 mole) of sodium hydroxide for 1 hr. at the end of which time ammonia evolution had ceased. The solution was cooled and 115 ml. of concentrated hydrochloric acid was added and the mixture taken to dryness *in vacuo*. The residue was triturated with 800 ml. of warm concentrated hydrochloric acid and the solution filtered through a sintered glass funnel to remove sodium chloride. The filtrate was taken to dryness *in vacuo* to leave a residue of 90.4 g. (99%) of 4(5)-imidazoleacetic acid hydrochloride, m.p. 220–225° (lit.[14] m.p. 223°).

β-Bromoethyl 4(5)-imidazolylacetate. A solution of 9.9 g. of 4(5)-imidazoleacetic acid hydrochloride in 100 ml. of ethylene bromohydrin was saturated with anhydrous hydrogen chloride and slowly distilled over a period of 90 min. to remove 50 ml. of solvent. The addition of ether to the cooled solution gave an oil which was separated and dissolved in ice water. The aqueous solution was extracted with methylene chloride, made alkaline with ammonia, and the precipitate taken up in methylene chloride. The organic layer was dried over anhydrous potassium carbonate, the solvent removed and the residue triturated with ether to give 9.9 g. of the crude ester, m.p. 74–80°. After several recrystallizations from acetone-ether the melting point was constant at 88–90°.

Anal. Calcd. for $C_7H_9N_2O_2Br$: C, 36.07; H, 3.89; N, 12.88. Found: C, 36.04; H, 3.49; N, 12.52.

4(5)-Imidazolylacetylcholine. The crude β-bromoethyl ester (prepared from 9.9 g. of 4(5)-imidazoleacetic acid hydrochloride), was dissolved in 100 ml. of acetone, the solution cooled with dry ice, 40 ml. of cold anhydrous trimethylamine added, and the solution shaken in a pressure bottle for 22 hr. at 28° (20 p.s.i.). The viscous oil which separated was washed with acetone, dissolved in absolute ethanol, and the solvent removed *in vacuo* at room temperature to remove traces of trimethylamine. The crude 4(5)-imidazolylacetylcholine bromide (11.1 g.) was again dissolved in absolute ethanol and converted to the hydrobromide salt with anhydrous ethanolic hydrogen bromide. After seeding the solution and allowing it to stand overnight at room temperature, the crystals which had separated were triturated with 50 ml. of absolute ethanol and collected to give 4.8 g. (21%) of 4(5)-imidazolylacetylcholine bromide hydrobromide as colorless crystals, m.p. 183–185°. The product was too hygroscopic to be recrystallized but was stable in a dry atmosphere.

Anal. Calcd. for $C_{10}H_{19}N_3O_2Br_2$: C, 32.19; H, 5.13; N 11.26. Found: C, 32.25; H, 4.89; N, 11.26.

The dipicrate of 4(5)-imidazolylacetylcholine crystallized from water as yellow crystals, m.p. 199–200°.

Anal. Calcd. for $C_{22}H_{23}N_9O_{16}$: C, 39.46; H, 3.46; N, 18.84. Found: C, 39.59; H, 3.62; N, 19.01.

β-Bromomethyl 2-pyridylacetate. The crude lithium salt of 2-pyridineacetic acid was prepared[15] from 97 ml. of α-picoline and dissolved in 1 kg. of ethylene bromohydrin. Anhydrous hydrogen chloride was passed into the cooled solution for 1 hr. After standing at room temperature for 4.5 days the solution was diluted to 4 l. with methylene chloride and extracted twice with a small volume of cold water. The cold aqueous solution was washed with ether, made alkaline with ammonia, and extracted with ether. The ether extract was washed once with water and dried over anhydrous potassium carbonate. The ether and unreacted α-picoline were removed *in vacuo* finally using a rotary evaporator at 45° and 1.0–2.0 mm. pressure. The residue was taken up in anhydrous ether and the solution filtered to remove a small amount of insoluble material and again evaporated *in vacuo* to give 23 g. of the crude ester as a yellow oil. A portion of the oil gave the picrate salt of β-bromoethyl 2-pyridylacetate as yellow crystals from aqueous ethanol, m.p. 126–128°.

Anal. Calcd. for $C_{15}H_{13}BrN_4O_4$: C, 38.07; H, 2.77; N 11.84. Found: C, 38.34; H, 2.45; N, 11.32.

2-Pyridylacetylcholine bromide hydrobromide. A solution of 20.0 g. of crude β-bromoethyl 2-pyridylacetate in 100 ml. of acetone was cooled in dry ice, 40 ml. of anhydrous liquid trimethylamine added and the mixture shaken in a pressure bottle at 26° (20 p.s.i.) for 17 hr. The precipitate was collected and washed with acetone to give 17.5 g. of a hygroscopic solid. The latter was dissolved in absolute ethanol and the solution acidified with alcoholic hydrogen bromide and cooled to give 18.5 g. of colorless crystals which melted at 120–130° with gas evolution. Two recrystallizations from absolute ethanol gave colorless platelets, m.p. 130–135°, which lost solvent of crystallization upon drying in high vacuum at 78° for 2 hr. and finally at 110° overnight; yield, 11.5 g.; m.p. 169–170°.

(6) V. Erspamer and A. Glasser [*Brit. J. Pharmacol.*, 12, 176 (1957)] report that imidazolylacetylcholine is less potent than imidazolylpropionylcholine in its nicotinic and neuromuscular blocking actions. However, the authors do not describe the physical constants of imidazolylacetylcholine [see ref. (3)] and no reference to the synthesis of 4(5)-imidazolylacetylcholine could be found in the literature.

(7) C. Pasini, A. Vercellone, and V. Erspamer, *Gass. chim. ital.*, 86, 266 (1956).

(8) C. Pasini, A. Vercellone, and V. Erspamer, *Ann.*, 578, 6 (1952).

(9) A. Stempel, U. S. Patent 2,774,769, Dec. 18, 1956 [*Chem. Abstr.*, 51, 5841g (1957)].

(10) M. M. Winbury, *Nature*, 180, 988 (1957).

(11) M. M. Winbury, J. K. Wolf, and I. I. A. Tabachnick, *J. Pharmacol. Exp. Therap.*, 122, 207 (1958).

(12) A. A. Rubin, J. Mershon, I. I. A. Tabachnick, and W. M. Govier, *J. Pharmacol. Exp. Therap.*, 123, 104 (1958).

(13) All melting points are corrected.

(14) H. Bauer and H. Tabor, *Biochemical Preparations*, John Wiley and Sons, Inc., New York, 1957, Vol. 5, p. 97.

(15) R. B. Woodward and E. C. Kornfeld, *Org. Syntheses*, Coll. Vol. III, 413 (1955).

Anal. Calcd. for $C_{12}H_{20}Br_2N_2O_2$: C, 37.52; H, 5.25; N, 7.29. Found: C, 37.46; H, 5.05; N, 7.01.

Anhydrous 2-pyridylacetylcholine bromide hydrobromide was kept for long periods over anhydrous calcium chloride but it rapidly absorbed water in a moist atmosphere.

Acknowledgment. The authors are thankful to Dr. I. I. A. Tabachnick of the Pharmacology Department of Schering Corporation for his interest and kind advice with regard to the pharmacological aspects of this work, to Dr. H. Tabor of the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md., for a copy of his manuscript[14] in advance of publication, and to Mr. Edwin Conner and his associates of the Microanalytical Laboratories of Schering Corporation for the microanalyses reported herein.

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A Seven-Membered Heterocycle from *o*-Aminobenzenethiol and Chalcone[1]

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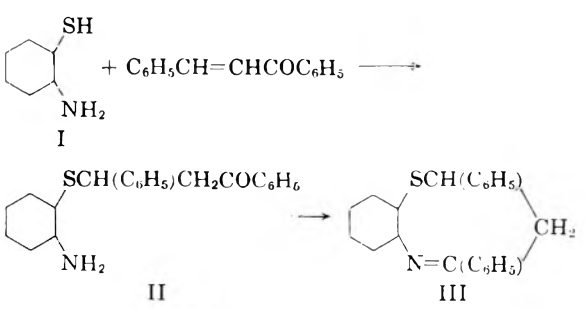
Herz and Tarbell found that the thiol group of a thiophenol could be blocked to permit operations elsewhere in the molecule by addition of the thiophenol to 3-nitrobenzalacetophenone, which subsequently could be removed.[2] When chalcone (benzalacetophenone)itself was used in essentially this procedure to protect the thiol group of *o*-aminobenzenethiol (I), prior to reactions of the amino group, two products were obtained. These proved to be the desired ketone (II) and a cyclized product (III).



Preparation of II (58% yield) could be achieved, however, by omitting acetic acid and using only piperidine in the procedure of Herz and Tarbell. Addition of acetic acid to the reaction mixture resulted in the isolation of the cyclized product (III) in 62% yield. Treatment of the isolated ketone II in methanol with acetic acid also converted it to III (78%).

The structures of II and III are supported by the elementary analyses and by the fact that II has a strong infrared-absorption band in the region expected for a carbonyl group, unlike III which lacks this band but has another in the region reasonably attributable to a C=N linkage. Further evidence is provided by the fact that since our work was completed Ried and Marx have demonstrated the same reactions with thiophene counterparts of chalcone; they reported the independent synthesis of a typical heterocyclic product.[3] It is interesting that the heterocyclic ring of III withstands the action of alkali, at least in water.

EXPERIMENTAL[4]

β-Phenyl-β-(o-aminophenylmercapto)propiophenone (II). Chalcone (5.00 g.) and *o*-aminobenzenethiol[5] (I, 3.00 g.) were dissolved in 50 ml. of boiling methanol. The heat was removed and piperidine (25 drops) was added. White needles of II precipitated upon cooling; yield, 4.64 g. (58%), m.p. 127–134°. Repeated recrystallization from hexane gave II with a constant m.p. of 134–135°. Strong infrared absorption at 1670 cm.$^{-1}$ is consistent with the presence of an aryl ketone linkage.

Anal. Calcd. for $C_{21}H_{19}NOS$: C, 75.64; H, 5.74. Found: C, 75.42; H, 5.59.

2,4-Diphenyl-6,7-benzo-1-thia-5-aza-4,6-cycloheptadiene (III). Chalcone (5.00 g.) and I (3.00 g.) were dissolved in 25 ml. of boiling methanol. The heat was removed and piperidine (25 drops) was added. After the mixture had cooled to room temperature, an additional 25-ml. portion of methanol was added and the slurry heated until all material dissolved. Glacial acetic acid (10 ml.) then was added and the mixture allowed to stand overnight at 25°. Yellow crystalline III separated which amounted to 4.70 g. (62%), m.p. 111.5–115°. This material was repeatedly recrystallized from *t*-butyl alcohol to a constant m.p. of 114–115°. Strong infrared absorption occurred at about 1613 cm.$^{-1}$ (C=N), which was absent in the spectrum of II, with no other appreciable absorption from 1613–2940 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{17}NS$: C, 79.95; H, 5.43. Found: C, 79.64; H, 5.31.

When 1.00 g. of the III was heated at 70° for 2 days with 50 ml. of 10% aqueous sodium hydroxide, 0.98 g. of III was recovered, m.p. and mixture m.p. 111–114.5°.

Conversion of II *to* III. A mixture of 0.50 g. of II and 25 drops of glacial acetic acid was heated in 10 ml. of methanol on a steam bath for 20 min. After standing overnight, the mixture was concentrated to about one-half volume; yield of III, 0.28 g. (59%), m.p. and mixture m.p. (with III as prepared above), 114–115°. A second crop of 0.09 g. (19%), m.p. and mixture m.p. 112–115°, brought the total yield to 78%.

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

(2) A. H. Herz and D. S. Tarbell, *J. Am. Chem. Soc.*, 75, 4657 (1953).

(3) W. Ried and W. Marx, *Chem. Ber.*, 90, 2683 (1957).

(4) Melting points are corrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn.

(5) Kindly provided by the American Cyanamid Company, New York, N. Y.

N-Bromosuccinimide. II. Allylic Bromination of Tertiary Hydrogens[1]

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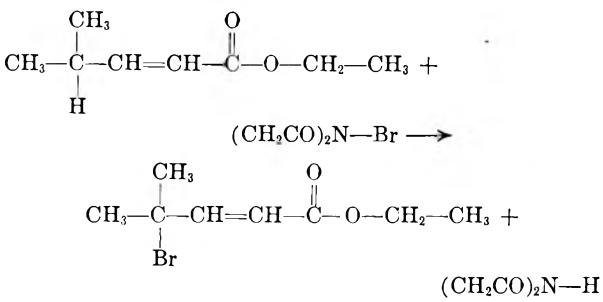
In a number of textbooks and reference books on organic chemistry it is stated that allylic brominations of tertiary hydrogens by NBS is not possible under Ziegler's original conditions (in refluxing carbon tetrachloride without irradiation or addition of initiators) but may be effected when initiators, such as benzoyl peroxide, are added; reference is usually made to the NBS review article by Djerassi,[3] to the paper of Schmid and Karrer in which they introduced the use of benzoyl peroxide,[4] or to the original paper by Ziegler and coworkers.[5] Careful perusal of the latter two papers indicates that this conclusion rests not on experimental grounds but, presumably, on a repeated, misconstrued statement in the original Ziegler paper.[3-5] Consequently, it was a matter of interest to determine if tertiary allylic hydrogens would undergo bromination by NBS under the original Ziegler reaction conditions. For this purpose, a study was made on the effect of environmental factors (preformed peroxides, light, oxygen) on the course and the reaction time of the reaction of NBS with ethyl 4-methyl-2-pentenoate, the same alkenic component used by Schmid and Karrer to demonstrate that benzoyl peroxide was needed to effect bromination of a tertiary allylic hydrogen. Previous studies[6] had clearly shown that these



environmental factors were responsible for initiation of the allylic bromination of the secondary allylic hydrogen in cyclohexene by NBS under the original Ziegler reaction conditions.

Ethyl 4-methyl-2-pentenoate when freshly distilled gives a negative test for peroxides but peroxidic impurities are formed, presumably by autoxidation, when this material is allowed to stand in a glass-stoppered bottle. Under the ordinary conditions (refluxing carbon tetrachloride, diffuse laboratory light, air access through top of condenser) stale ethyl 4-methyl-2-pentenoate reacts completely with NBS in <20 min. to give an 81% yield of ethyl 4-bromo-4-methyl-2-pentenoate (Table I, Run 1); with 0.5 mole % benzoyl peroxide Schmid and Karrer obtained, after several hours reflux, a 67% yield of the same product. When preformed peroxides or light are excluded, the reaction times are lengthened about 3-fold but the yields remain about the same (Table I, Runs 2 and 3); these results indicate that either preformed peroxides or light catalyze the allylic bromination of this tertiary hydrogen compound. When preformed peroxides and oxygen are both excluded, reaction times either in the presence or the absence of diffuse light are about the same and about 10-fold longer than for the ordinary run, and the yields are somewhat lower (Table I, Runs 4 and 5); these results indicate that even atmospheric oxygen, possibly by the *in situ* formation of tertiary hydroperoxides, exerts a catalytic action. The pattern for the effects of environmental factors (catalysis by preformed peroxides, light, and oxygen) on the bromination of tertiary allylic hydrogens by NBS qualitatively resembles those obtained earlier[6] for reaction with secondary allylic hydrogens.[7] These results establish beyond doubt

TABLE I

EFFECT OF ENVIRONMENTAL FACTORS ON REACTION OF NBS WITH ETHYL 4-METHYL-2-PENTENOATE

Run No.	Preformed[a] Peroxides	Light[b]	Oxygen[c]	Time for Complete[d] Reaction (min.)	Yield of Tertiary Bromide (%)
1	+	+	+	<20	81
2	−	+	+	55–70	86
3	+	−	+	60–75	83
4	−	+	−	205–320	66
5	−	−	−	215–240	65

[a] Presence or absence of preformed peroxides, qualitatively determined by color test with ammonium thiocyanate and ferrous ammonium sulfate; since sensitivity of this test was not determined, minute amounts of peroxides may be present in samples giving a negative color test. [b] Presence or absence of diffuse laboratory light. [c] Presence or absence of atmospheric oxygen. [d] Times for last positive and first negative tests for positive bromine with moistened starch–iodide paper.

(1) (a) Taken from the Ph.D. Thesis of Layton L. McCoy, University of Washington, 1951. (b) Supported in part by research contract No. N8-onr-52007 with the Office of Naval Research, U. S. Navy.

(2) Predoctoral Fellow, Atomic Energy Commission, 1950–1951.

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

(4) H. Schmid and P. Karrer, *Helv. Chim. Acta*, 29, 573 (1946).

(5) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winklemann, *Ann.*, **551**, 80 (1942), reported that both primary and secondary allylic hydrogens undergo bromination with NBS, the latter more rapidly, but made no specific statement that tertiary allylic hydrogens will not react; in fact, this paper contains no mention of any attempt to effect allylic brominations of alkenes containing tertiary allylic hydrogens.

(6) H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 4863 (1959).

(7) The major difference appears to be that light in the absence of peroxides and oxygen acts as a catalyst for the reaction with secondary hydrogens but not with tertiary hydrogens.

that the tertiary hydrogen in ethyl 4-methyl-2-pentenoate reacts with NBS under Ziegler's original conditions.

A number of other examples have been reported in which allylic bromination reactions have been conducted on alkenes containing allylic tertiary hydrogens, either alone[8a] or along with primary[8b-d] or secondary[8e-i] allylic hydrogens, available for substitution; with one exception, 3-methylcyclohexene,[8i] all of these compounds belong to the steroid or triterpenoid series. In none of the cases was an initiator added to the reaction[9] but several of these examples were strongly irradiated.[8a,b,d-f] Even though tertiary allylic bromides were not isolated from any of these reactions, in four cases unsaturated products were obtained which probably arose by bromination at the tertiary position and subsequent dehydrobromination,[8c,e,g,h,10] and in three cases where primary or secondary bromides, or the corresponding dehydrobromination products, were obtained in only 30–70% yields,[8b,f,i] tertiary bromination products or the resultant alkenes might have been formed but not isolated; the one compound that failed to react with NBS contained only a tertiary allylic hydrogen.[8a] The collective evidence indicates that most, if not all, tertiary allylic hydrogens undergo bromination by NBS and, in at least several cases, without deliberate addition of initiating substances or the use of strong irradiation.

Adequate experimental evidence is lacking at the present time to decide definitely about the relative reactivity of tertiary allylic hydrogens with respect to secondary or primary allylic hydrogens in the NBS-allylic bromination reaction. In their original work on this reaction, Ziegler and coworkers[5] showed that secondary allylic hydrogens reacted faster than primary ones, in comparable systems the latter requiring 10- to 100-fold longer reaction times for complete reaction. Some evidence has also been obtained that tertiary hydrogens in benzylic[11a,b] and saturated[11c] systems are quite reactive toward NBS. It would be expected, however, on mechanistic and energetic grounds that allylic hydrogens would show the usual reactivity order of primary < secondary < tertiary in the NBS reaction. Kinetic studies[12] have shown that the rate-determining step in the allylic bromination reaction involves abstraction of an allylic hydrogen atom by the succinimidyl radical and the ease of abstraction of different types of allylic hydrogens will be determined, in the first approximation, by their bond dissociation energies and by stabilization due to introduction of polar structures in the transition states of their reactions with succinimidyl radicals. Since both bond dissociation energies of the allylic C–H bonds and ionization potentials of the substituted allyl radicals (which will determine the amount of polar character in their transition states) would be expected to decrease in order primary > secondary > tertiary,[13] the reactivity order for the reaction of different types of allylic hydrogens toward succinimidyl radicals, and consequently in the NBS reaction, should be: primary < secondary < tertiary. Steric factors may reduce the relative reactivity of tertiary allylic hydrogens and the apparent lack of reactivity of certain highly hindered hydrogens of this type in steroid and triterpenoid compounds[10a,b,c] may be due to this factor.

EXPERIMENTAL

Ethyl 4-methyl-2-pentenoate. 4-Methyl-2-pentenoic acid (b.p. 111.5–112.0° (19 mm.), n_D^{21} 1.4481; reported,[14b] b.p. 115–116° (20 mm.), $n_D^{20.6}$ 1.4489), prepared by the method of Goldberg and Linstead,[14a] on direct esterification according to the method of Linstead[14b] yielded ethyl 4-methyl-2-pentenoate (b.p. 68–69.5° (19 mm.), $n_D^{17.4}$ 1.4340; re-

(8) (a) C. Meystre, L. Ehrmann, R. Neber, and K. Miescher, *Helv. Chim. Acta*, **28**, 1252 (1945); (b) C. Meystre and A. Wettstein, *Helv. Chim. Acta*, **30**, 1037, 1256 (1947); (c) L. Ruzicka, P. A. Plattner, and J. Pataki, *Helv. Chim. Acta*, **28**, 1360 (1945); (d) A. Wettstein and C. Meystre, *Helv. Chim. Acta*, **30**, 1262 (1945); (e) L. Ruzicka, P. A. Plattner, and H. Heusser, *Helv. Chim. Acta*, **29**, 473 (1946); (f) P. A. Plattner, L. Ruzicka, H. Heusser, J. Pataki, and K. Meier, *Helv. Chim. Acta*, **29**, 942 (1946); (g) L. Ruzicka, O. Jeger, and J. Redel, *Helv. Chim. Acta*, **26**, 1235 (1943); (h) M. Rubin and B. H. Ambrecht, *J. Am. Chem. Soc.*, **75**, 3513 (1943); (i) M. Mousseron and R. Jacquier, *Bull. soc. chim. France*, 106 (1951).

(9) Mousseron and Jacquier[8i] state that benzoyl peroxide was useless in their studies of the reaction of NBS with substituted cyclohexenes.

(10) It is not surprising that most tertiary allylic bromide products are not stable with respect to elimination under these reaction conditions since it has been shown that even a secondary allylic bromide product, 3-bromocyclohexene, undergoes slow dehydrobromination during the NBS reaction.[6] Ethyl 4-methyl-2-pentenoate, isolated in the present work, is more stable than the other tertiary bromide products but it evolves hydrogen bromide slowly on standing at room temperature.

(11) (a) R. A. Barnes and G. R. Buchwalter, *J. Am. Chem. Soc.*, **73**, 3858 (1951), found that *p*-cymene with NBS and benzoyl peroxide catalyst brominates preferentially in the tertiary benzylic position; (b) J. Klein and E. D. Bergmann, *J. Org. Chem.*, **22**, 1019 (1957); (c) J. Cason, N. L. Allinger, and D. E. Williams, *J. Org. Chem.*, **18**, 842 (1953).

(12) E. A. Youngman, Ph.D. Thesis, University of Washington, 1952; *cf.* ref. (6).

(13) Bond dissociation energies for all of the different types of allylic C—H bonds have not been determined but will probably differ from those for the corresponding types of bonds in alkanes (D(I°C—H) = 98, D(II°C—H) = 94, D(III°C—H) = 90 kcal. mole^{-1}) by the allyl radical resonance energy (18–22 kcal. mole^{-1}). Assuming comparable bond distances in the transition states, the amount of polar character in the transition states will be determined by the electron affinity of the succinimidyl radical and the relative magnitudes of the ionization potentials of the different types of allyl radicals; the latter would be expected to decrease in the same manner as found for the ionization potentials of the corresponding types of saturated radicals (I^e(I°R·) ≃ 200, I^e(II°R·) ≃ 182, I^e(III°R·) ≃ 171 kcal. mole^{-1}; F. P. Lossing and J. B. deSousa, *J. Am. Chem. Soc.*, **81**, 281 (1959).

(14) (a) A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, 2343 (1928); (b) R. P. Linstead, *J. Chem. Soc.*, 2498 (1929).

ported:[14b] for the α,β-unsaturated ester, b.p. 60° (13 mm.), n_D^{17} 1.4341; for the β,γ-unsaturated ester, b.p. 58° (11 mm.), n_D^{17} 1.4329).

Reaction of ethyl 4-methyl-2-pentenoate with NBS. Ethyl 4-methyl-2-pentenoate (7.1 g., 0.05 mole; contained peroxides (ammonium thiocyanate–ferrous ammonium sulfate color test) formed by autoxidation on standing in a glass-stoppered bottle), NBS (7.3 g., 0.04 mole; purified by method Aa[6]) and carbon tetrachloride (30 ml.) were refluxed until a test with starch-iodide paper showed the absence of positive bromine; time for complete reaction, <20 min. The reaction mixture was cooled in an ice bath, filtered, and the succinimide (4.1 g., 100%) washed twice with 5-ml. portions of carbon tetrachloride. The washings and filtrate were combined and concentrated under reduced pressure (water aspirator). Distillation of the residue gave ethyl 4-bromo-4-methyl-2-pentenoate [7.1 g., 81%, b.p. 108–111° (18 mm.), n_D^{20} 1.4848]; reported[4] (same general procedure except benzoyl peroxide initiator present), 67%, b.p. 105–110° (13 mm.); the bromo product is unstable, slowly evolving hydrogen bromide and becoming dark colored.

Runs in which preformed peroxides, light, and oxygen were singly or collectively excluded were performed by essentially the same technique as employed earlier in the study of effects of these environmental factors on the reaction of cyclohexene with NBS.[6] Freshly distilled ester gave a negative test for peroxides and was used in Runs 2, 4 and 5; addition of any material to decompose peroxides was omitted to avoid possible isomerization of the β,γ-isomer during the distillation. In Runs 4 and 5 oxygen was excluded by flushing the apparatus with deoxygenated nitrogen before distillation of the ester into it and a slight positive pressure of nitrogen was maintained in the system throughout the run. Results of these runs are summarized in Table I.

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Preparation of Propene-d-1

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Propene-d-1 has been prepared previously in poor yield and of undisclosed deuterium content by reduction of propyne-d-1.[1]

In the present work propene-d-1 was prepared by treating propenyl-1-magnesium bromide with deuterium oxide. The yield of product was 70% based on 1-bromo-1-propene and, according to parent peak analysis on the mass spectrometer, was at least 99% mono-deuterated propylene. The infrared spectrum of this propene-d-1 exhibited absorption peaks at 10.26 μ (*trans* isomer) and 12.52 μ (*cis* isomer).[2] By comparing the relative intensities of the two peaks, the propene-d-1 prepared is judged to be 60% *cis* and 40% *trans* isomer. Very small peaks appeared at 10.09 μ and 11.00 μ which are probably due to undeuterated propene.[3] From the work of Normant,[4] it may be assumed that position isomerization did not occur either in the preparation of the Grignard or in the reaction of the Grignard reagent with deuterium oxide. Geometric isomerization did occur in the reaction sequence, as the Grignard reagent was prepared from 1-bromopropene which was 98% *cis* isomer.

The 1-bromo-1-propene used in the preparation of the propenylmagnesium bromide was prepared by a modification of an existing method.[5] Instead of treating *trans*-crotonic acid dibromide with sodium carbonate in hot water or with refluxing pyridine, both of which reportedly gave yields of *cis*-1-bromo-1-propene in the range of 16–20%, the acid was treated with an excess of sodium bicarbonate in dimethylformamide at 70°. A 38% yield of 1-bromo-1-propene was obtained which was at least 99% *cis*-1-bromo-1-propene as determined by vapor phase chromatography and infrared analysis. By raising the temperature to 90° and distilling under reduced pressure, it is possible to obtain another 38% yield of 1-bromo-1-propene which analyzes for 96% *cis* and 4% *trans*-1-bromo-1-propene. This gives a total yield of 76% of 1-bromo-1-propene.

The infrared spectrum of the first fraction was identical with the spectrum of *cis*-1-bromo-1-propene prepared by Skell and Allen[6] by the *trans* radical addition of hydrogen bromide to propyne.

The *cis*-1-bromo-1-propene is the isomer expected from this series of reactions because of the stereochemistry involved.[7,8] *Cis*-1-bromo-1-propene is easily isomerized to the *trans* isomer. When a portion of the first fraction was redistilled, b.p. 55–55.2°, without protection from light, analysis by vapor phase chromatography showed the composition to be 90% *cis* and 10% *trans* isomer.

EXPERIMENTAL

Preparation of 1-bromo-1-propene. Three hundred and seventeen g. (1.20 mole) of *trans*-crotonic acid dibromide, m.p. 85–87°, was dissolved in the minimum amount of dimethylformamide. This solution was added, over a 20 minute period, to a reaction vessel which contained 163 g. (1.29 mole) sodium bicarbonate suspended in 500 ml. of dimethylformamide and which was connected to a Dry Ice trap. The reaction mixture was held at 70° during the addition. When

(1) B. S. Rabinovitch and F. S. Looney, *J. Am. Chem. Soc.*, **75**, 2652 (1953).

(2) Infrared spectra of essentially pure *cis*- and *trans*-propene-d-1 were provided by B. S. Rabinovitch of the University of Washington, Seattle, Washington.

(3) R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 120 (1947). R. H. Pierson, A. N. Fletcher and E. Gantz, *Anal. Chem.*, **28**, 1218 (1956).

(4) H. Normant, *Compt. rend.*, **239**, 1510, 1811 (1954); **240**, 314, 440, (1955).

(5) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2078 (1951). J. Wislicenus, *Ann.*, **248**, 281 (1888).

(6) P. S. Skell and R. G. Allen, Abstracts of Papers Presented at Chicago, Illinois, September 7–12, 1958, p. 27P. The infrared spectra of *trans* and *cis*-1-bromo-1-propene were kindly provided by Skell and Allen.

(7) A. McKenzie, *J. Chem. Soc.*, **101**, 1196 (1912).

(8) S. J. Cristol and W. P. Norris, *J. Am. Chem. Soc.*, **75**, 2645 (1953). E. Grovenstein, Jr., and D. E. Lee, *J. Am. Chem. Soc.*, **75**, 2639 (1953).

the addition was completed, the Dry Ice trap was replaced with another and the system was evacuated at 100 mm. pressure while the reaction vessel was heated to 90°.

The first fraction was washed with 3 portions of cold water, dried over Drierite and then filtered to give 60 g. (38% yield) of 1-bromo-1-propene, b.p. 55–55.2°/708 mm., which was 99% *cis* isomer, before distillation, according to vapor phase chromatographic analysis.[9]

The second fraction was treated in the same manner to give an additional 60 g. (38% yield) of 1-bromo-1-propene. The product consisted of 96% *cis*- and 4% *trans*-1-bromo-1-propene as determined by vapor phase chromatographic analysis.[9] The total yield of 1-bromo-1-propene was 76%.

Preparation of Propene-d-1. Fifty g. (0.41 mole) of 1-bromo-1-propene (98% *cis* isomer) was added to 10 g. (0.41 mole) of magnesium in 250 ml. of dry tetrahydrofuran in a flask protected from atmospheric moisture and provided with means for distillation. When all the magnesium had reacted, 25 ml. of tetrahydrofuran was distilled out to remove any propene which might have been present. Receivers were changed and 17 ml. of 99.8% deuterium oxide was added dropwise to the stirred Grignard solution. The evolved gas was trapped in a Dry Ice-acetone trap to give 12 g. (70% yield) of propene-d-1. The propene-d-1 contained a small amount of tetrahydrofuran. A sample was purified by gas chromatography[9] and parent peak analysis on the mass spectrometer indicated that it was at least 99% monodeuterated propene.

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(9) The analysis was performed by Charles M. Drew of this laboratory.

The Reaction of Oxalyl Chloride with Amine Hydrochlorides

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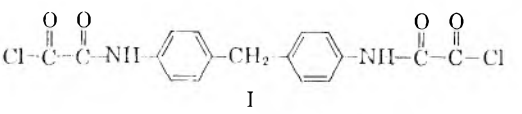
Stolle[1] successfully prepared oxamic acid chlorides from *N*-substituted anilines by reaction with oxalyl chloride. However, primary aromatic amines and oxalyl chloride gave only oxamides under similar conditions. Several patents[2] show that the oxamic acid chlorides of certain primary aromatic amines could be prepared by treating the amine hydrochlorides with oxalyl chloride, either in excess oxalyl chloride, or in an inert diluent.

This latter method has now been found applicable to the synthesis of 4,4′-(diphenylmethane)-bis-oxamic acid chloride (I). Good yields of I could be obtained when the dihydrochloride of 4,4′-diaminodiphenylmethane was heated under reflux with excess oxalyl chloride for 12 hours. Poorer yields were obtained when shorter reflux times were used.

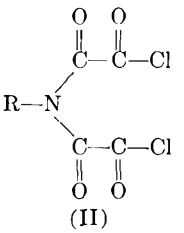


I

It was found that I reacted readily with ethanol to give the diester. This was shown to be identical to the diester obtained by reaction of 4,4′-diaminodiphenylmethane with diethyl oxalate by comparison of their infrared spectra and melting points, and no depression in the mixture melting point.

Surprisingly, the dihydrochlorides of *m*-phenylenediamine, piperazine, and *trans*-2,5-dimethylpiperazine were found to be unreactive towards oxalyl chloride. It is felt that this is probably due to the insolubility of these hydrochlorides as opposed to that of 4,4′-diaminodiphenylmethane, which appears to dissolve to some extent at the beginning of the reaction.

In looking for a possible extension of this reaction it was noted that Bornwater[3] had reacted methylamine hydrochloride with oxalyl chloride and obtained *N*,*N*′-dimethyltetraketopiperazine. It appeared likely from our experience that an intermediate in this synthesis might be II (R = CH_3). This could then react with another molecule of amine hydrochloride to form the tetraketopiperazine.



(II)

This work indicates that this is indeed the case. A substantial yield of a hygroscopic, hexane soluble diacid chloride was obtained when a mixture of ethylamine hydrochloride and a large excess of oxalyl chloride was heated at reflux for 50 hr. Though the elemental analysis of the product, *N*-ethyloximidic acid chloride[4] (II; R = C_2H_5), did not agree with the theoretical, that of its di-*N*-methylanilide derivative did. The infrared spectrum of the acid chloride was consistent with what would be expected of a compound having the structure of II.

EXPERIMENTAL[5]

4,4′-Diaminodiphenylmethane dihydrochloride. Fifteen g. of 4,4′-diaminodiphenylmethane dissolved in 350 ml. of anhydrous ether was treated with dry hydrogen chloride for 5 hr. whereupon the colorless, solid product precipitated. This was filtered, washed twice with 300-ml. portions of ether, and dried in a desiccator under vacuum. The dry weight was 19.7 g. (96%), m.p. 282° (dec.) [reported,[6] m.p. 285° (dec.)].

(1) R. Stolle, *Ber.*, **46**, 3915 (1913); R. Stolle, R. Bergdoll, M. Luther, A. Auerhahn, and W. Wacker, *J. prakt. Chem.*, **128**, 1 (1930).

(2) I. G. Farben A-G., Brit. Patent **282,891**, Sept. 30, 1926; I. G. Farben A-G., Ger. Patent **463,140**, July 5, 1928; J. Haller, U. S. Patent **1,685,698**, Nov. 26, 1926.

(3) J. Th. Bornwater, *Rec. trav. chim.*, **31**, 105 (1912).

(4) We are assigning the name oximidic acid to the structure $HO_2CCONHCOCO_2H$.

(5) All melting points are uncorrected.

4,4'-(Diphenylmethane)bisoxamic acid chloride (I). To 99.3 g. (0.78 mole) of oxalyl chloride was added 10.0 g. (0.037 mole) of 4,4'-diaminodiphenylmethane dihydrochloride in one portion with stirring. The heterogeneous mixture was heated at reflux with stirring for 12 hr. in a dry atmosphere. After removal of the excess oxalyl chloride at reduced pressure with gentle heating, the residual solid was dissolved in about 3 l. of dry, ethanol-free chloroform. The almost clear solution was filtered to remove some fine particles of unchanged dihydrochloride and evaporated on the steam bath to about 500 ml. At this concentration a large amount of yellow, crystalline solid was present. After cooling to room temperature, the yellow needles were filtered off in a dry-box under a dry nitrogen atmosphere, weight 9.9 g. (71%), m.p. 165–167° (dec.).

Anal. Calcd. for $C_{17}H_{12}O_4N_2Cl_2$: C, 53.85; H, 3.19; O, 16.88; N, 7.39; Cl, 18.70. Found: C, 52.65, 52.64; H, 3.08, 3.17; O, 17.0, 16.8; N, 7.16, 7.13; Cl, 19.7, 20.0.

Diethyl 4,4'-(diphenylmethane)bisoxamic acid. To 73.7 g. (0.505 mole) of diethyl oxalate warmed to about 30° was added 10.0 g. (0.0505 mole) of 4,4'-diaminodiphenylmethane with stirring. The solution was heated under reflux for 1.5 hr., then allowed to cool to room temperature. The solid was filtered and dried in a vacuum oven at 20 mm. pressure and 60°. The weight of tan colored product was 17.6 g. (88%), m.p. 150–153°. Recrystallization from ethanol gave colorless needles, m.p. 153–153.5°.

Anal. Calcd. for $C_{21}H_{22}O_6N_2$: C, 63.3; H, 5.60; N, 7.05; O, 24.1. Found: C, 63.28, 63.35; H, 5.83, 5.77; N, 6.94, 6.96; O, 23.9, 24.0.

The diethyl ester was also obtained by using chloroform containing ethanol as recrystallizing medium for 4,4'-(diphenylmethane)bis-oxamic acid chloride. It was obtained as colorless needles (from *n*-hexane/chloroform) in 91% yield, m.p. 152–152.5°. The infrared absorption spectra and mixed melting point of these two samples showed them to be identical.

N-Ethyloximidic acid chloride (II; R = C_2H_5). To 158.4 g. (1.25 mole) of oxalyl chloride protected from the atmosphere by calcium chloride tubes was added 5.0 g. (0.061 mole) of ethylamine hydrochloride with stirring. The mixture was heated at reflux for 50 hr., then the excess oxalyl chloride was removed at reduced pressure. The solid residue was dissolved in a chloroform/*n*-hexane (3/1) mixture and the chloroform boiled off leaving a small amount (100 mg.) of tan crystals, m.p. >220° which showed a negative silver nitrate test. This is believed to be *N,N'*-diethyltetraketopiperazine.

After filtration of this high melting solid the brown filtrate was evaporated to about 80 ml. and allowed to cool in a dry-box. A large amount of tan needles formed which were filtered. These were dried in a vacuum desiccator and the dry weight was 8.0 g. (77%). It was recrystallized from *n*-hexane giving tan needles, m.p. ~85–90°. It showed an immediate positive silver nitrate test and the infrared spectrum was consistent with the structure proposed.

Anal. Calcd. for $C_6H_5O_4NCl_2$: C, 31.88; H, 2.23; N, 6.20; Cl, 31.38. Found: C, 32.1, 32.5; H, 2.71, 2.84; N, 6.25, 6.03; Cl, 28.2, 27.5.

The di-*N*-methylanilide was prepared by adding a large excess of *N*-methylaniline to a chloroform solution of the acid chloride. This had a melting point of 118.5–119.5°. Two crystallizations from aqueous ethanol gave colorless crystals, m.p. 132–133°.

Anal. Calcd. for $C_{20}H_{21}O_4N_3$: C, 65.38; H, 5.76; O, 17.4; N, 11.44. Found: C, 65.32, 65.32; H, 5.81, 5.76; O, 17.4, 17.6; N, 11.23, 11.25.

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(6) C. Eberhardt and A. Welter, *Ber.*, **27**, 1811 (1894).

Acid Dissociation Constants and Copper Chelate Stability Constants of *N*-Aralkylethylenediamines

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Although the proton and copper(II) complexes of ethylenediamine and its *N*-alkyl-derivatives have been reported,[2–6] no such data is available for the *N*-aralkylethylenediamines.

N-alkylation of ammonia[4] leads to an increase in basicity or to stronger proton complexes. Since increased basicity generally produces increased complex stability in a given series of ligands enhanced stability of metal-amine complexes is expected. This reasoning holds true in the case of primary amines but not in the case of secondary or tertiary amines wherein the increased basicity due to *N*-alkyl substitution is simultaneously accompanied by an increase in steric interference and lower stability.[3] The same behavior exists in the *N*-alkylethylenediamines which form weaker metal complexes than does ethylenediamine. The observed order of complex stability: ethylenediamine > *N*-methylethylenediamine > *N*-ethylethylenediamine > *N*-isopropylethylenediamine is the reverse of the order of pK_a values (Table II). The effect of steric interference, absent in the proton complexes, becomes more pronounced as R increases in size. It, therefore, became of interest to examine the effect of *N*-monoaralkyl substitution on the proton and copper complexing ability of ethylenediamine.

The acid dissociation constants of the dihydrochlorides of *N*-benzylethylenediamine, *N*-(β-phenethyl)ethylenediamine and *N*-(*p*-methylbenzyl)ethylenediamine, together with the stability constants of their copper(II) complexes at 25° in 0.1*M* KCl have been determined and are reported here.

EXPERIMENTAL

Reagents. The *N*-aralkylethylenediamines were prepared by direct condensation of the appropriate aralkyl chloride with ethylenediamine in a five to one molar ratio at 85–90° for 4 to 6 hr. The products were liberated from their hydrochloride salts by adding a slight excess of 30% sodium hydroxide solution to the hot reaction mixture and stirring for 1 hr. The aqueous phase was removed and the remaining organic phases dried with solid KOH followed by metallic

(1) Now at Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

(2) J. Bjerrum, *Chem. Revs.*, 46, 381 (1950).

(3) F. Basolo and R. K. Murmann, *J. Am. Chem. Soc.*, 74, 2373 (1952).

(4) R. N. Keller and L. J. Edwards, *J. Am. Chem. Soc.*, 74, 2931 (1952).

(5) D. H. Everett and B. R. W. Pinsent, *Proc. Roy. Soc. (London)*, 215, A, 417 (1952).

(6) H. Irving and M. Griffiths, *J. Chem. Soc.*, 213 (1954).

TABLE I

N-Aralkylethylenediamines and their Dihydrochloride Salts

	Diamines	Dihydrochlorides	N		Cl	
	B.P., °C.	M.P., °C.	Calcd.	Found	Calcd.	Found
Benzyl-	111–113 (5 mm.)[7]	260 (dec.)	12.6	12.3	31.8	31.8
β-Phenethyl-	136–140 (12 mm.)[8]	240–260 (dec.)	11.8	11.6	30.0	29.7
p-Methylbenzyl-	107–110 (1 mm.)	>250 (dec.)	11.8	11.2	30.0	29.1

sodium to remove the final traces of water. Fractional distillation over sodium gave the products as colorless oils.

The dihydrochloride salts were prepared in the conventional manner and purified by recrystallization from aqueous ethanol.

Apparatus and Procedure. The titration assembly and procedure were essentially the same as that described by Chaberek and Martell.[9] The diamine dihydrochlorides were used at a concentration of about 1×10^{-3} mole of ligand per run. For the determination of copper complex stability constants a two to one molar ratio of ligand to copper(II) was used.

Acid Dissociation Constants. The consecutive dissociation constants of the acids conjugate to the diamines were calculated from potentiometric titration data of the free ligands by the algebraic method.[9]

Stability of the Copper-Diamine Complexes. The stability constants of the copper-diamine complexes (1–2) were calculated from the 1–2 titration curves by the method of Bjerrum.[10] From the plot of $\bar{n}$ (the degree of formation of the complex) versus *p*B (the negative logarithm of the ligand concentration), the values of log K_1 and log K_2 were read at $\bar{n}$ values of 1.5 and 0.5 respectively. In the titration of *N*-(*p*-methylbenzyl)ethylenediamine with copper(II), precipitation of a deep violet crystalline solid occurred at *p*H 5.9 even at ligand concentrations of 5×10^{-4} (2.5×10^{-4} mole copper(II)). However, a sufficient number of points was obtained to permit calculation of log K_1 and log K_2. The plots of $\bar{n}$ versus *p*B exhibited a definite inflection indicative of a greater tendency for complex formation with the first ligand molecule than with the second.

The marked base weakening effect of the aralkyl substituents on the acid dissociation constants of ethylenediamine compared to the base strengthening effect of alkyl substituents[3,4] is evident from a comparison of the data in Table II.

TABLE II

Acid Dissociation Constants and Copper Complex Stability Constants of *N*-Substituted Ethylenediamines $RNHCH_2CH_2NH_2$

R	$pK_{H_2B}{}^{+2}$	$pK_{HB}{}^{+}$	ΔpK	Log K_1	Log K_2	Log K_1/K_2
Benzyl-	6.48	9.41	2.93	9.12	7.56	1.56
p-Methylbenzyl-	6.51	9.41	2.90	9.23	7.57	1.66
β-Phenethyl-	6.59	9.44	2.85	9.11	7.38	1.73
H—[6]	7.47	10.18	2.71	10.76	9.37	1.43
CH_3—[5,6]	7.56	10.40	2.84	10.55	8.56	1.99
C_2H_5—[3,6]	7.63	10.56	2.93	10.19	8.38	1.81
i-C_3H_7—[3,5]	7.70	10.62	2.92	9.07	7.45	1.62

(7) J. Van Alphen, *Rec. trav. chim.*, **54**, 595 (1935).

(8) A. Funke and J. P. Fourneau, *Bull. soc. Chim.*, **9**, 805 (1942).

(9) S. Chaberek, Jr., and A. E. Martell, *J. Am. Chem. Soc.*, **74**, 5052 (1952).

(10) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Sons, Copenhagen (1941).

The inductive effect of the phenyl group, previously pointed out by Wepster,[11] appears to be responsible for the considerable increase in acid strength observed, as resonance interactions between the phenyl groups and nitrogen are prohibited by the intervening alkylene bridges.

Although the pK_{H_2B} values increase slightly in the expected order, the increase on going from the benzyl- to the phenethyl derivative is not as great as anticipated in view of the known marked attenuation of the inductive effect with increasing distance from the reaction center. This effect is prominent in the monoamines wherein pK_{HB} increases approximately 0.5 *p*K unit in going from benzylamine (pK_{HB} 9.37) to phenethylamine (pK_{HB} 9.83).[12] The strong inductive effect of the aralkyl group on the pK_{HB} values of the alkylamines is also evident.

The lower basicity of the donor nitrogens is reflected in the lower log K_1 and log K_2 values of the copper complexes. In addition, steric effects at least with respect to log K_2, undoubtedly contribute to the lower stability values observed. The steric effect on log K_2 can be attributed to the interference of the donor groups of the two ligands. The nature of the steric effects, if such are operative on log K_1, are not known. The overall effect of the *N*-aralkyl groups appears to be approximately equal to that of the bulky *N*-isopropyl substituent.[6]

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Framingham, Mass.

(11) B. M. Wepster, *Rec. trav. chim.*, **71**, 1171 (1952).

(12) H. C. Brown, D. H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," Edited by E. A. Braude and F. C. Nachod, Academic Press, Inc., N. Y., Ch. 14 (1955).

Anomalous Optical Rotatory Dispersion in the Morphine Series

J. M. Bobbitt,[1a] Ulrich Weiss,[1b] and Dimitra D. Hanessian[1c]

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The study of the optical rotatory dispersion of organic compounds is an old idea[2,3] which has been extensively developed in recent years by Djerassi

(1) (a) Department of Chemistry of the University of Connecticut; (b) National Institute of Arthritis and Metabolic Diseases, National Institutes of Health; (c) Department of Chemistry of the Ohio State University.

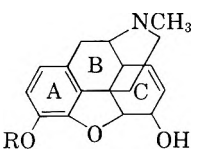
(2) T. M. Lowry, *Optical Rotatory Power*, Longmans Green, London, 1935.

(3) P. A. Levene and A. Rothen in H. Gilman, *Organic Chemistry*, Vol. II, John Wiley and Sons, New York, 1938, p. 1779.

and his co-workers.[4] Investigation of the anomalous[5] dispersion of the optical rotatory power due to the ultraviolet absorption of a carbonyl group located in the vicinity of an asymmetric center has been particularly fruitful.

The application of dispersion techniques to the alkaloids and their derivatives has so far been limited to a relatively small number of compounds. Dispersion curves have been published for garryfoline, cuauchichicine, and their F-dihydroderivatives[6]; yohimbone,[6,7] alloyohimbone,[7] 3-epi-alloyohimbone[7] and yohimbane[6]; jervine[8]; seredone (from seredine)[7]; and 18-dehydrotetramethylholarrhimine.[9] In addition, the rotatory dispersions of two antipodal bases derived from haemanthamine and buphanisine,[10] of emetine and isoemetine,[11] morphinone,[12a] and a number of alkaloids from amaryllidaceous plants[12b] have been measured, although complete curves are not recorded. Of the compounds for which detailed data are available, only the ketonic bases (cuauchichicine, its F-dihydroderivative, yohimbone, alloyohimbone, 3-epialloyohimbone, seredone, jervine, and morphinone) have shown a pronounced anomalous dispersion. Two nonketonic bases (yohimbane and isoemetine) show a slightly anomalous curve while the others exhibit normal dispersion.

We would like to record evidence (Fig. 1) that pronouncedly anomalous optical rotatory dispersion curves are given by three bases, morphine (I), codeine (II), and dihydrocodeine (III), which contain no carbonyl group. In fact, dihydrocodeine has no ultraviolet chromophore other than the



I. R = H
II. R = CH_3
III. R = CH_3, no double bond in ring C

benzene ring. All three dispersion curves were measured down to 298 mμ and show distinct troughs at 304–305 mμ. Thus, by definition,[2,4] they are

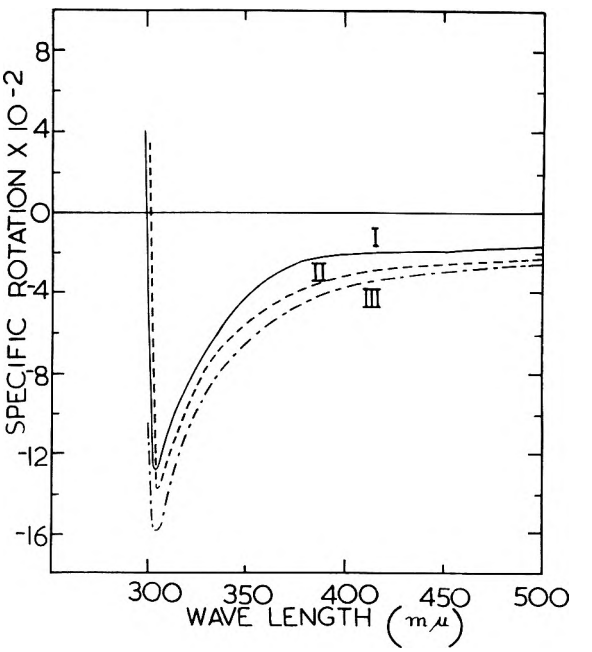


Fig. 1. Rotatory dispersion curves (dioxane solution) of: morphine (I), codeine (II), and dihydrocodeine (III)

anomalous. Below 298 mμ the strong absorption band (λmax. 282–284, log ϵ *ca.*, 3.2)[13] produced by the aromatic ring prevented the passage of light at the concentrations investigated (0.209–0.358%). At much lower concentrations (0.01%), the solutions were transparent to 268 mμ, and it appeared that curves with two troughs were obtained. These latter data are not reported since the accuracy of the measurement of such low rotations (α = 0.008–0.03°) is questionable[14] and because, as might be expected (ref. (2), p. 107), the wave length of the trough varies with the concentration.

The optical rotatory dispersion curves of morphine, codeine, and dihydrocodeine appear to constitute the first published evidence of *pronounced* anomalous behavior in non-ketonic bases[15] (note however the indistinct trough of yohimbane[6] and peak of isoemetine[11]). Interpretation of the observed anomalous dispersion effects is greatly complicated by the fact that they could arise from two sources: The superposition of the partial rotations produced by two asymmetric carbon atoms in the same molecule[16] and the presence of a chro-

(4) See C. Djerassi, *Bull. soc. chim. France*, 741 (1957), for a review with leading references.

(5) See C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957), for precise definitions of terms used in this paper.

(6) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(7) J. Poisson, N. Neuss, R. Goutarel, and M.-M. Janot, *Bull. soc. chim. France*, 1195 (1958).

(8) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

(9) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(10) W. C. Wildman and H. M. Fales, *J. Am. Chem. Soc.*, **80**, 6465 (1958).

(11) E. E. van Tamelen and J. B. Hester, *J. Am. Chem. Soc.*, **81**, 507 (1959).

12) (a) C. Djerassi, private communication; (b) H. M. Fales, private communication. We are indebted to these authors for permission to mention their unpublished work.

(13) A. E. Gillam and E. S. Stern, *Electronic Absorption Spectra*, Edward Arnold, London, 1958, p. 173.

(14) C. Djerassi, E. W. Foltz, and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955).

(15) Since the completion of the present work, we have been informed by Dr. Gloria Lyle (National Heart Institute) that some, although not all, nonketonic aromatic bases studied by her show strongly anomalous optical rotatory dispersion. Among the bases giving pronounced anomalies are the alkaloids ephedrine and tetrahydropalmatine. We are indebted to Dr. Lyle for permission to mention these results, which support and extend our findings.

(16) L. Tschugaeff, *Trans. Faraday Soc.*, **10**, 70 (1914).

mophore in the vicinity of an asymmetric carbon atom[4] (ref. (2), p. 146). The latter possibility is apparently more important with Djerassi's ketonic compounds,[4,6,8] but the former might play an important role in nonketonic substances [*cf.* emetine, ref. (11)]. Three other nonketonic aromatic compounds for which data are available: estradiol,[17] 6-dehydroestradiol,[17] and *cis*-13-methyl-3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene,[6] show normal behavior; however, their dispersion curves were followed only down to 315, 335, and 337.5 mμ, respectively. The present findings, together with those mentioned in ref. (15), suggest that the investigation of other aromatic nonketonic substances might be of great interest.

EXPERIMENTAL

The codeine and morphine samples were commercial samples manufactured by the New York Quinine and Chemical Works and Merck and Co., respectively; they were obtained through the Pharmacy School of the University of Connecticut. The dihydrocodeine was obtained from the L. F. Small Collection through the kind cooperation of Dr. L. J. Sargent of the National Institutes of Health. The measurements were made with a Model No. 200S Rudolph Photoelectric Spectropolarimeter[18] at the Ohio State University. A 0.1 decimeter tube with quartz ends was used.

Morphine (I), R. D. in dioxane (*c* 0.209): $[\alpha]^{19}$ (500 mμ), −160°; (340), −1280°; (298), 420°.

Codeine (II), R. D. in dioxane (*c* 0.358): $[\alpha]^{21-21.7}$ (650 mμ), −130°; (589), −200°; (305), −1360°; (300), 360°.

Dihydrocodeine (III), R. D. in dioxane (*c* 0.246): $[\alpha]^{20.7-21}$ (600 mμ), −210°; (589), −220°; (305), −1580°; (300), −1050°.

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(17) E. W. Foltz, A. E. Lippman, and C. Djerassi, *J. Am. Chem. Soc.*, **77**, 4359 (1955).
(18) O. C. Rudolph and Sons, Caldwell, N. J.

Characterization of Cupressaceae Tropolones as Dicyclohexylamine Salts

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Although a number of reactions can be used to characterize tropolones through the preparation of derivatives, only a few reagents appear to be generally satisfactory. For instance, transition metal chelates tend to have rather high melting points[1,2]; the nuclear substitution often yields several isomers, and the parent tropolone cannot be readily recovered from the derivative.[1] Similarly, several isomers usually result from esterification or etherification of the tropolonic hydroxyl;[1] hydrochloride salts do not appear to be very convenient for handling, and melting points often seem insufficiently sharp.[3,4] Picrates and ethylenediamine salts have been used with success in the case of a number of synthetically prepared tropolones.[3,5,6]

In our work on the natural tropolones from the heartwood of *Cupressaceae* species, (*i.e.*, tropolones of relatively weak acidity, carrying alkyl, methoxy, or hydroxy substituents), a question of identification of the isolated compounds often arose. The formation of amine salts appeared rather promising, and as it was felt to be generally desirable to have several convenient reagents available,[7] the whole area was reinvestigated using a number of amines in combination with several tropolones.

No derivatives could be obtained by using aromatic amines. This is understandable in view of their weaker basicity. Assuming *p*K values of 9.42 and 3.02[10] for aniline and diethylamine, respectively, and a *p*K of 7.21 for β-thujaplicin,[1] a rough calculation indicated that the corresponding salts should be hydrolyzed to 96% in the first case, and to only 1.4% in the second. Experimentally, using aniline and cyclohexylamine with nootkatin in 0.05 *N* ethanol solution, and utilizing change in absorbance at 490 m. as the measure of the degree of ionization, it was found that, with aniline, the hydrolysis of the salt was 96% complete, whereas with cyclohexylamine, hydrolysis could not be detected by the method used.

The lower boiling amines and ammonia were unsuitable for preparation of derivatives, the adducts being unstable to recrystallization, drying, or heating because of the gradual volatilization of the amine from the salt. Thus, the ammonia salts of a number of tropolones tested transformed into

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(2) T. Nozoe, *Bull. Chem. Soc. Japan*, **2**, 295 (1936).
(3) T. Nozoe, T. Mukai, and K. Takase, *Sci. Rep. Tohoku Univ.*, **36**, 40 (1952).
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(5) E. Sebe, T. Nozeo, P. Y. Yeh, and S. Iwamoto, *Sci. Rep. Tohoku Univ.*, **36**, 307 (1952).
(6) The formation of aliphatic amine salts is also commonly utilized for separation of resin acids. G. C. Harris and R. F. Sanderson, *Jour. Am. Chem. Soc.*, **70**, 334 (1948).
(7) Ethylenediamine apparently does not give any adduct with β-thujaplicin[8] nor with nootkatin.[9]
(8) T. Nozoe, E. Sebe, S. Mayama, and S. Iwamoto, *Sci. Rep. Tohoku Univ.*, **36**, 184 (1952).
(9) Our observations.
(10) *Taschenbuch für Chemiker und Physiker*, ed. by J. d'Ans and E. Lax; Berlin, Gottingen, Heidelberg, Springer-Verlag, 1949, p. 845.

a viscous liquid under evolution of ammonia after a short storage period at room temperature and atmospheric pressure. The diethylamine salt of nootkatin decomposed in a similar way within one hour at 1 mm. pressure. Some salts of cyclohexylamine showed an extremely strong tendency to sublime, and the melting points had to be taken in a sealed tube.

In view of these findings, it seemed that the best procedure would involve the strongly basic amines of high boiling points which, to minimize any decomposition during recrystallization, should also have the solubility characteristics similar to those of the tropolones in question.

Among amines used, dicyclohexylamine appeared to give the best results. It is easily soluble in all common organic solvents, including saturated hydrocarbons, but is insoluble in water. Its basicity compares with that of other aliphatic amines, and it has a high boiling point (254°–256° at atmospheric pressure). Because of its high molecular weight, it is capable of giving high weight yields of derivatives. Thus, 1 g. of β-thujaplicin could theoretically yield 2.1 g. of the derivative. In all cases, the derivatives had a high tendency to crystallize. The yields in all cases were near theoretical, as the only losses were those inherent in the process of crystallization. The derivatives could be purified by recrystallization from isooctane or similar solvents or from ethanol/water mixtures. The melting points fell within the desired temperature range, were characteristic and sharp, with mixed melting points showing depressions from 5–12°. The original tropolones can be easily liberated by treating the derivatives with 10% sulfuric acid.[11]

Table I lists the dicyclohexylamine derivatives prepared from a number of tropolones, together with their melting points and analyses.

TABLE I[12]

DICYCLOHEXYLAMINE DERIVATIVES OF TROPOLONES

Tropolone	Melting point, °C.	Calcd. % C	Calcd. % H	Found % C	Found % H
β-thujaplicin	134–135	76.47	10.21	76.57	10.36
γ-thujaplicin	138–139	76.47	10.21	76.54	10.11
Nootkatin	114–115	78.40	10.48	78.42	10.56
Pygmaein[13]	86–87	73.56	9.93	73.70	9.74
3,5-Dibromo-α-thujaplicin	179–180	52.50	6.61	52.66	6.58
β-thujaplicinol	124–125	73.09	9.76	73.44	9.87

(11) The hydrochloric acid salt of dicyclohexylamine is not very soluble in water.

(12) All melting points are corrected; microanalysis by Microchemical Laboratory, University of California, Berkeley, California.

(13) A methoxy thujaplicin isolated from *Cupressus pygmaea*, the structure of which will be the subject of a forthcoming publication.

EXPERIMENTAL

Reagent. Monsanto's dicyclohexylamine was purified by fractional distillation, and the fraction that boiled within 120–121° at 8.3–8.5 mm. pressure was used in the experiments.

Preparation of a derivative. Pygmaein, 263 mg., m.p. 37.1–38.1°, was mixed with 500 mg. of dicyclohexylamine, and heated to 100° on a steam bath to effect solution. The resulting material was cooled to 0°, diluted with 5 ml. of cold isooctane, and allowed to stand for 1 hr. The separated crystals were filtered, the filtrate was reduced to 2 ml., cooled to 0°, and the second crop of crystals was recovered. The combined crystallization fractions were recrystallized from 10 ml. of isooctane to give 479 mg. of the derivative, m.p. 86–87° (94% yield).

Recovery of a tropolone from a derivative. A 246 mg. portion of nootkatin dicyclohexylamine salt, m.p. 113–114°, was stirred with 25 ml. of 10% sulfuric acid, and the precipitate was filtered, washed with 50 ml. of distilled water, air dried, and recrystallized from methanol-water to give 190 mg. of nootkatin, m.p. 93–94° (98% yield).

Acknowledgments. We are indebted to Monsanto Chemical Company for a sample of dicyclohexylamine and to Mr. G. M. Barton for β-thujaplicinol.

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Rates of Diisocyanate-Alcohol Reactions at Elevated Temperatures. Effect of Tri-*n*-butyl Amine Catalysis[1]

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Considerable work has been done in the past decade on the rates and mechanism of the reaction of organic isocyanates with hydroxyl-containing compounds to form urethanes, starting with the pioneering work of Baker and his associates.[2–6] It is difficult to relate many of the fundamental kinetic studies directly with the industrial production of polyurethanes. Hence, it was of interest to obtain reaction rate data on systems which

(1) Paper presented in part before the Division of Polymer Chemistry, 134th meeting, ACS, Chicago, Ill., September 1958.

(2) (a) J. W. Baker and J. B. Holdsworth, *J. Chem. Soc.*, 713 (1947); (b) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 9 (1949); (c) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 19, (1949); (d) J. W. Baker, M. M. Davies, and J. Gaunt, *J. Chem. Soc.*, 24 (1949); (e) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 27 (1949).

(3) E. Dyer, H. A. Taylor, S. J. Mason, and J. Samson, *J. Am. Chem. Soc.*, **71**, 4106 (1949).

(4) C. E. McGinn and R. G. Spaunburgh, paper presented before the Division of Paint, Plastics, and Printing Ink Chemistry, 130th meeting, ACS, Atlantic City, N. J., September 1956.

(5) M. E. Bailey, V. Kirss, and R. G. Spaunburgh, *Ind. Eng. Chem.*, **8**, 794 (1956).

(6) J. Burkus and C. F. Eckert, *J. Am. Chem. Soc.*, **80**, 5948 (1958).

TABLE I

SECOND-ORDER REACTION RATE CONSTANTS FOR ARYL DIISOCYANATES *vs.* 1- OR 2-OCTANOL AT 115° IN CHLOROBENZENE SOLUTION

Diisocyanate	With 1-octanol[b] Cat.	Uncat.	k cat./k uncat.	With 2-octanol[b] Cat.	Uncat.	k cat./k uncat.
m-Phenylene diisocyanate (k_1)[a]	75.0	14.0	5.4	20.8	8.25	2.5
m-Phenylene diisocyanate (k_2)	46.2	11.8	3.9	14.6	4.16	3.5
2,4-Tolylene diisocyanate (k_1)	30.3	5.41	5.6	10.1	3.29	3.1
2,4-Tolylene diisocyanate (k_2)	15.8	2.67	5.9	4.64	0.69	6.7
4,4′-Methylenebis(phenyl isocyanate)	29.3	4.02	7.3	8.42	3.11	2.7
3,3′-Dimethyl-4,4′-biphenylene diisocyanate	10.1	1.06	9.5	3.49	0.70	5.0

[a] For explanation of k_1 and k_2 values, see experimental section. [b] All k values are multiplied by 10^2. Units of k are liters equiv.$^{-1}$ min.$^{-1}$

more nearly simulate conditions under which polyurethanes are made commercially (*i.e.*, reactions of organic diisocyanates with primary and secondary alcohols, at elevated temperatures and in the presence of a basic catalyst, with the isocyanate and alcohol groups at equal initial concentrations). In this work, studies were confined to model alcohols; 1- and 2-octanol were used as representative primary and secondary alcohols. Four common aryl diisocyanates were used, which are listed in Table I. Because of the mechanical difficulty of handling a bulk reaction between these materials, these studies were also confined to reactions in dilute chlorobenzene solution.

The second order rate constants for the various reactants at 115° are listed in Table I. The diisocyanates are listed in their general decreasing order of reactivity, using the k_1 values for 2,4-tolylene diisocyanate and *m*-phenylene diisocyanate. The primary alcohol reacts faster with a given diisocyanate than does the secondary, either catalyzed or uncatalyzed. This agrees with data in the literature.[2,3]

Uncatalyzed reactions. For uncatalyzed reactions with 1-octanol, the four diisocyanates are listed in decreasing order of reactivity in Table I, on the basis of initial rates of reaction. Because of the smaller k_1 value for 2,4-tolylene diisocyanate, however, this diisocyanate may approach 100% reaction, with 1-octanol, in about the same length of time as 4,4′-methylenebis(phenyl isocyanate). Likewise in the uncatalyzed reactions with 2-octanol, 4,4′-methylenebis(phenyl isocyanate) is undoubtedly more reactive than 2,4-tolylene diisocyanate at high extents of reaction, because of the markedly smaller k_2 value of the latter diisocyanate.

Catalyzed reactions. In order to express the effect of basic catalysis on the rates of these various reactions, the ratio of the rate constant for the catalyzed reaction to that for the uncatalyzed reaction was used. These ratios have been included in Table I. From the data for the catalyzed reactions, the following observations can be made:

(1) Considering the rates of reaction of the primary and secondary alcohols with a given diisocyanate, it can be seen that a basic catalyst usually affects the reactivity of the primary more than the secondary. One exception can be noted, however. The k_2 values for 2,4-tolylene diisocyanate show that, in this case, the reactivity of 2-octanol is increased more by basic catalysis than that of 1-octanol.

(2) The slowest reacting diisocyanate, 3,3′-dimethyl-4,4′-biphenylene diisocyanate, is affected the most by basic catalysis. The absolute value of its rate constant for the catalyzed reaction with either alcohol is still less, however, than that of any of the other diisocyanates.

(3) For the reaction of *m*-phenylene diisocyanate with 1-octanol, basic catalysis affects the early stages more than the latter stages (k_2). With 2-octanol, the opposite is true; here k_2 is affected more than k_1.

(4) For 2,4-tolylene diisocyanate, k_2 is always increased more by basic catalysis than k_1, but the effect is much more marked with 2-octanol.

(5) As was the case with the uncatalyzed reactions, the order of decreasing reactivity of the diisocyanates, as listed in Table I, probably changes at high extents of reaction. For catalyzed reactions with either 1- or 2- octanol, 4,4′-methylenebis(phenyl isocyanate) should approach 100% reaction faster than 2,4-tolylene diisocyanate, because of the smaller k_2 values of the latter diisocyanate.

EXPERIMENTAL

Materials. All materials, except the diisocyanates, were distilled before use. Their boiling points corresponded to values in the literature. The diisocyanates were commercial samples, used as received. The 4,4′-methylenebis(phenyl isocyanate) analyzed as 97% pure; all the others were 99+% pure.

Procedure. Reactions were carried out in a double chambered vapor bath, using boiling *n*-butanol as the bath material. This gave an average working temperature of about 115°. Bath temperatures varied slightly from day to day (from a minimum of 113° to a maximum of 115.5°) due to the influence of varying barometric pressure on the boiling point of the *n*-butanol. Within a given run, however, the temperature was usually quite constant.

Stock solutions (0.10*N*) of the alcohols were prepared in chlorobenzene. For a kinetic run, 100 ml. of solution were

placed in the inner chamber of the vapor bath and brought to temperature. Then weighed amounts of tri-*n*-butyl amine (when used) and diisocyanate were added in amounts sufficient to prepare 0.01*N* and 0.1*N* solutions respectively. The inner chamber of the bath was stoppered to prevent undue exposure of the reaction mixture to moisture.

Reaction rates were determined by following the disappearance of isocyanate by a modified Stagg method.[7] Samples were removed periodically, and warmed with excess dibutyl amine to react completely the remaining diisocyanate in the sample. Unreacted dibutyl amine was titrated potentiometrically with 0.025*N* HCl, using a Beckman Model K Automatic Titrator. In catalyzed runs, titrations were corrected for the amount of tri-*n*-butyl amine in the sample.

Data were calculated and plotted according to the usual second-order reaction rate equation for reactants at equal initial concentration. Representative rate plots are given in Fig. 1. Rate constants were determined from the slope of

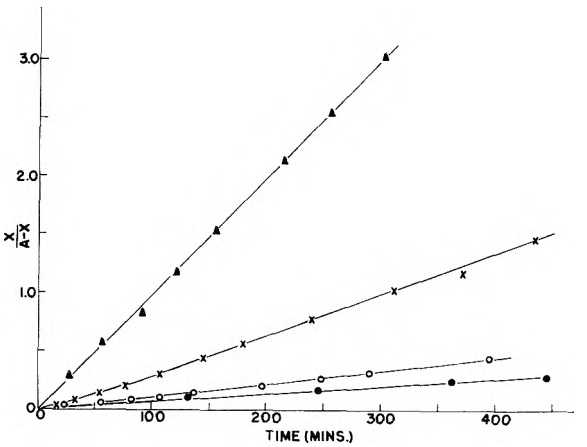

Fig. 1. Representative second-order rate plots for the reaction of 3,3′-dimethyl-4,4′-biphenylene diisocyanate with ▲ 1-octanol, catalyzed; × 2-octanol, catalyzed; ○ 1-octanol, uncatalyzed; ● 2-octanol, uncatalyzed. Additional points were obtained on the first and last curves which established the linearity of the plots at higher extents of reaction.

the best straight line drawn (by visual methods) through the points of the plot. Reproducibility of runs was quite good (*i.e.*, agreement of duplicate runs was ±1.5%), and all sets of data fitted the second-order rate equation with two exceptions. For both catalyzed and uncatalyzed reactions of 1-octanol with 4,4′-methylenebis (phenyl isocyanate), the rate plots drifted upward slightly at high extents of reaction. No satisfactory explanation could be found for this, so rate constants for these reactions were determined from the best straight lines drawn through the first few points of the plots (up to about 30% reaction). Blank runs, in which the diisocyanates were heated alone, with or without the amine catalyst, resulted in negligible or no disappearance of the diisocyanate. No evidence was found for any reaction taking place other than urethane formation except for the above-mentioned reactions of 4,4′-methylenebis(phenyl isocyanate) and 1-octanol. Even in these cases, deviation of the rate plots from linearity corresponded to only a few percent of the total diisocyanate that had reacted. Consideration of data in the literature,[8] as well as the experiments of this work, indicated that allophanate formation, or dimerization or trimerization of the diisocyanate, either would not occur at all under the experimental conditions of this work, or would take place only slowly in comparison to the rate of urethane formation.

When two isocyanate groups are attached to the same benzene nucleus, as in *m*-phenylene diisocyanate and 2,4-tolylene diisocyanate, two separate rate constants are obtained for each diisocyanate.[4-6] With *m*-phenylene diisocyanate, the two isocyanate groups have equal initial reactivity. Beyond 50% reaction, however, when one isocyanate group has been converted to a urethane group, the second isocyanate group exhibits a slightly lower reactivity, due to the lesser activating effect of a *m*-urethane group in comparison to that of a *m*-isocyanate group.[4-6] With 2,4-tolylene diisocyanate, because of the presence of the methyl group on the benzene nucleus, the 4-isocyanate group has higher initial reactivity.[4-6] When rate data for such diisocyanates are plotted, curvatures are obtained in the plots near 50% reaction. The best straight line was drawn through the first few points of the plot, and from this k_1, the rate constant for the more reactive isocyanate group, was determined. Similarly, k_2, the rate constant for the less reactive group, was determined from the last few points on the curve beyond 50% reaction.

For all such reactions, the two rate constants so obtained were of the same order of magnitude. Hence, there was probably some overlapping and interfering reaction of both isocyanate groups throughout the entire course of each reaction. It was felt, however, that because of the reasonably good linearity obtained in the early and late stages of each such rate plot, there was sufficient justification for determining the two rate constants independently of each other by simple graphical means. All such rate constants in this work probably do contain some degree of approximation, however.

Acknowledgment. The kind permission of the Goodyear Tire and Rubber Company to publish this work is gratefully acknowledged. This is Contribution No. 236 from the Goodyear Research Laboratory.

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(7) H. E. Stagg, *The Analyst*, **71**, 557 (1946).

(8) J. H. Saunders, *Rubber Chem. and Technol.*, **32**, 337 (1959), and references therein.

Some 2,2-Disubstituted-3,5-morpholinediones

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These compounds were synthesized for comparison with the previously reported 2,2-disubstituted-3,5-thiomorpholinediones.[3] In general, the 3,5-morpholinediones were prepared from the suitably substituted esters of glycolic acid by converting them to diesters of diglycolic acid, then to the diamides or ammonium salts which were pyrolyzed to the substituted 3,5-morpholinediones. Preliminary pharmacological screening tests indicate that compounds with like substituents possess similar activities as hypnotics and anticonvulsants.

(1) Work done at University of Delaware, Newark, Del.

(2) Work done at Merck, Sharp and Dohme Laboratories, West Point, Pa.

(3) G. S. Skinner and J. B. Bicking, *J. Am. Chem. Soc.*, **76**, 2776 (1954).

EXPERIMENTAL

α,α-Dimethyldiglycolamide.[2] To a refluxing suspension of 19.5 g. (0.5 mole) of sodium amide in 300 cc. of ether was added dropwise ethyl α-hydroxyisobutyrate (66.0 g., 0.5 mole). After refluxing 45 min. longer to expel the ammonia ethyl bromoacetate (83.5 g., 0.5 mole) was added dropwise during 30 min. The stirred mixture was refluxed 2 hr. Water was added and the dried ether layer was distilled to yield 23.0 g. of product, b.p. 125–128° (13 mm.). This was dissolved in a solution of 25 cc. of liquid ammonia in 175 cc. of ethanol. The solution was heated in a pressure bottle 5 days at 70–80°. The solution was concentrated to 100 cc. and chilled to give 15.4 g. of crude amide, m.p. 160–162°. One crystallization from ethanol gave the pure product, m.p. 162–163°.

Anal. Calcd. for $C_6H_{12}N_2O_3$: N, 17.48. Found: N, 17.51.

2,2-Dimethyl-3,5-morpholinedione.[2] The above amide (14.3 g., 0.09 mole) was heated at 200° (60 mm.) for 30 min. The temperature of the bath was raised to 260° whereupon the imide distilled at 20 mm. pressure and solidified in the receiver. The product was triturated with sodium bicarbonate solution to give 6.3 g., m.p. 73–76°. One recrystallization from benzene-ligroin yielded 5.0 g. of pure product, m.p. 74–76°.

Anal. Calcd. for $C_6H_9NO_3$: N, 9.79. Found: N, 9.75.

α,α-Diethyldiglycolic acid.[2] To a stirred suspension of 2.4 g. of sodium hydride in 100 cc. of dry benzene was added during 25 minutes 16.0 g. (0.10 mole) of ethyl α-ethyl-α-hydroxybutyrate and the stirring continued 40 min. until a clear yellow solution resulted. Ethyl bromoacetate (18.4 g., 0.11 mole) was added dropwise and the mixture was refluxed for 2 hr. Water was added. The organic layer was dried and distilled to give 9.2 g. of colorless oil, b.p. 152–157° (22 mm.). A total of 90.7 g. of this oil was dissolved in 340 cc. of hot hydrochloric acid (Sp. gr. 1.18) and the solution was heated 16 hr. in a steam bath. The solution was concentrated to 200 cc. and chilled. The crystalline product (41.5 g.) had m.p. 140–147° and was suitable for preparation of the ammonium salt. A small sample was crystallized twice from ethyl acetate to give the pure acid, m.p. 146–148°.

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.58; H, 7.50.

2,2-Diethyl-3,5-morpholinedione.[2] A solution of 28.5 g. (0.15 mole) of α,α-diethyldiglycolic acid in 90 cc. ammonia water (Sp. gr. 0.90) was evaporated to dryness. The resulting salt was heated at 190° for 25 minutes at a pressure of 50 mm. The bath temperature was raised to 210° and the pressure was lowered to 14 mm., whereupon the product distilled and crystallized. It was triturated with sodium bicarbonate solution and recrystallized from a mixture of isopropyl alcohol and water to give 10.4 g. of the imide, m.p. 62–63°.

Anal. Calcd. for $C_8H_{13}NO_3$: N, 8.18. Found: N, 8.18.

Methyl ethylphenylhydroxyacetate.[1] Ethylphenylhydroxyacetic acid[4] (11.4 g., 0.063 mole) was refluxed for 2.5 hr. with 60 cc. of methanol containing 0.3 cc. of sulfuric acid. The mixture was treated with 50 cc. of water and 50 cc. of saturated sodium bicarbonate solution. The solution was saturated with salt and extracted with ether. From the aqueous layer there was obtained unchanged acid (0.48 g.) and from the ether extract 11.11 g. of the ester, b.p. 86–88° (0.9 mm.), n_D^{25} 1.5080.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.98; H, 7.37.

Methyl α-ethyl-α-phenyl-α-carbethoxymethoxyacetate.[1] In a nitrogen atmosphere methyl ethylphenylhydroxyacetate (18.8 g., 0.097 mole) was added dropwise during 2 hr. to a rapidly stirred suspension of sodium hydride (1.9 g., 0.08 mole) in 200 cc. of dry benzene at room temperature. Nearly all of the sodium hydride dissolved after stirring 6.5 hr. Complete solution was then effected by refluxing for 1.5 hr. To the stirred solution at room temperature was added dropwise ethyl bromoacetate (13.4 g., 0.08 mole). After stirring overnight the reaction mixture was refluxed for 1 hr., cooled and treated with 100 cc. of cold water. Less than 0.002 mole of hydrogen ions was required for neutrality. The benzene layer was washed with sodium bicarbonate solution, dried, and distilled, yield 14.7 g. (65.6%), b.p. 133–135.5° (0.7 mm.), n_D^{25} 1.4945.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.11.

α-Ethyl-α-phenyldiglycolamide.[1] A solution of the above ester (4.2 g., 0.015 mole) in 100 cc. of anhydrous methanol contained in a pressure bottle was saturated at −5° with dry ammonia gas. The bottle was capped and allowed to stand for a week at 45–55°. Removal of the solvent afforded a quantitative yield of crude diamide, m.p. 169–173°. Recrystallization from methanol-ether gave the pure product, m.p. 175° (dec.).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 60.99; H, 6.82; N, 11.86. Found: C, 60.90; H, 6.87; N, 11.86.

2-Ethyl-2-phenyl-3,5-morpholinedione.[1] The above amide was pyrolyzed at 210–220° to yield an amber oil which was dissolved in hot methanol and treated with boneblack to remove color. Hot water was added to the filtrate to the point of incipient precipitation. The crude imide (0.7 g., m.p. 115–125°) separated from the cold solution. This was crystallized from methanol-water to give 0.67 g. (73%) of the pure product, m.p. 124–125°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.97; N, 6.39. Found: C, 65.87; H, 5.97; N, 6.41.

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(4) A. McKenzie and A. Ritchie, *Ber.*, **70B**, 33 (1937).

Scission of the Silicon-Silicon Bond in Halogenated Polysilanes by Organometallic Reagents

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Cleavage of the silicon-silicon bond by organometallic reagents has been long known. First reports of cleavages of this nature were by Friedel and Ladenburg,[1–3] who demonstrated that treatment of hexaiododisilane with diethylzinc gave a mixture of tetraethylsilane and hexaethyldisilane. Shortly thereafter it was reported[4] that tetraphenyldisilane was the sole product from the reaction of hexachlorodisilane, chlorobenzene, and sodium. No yields or experimental details were mentioned. From the reaction of hexachlorodisilane with methyl magnesium iodide, Martin[5] obtained oils which he postulated were mixtures of monosilanes containing methyl and chloro groups. From hexachlorodisilane

(1) C. Friedel and A. Ladenburg, *Compt. rend.*, **68**, 923 (1869).

(2) C. Friedel and A. Ladenburg, *Ann.*, **203**, 251 (1880).

(3) C. Friedel and A. Ladenburg, *Ann. Chim. Phys.*, [5] **19**, 401 (1880).

(4) L. Gattermann and K. Weinlig, *Ber.*, **27**, 1946 (1894).

(5) G. Martin, *Ber.*, **46**, 2442, 3294 (1913).

and phenylmagnesium bromide, dichlorodiphenylsilane was isolated.[6]

In a series of three papers,[7-9] Schumb and coworkers investigated the reactions of chlorinated polysilanes, notably hexachlorodisilane, with organometallic reagents. It was found[7] that hexasubstituted disilanes could not be prepared under Wurtz-type coupling conditions by treatment of alkyl or aryl halides with sodium in the presence of hexachlorodisilane. In each case, only the tetrasubstituted monosilane was obtained. When reactions were carried out[9] using preformed organosodium compounds and hexachlorodisilane, the main products isolated were the hexasubstituted disilanes. Some tetrasubstituted monosilanes were also isolated. Better yields of the hexasubstituted disilanes were obtained using Grignard reagents[8] instead of organosodium compounds. From the reaction of octachlorotrisilane with phenylmagnesium bromide, only hexaphenyldisilane and tetraphenylsilane were isolated. On this basis, it was postulated[8] that the instability of the silicon-silicon bond in halogenated polysilanes increases as the number of silicon atoms increases.

From the reaction of hexachlorodisilane with *p*-xenyllithium there was obtained[10] a mixture of tetraxenylsilane and hexaxenyldisilane. Similarly, from hexachlorodisilane and *p*-tolyllithium, tetra-*p*-tolylsilane was isolated[11] in 42% yield. From hexachlorodisilane and 2,2′-biphenylenedilithium there was obtained 5,5′-spirobi[dibenzosilole] and a large amount of resinous material.[12] When triphenylsilyllithium is allowed to react with silicon tetrachloride, hexaphenyldisilane is obtained along with a large quantity of polymer.[13] Since it is known that hexaphenyldisilane is not cleaved by phenyllithium in ether[14] it may be assumed that a totally halogenated or partially halogenated disilane is the species undergoing cleavage. It seems possible that a number of halogenated disilanes may cleave.

In an attempt to prepare 1,1,2,2-tetraphenyldisilane by the reaction of 4 moles of phenylmagnesium bromide with one mole of hexachlorodisilane, followed by reduction with lithium aluminum hydride, diphenylsilane was isolated. In a subsequent experiment, in which no reduction with lithium aluminum hydride was carried out, dichlorodiphenylsilane was isolated in 7% yield along with a trace of tetraphenylsilane and a large amount of resin. Thus we suggest that the first step of the reaction may be the formation of pentachlorophenyldisilane. Cleavage of this compound by phenylmagnesium bromide could give rise to dichlorodiphenylsilane and an intermediate species, trichlorosilylmagnesium bromide. Disproportionation of the trichlorosilylmagnesium bromide would give a dichlorosilane, which would then polymerize to give polymeric $SiCl_2$, which appears to be analogous to the material isolated by Schmeisser and Schwarzmann.[15]

$$Cl_3SiSiCl_3 + PhMgBr \longrightarrow Cl_2SiSiCl_2Ph + MgBrCl$$

$$Cl_3SiSiCl_2Ph + PhMgBr \longrightarrow Ph_2SiCl_2 + BrMgSiCl_3$$

$$BrMgSiCl_3 \longrightarrow [:SiCl_2] + MgBrCl$$

$$n[:SiCl_2] \longrightarrow [—SiCl_2—]_n$$

Polymeric resins were also obtained in some recently reported studies.[12,13] Also, the results[13] involving the formation of hexaphenyldisilane from the reaction of excess triphenylsilyllithium with silicon tetrachloride would suggest that initially 1,1,1-trichloro-2,2,2-triphenyldisilane is formed. Cleavage of this compound with triphenylsilyllithium would give hexaphenyldisilane and the intermediate trichlorosilyllithium.

$$Ph_3SiLi + SiCl_4 \longrightarrow Ph_3SiSiCl_3 + LiCl$$

$$Ph_3SiSiCl_3 + Ph_3SiLi \longrightarrow Ph_3SiSiPh_3 + LiSiCl_3$$

EXPERIMENTAL[16]

Reaction of hexachlorodisilane with phenylmagnesium bromide (Run 1). To a stirred solution of 63.7 g. (0.237 mole) of hexachlorodisilane in 100 ml. of ether was added 745 ml. of an ethereal solution containing 0.95 mole of phenylmagnesium bromide. After stirring overnight, the reaction mixture gave a positive Color Test I.[17] The ether was distilled and replaced by benzene. After heating for several hours at the benzene reflux temperature, Color Test I was negative. The reaction mixture was cooled and treated with 4.75 g. (0.125 mole) of lithium aluminum hydride suspended in ether. After a short reflux period, the reaction mixture was treated with ethyl acetate and then aqueous ammonium chloride. The only product identified was 17.6 g. of crude diphenylsilane, b.p. 82–86° (0.6 mm.), which on redistillation boiled at 123–126° (11 mm.).[18] The infrared spectrum showed a strong Si-H band at 4.8μ, but the product was badly contaminated with biphenyl.

Run 2. In this experiment, 290 ml. of an ethereal solution containing 0.335 mole of phenylmagnesium bromide was added to a solution of 22.6 g. (0.0837 mole) of hexachloro-

(6) R. Schwarz and W. Sexauer, *Ber.*, **59**, 333 (1926).

(7) W. C. Schumb, J. Ackerman, and C. M. Saffer, *J. Am. Chem. Soc.*, **60**, 2486 (1938).

(8) W. C. Schumb and C. M. Saffer, *J. Am. Chem. Soc.*, **61**, 363 (1939).

(9) W. C. Schumb and C. M. Saffer, *J. Am. Chem. Soc.*, **63**, 93 (1941).

(10) H. Gilman and G. E. Dunn, *J. Am. Chem. Soc.*, **73**, 5077 (1951).

(11) H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, **75**, 3762 (1953).

(12) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **80**, 3243 (1958).

(13) D. Wittenberg, M. V. George, and H. Gilman, *J. Am. Chem. Soc.*, **81**, 4812 (1959).

(14) G. E. Dunn, unpublished studies. However, unpublished studies by B. J. Gaj have shown that a solvent like tetrahydrofuran can have a significant effect.

(15) M. Schmeisser and M. Schwarzmann, *Z. Naturforsch.*, **11b**, 228 (1956).

(16) Organometallic reactions were carried out under an atmosphere of dry, oxygen-free nitrogen. Melting points are uncorrected.

(17) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(18) Reported 75–76° (0.5 mm.), R. A. Benkeser, H. Landesman, and D. J. Foster, *J. Am. Chem. Soc.*, **74**, 648 (1952).

disilane in 100 ml. of ether. The ether was distilled and the resulting paste was heated at about 50° for 3 hr. Color Test I was then negative. Petroleum ether (b.p. 60–70°) was added. Filtration gave a clear solution which on cooling deposited an oil. After stripping off the petroleum ether, distillation of the residue gave three main fractions.

The first, b.p. 169–180° (20 mm.), 3.24 g. (7.6%), was redistilled at 15 mm. and boiled at 165–167°. The infrared spectrum of this oil was identical with that of an authentic specimen of dichlorodiphenylsilane. Further confirmation that the product was dichlorodiphenylsilane was obtained by treatment of 1.22 g. of the chlorosilane with *p*-biphenylyllithium. There was obtained 1.86 g. (81%) of di-*p*-biphenylyldiphenylsilane, m.p. 169–171° (reported[19] 169–170°). A mixed melting point with an authentic specimen of di-*p*-biphenylyldiphenylsilane was not depressed.

A second fraction distilled over the range 229–240° (20 mm.) and weighed 3.45 g. This was recrystallized from petroleum ether (b.p. 60–70°) and melted partially at 97°, indicative of the possible presence of chlorotriphenylsilane. Distillation of this solid gave no pure products.

A third fraction distilled over the range 185–215° (0.3 mm.), 7.1 g., and crystallized on standing. Recrystallization from petroleum ether (b.p. 60–70°) gave 3.5 g., melting at 125–128° (partial). Several recrystallizations did not sharpen the melting point. One g. of this material was treated with excess methyllithium. Hydrolysis, followed by work-up in the usual way, gave some solid, m.p. 133–143°. This was dissolved in hot petroleum ether (b.p. 60–70°) and chromatographed on an alumina column to give 0.3 g. of solid, m.p. 140–142° (cloudy). A mixed melting point with 1,2-dimethyl-1,1,2,2-tetraphenyldisilane was not depressed.

A small amount of tetraphenylsilane was scraped from the condenser walls after the distillation and recrystallized from benzene, m.p. 236°.

The distillation residue consisted of a large amount of brown polymer which, though insoluble in most common solvents, dissolved slowly in benzene.

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(19) L. Spialter, D. C. Priest, and C. W. Harris, *J. Am. Chem. Soc.*, **77**, 6227 (1955).

Magnesium Salts of Aromatic Arsonic Acids. The Nitration of Benzenearsonic Acid

LEON D. FREEDMAN AND G. O. DOAK

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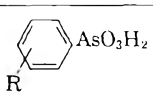
Magnesium salts of most phosphonic acids are soluble at room temperature but are precipitated on heating.[1] However, arylphosphonic acids containing bulky *ortho* substituents do not form insoluble magnesium salts either at room temperature or when heated. This fact permitted the isolation of *o*-nitrophenylphosphonic acid from the mixture of isomers obtained by nitrating phenylphosphonic acid.[1] It has been known for over half a century that the magnesium salts of arsonic acids are more soluble in cold water than in hot.[2] And, indeed, the fact that atoxyl[3] yields a precipitate with magnesia mixture only upon boiling was cited by Ehrlich and Bertheim[4] as evidence that atoxyl is an arsonic acid derivative. However, a survey of the literature revealed very little information concerning the effect of the substituents on the solubility of magnesium salts of aromatic arsonic acids.[5] Since we had available in this laboratory a number of aromatic arsonic acids, it was of interest to determine whether the generalizations previously noted[1] for arylphosphonic acids were also valid for the analogous arsonic acids.

A sample of each arsonic acid listed in Table I was dissolved in dilute aqueous ammonia and treated with magnesia mixture exactly as described for the phosphonic acids.[1] The following results were obtained: (1) Only one arsonic acid (*N*-*p*-toluylarsanilic acid) gave an insoluble magnesium salt at room temperature. (2) *o*-Toluenearsonic and *o*-bromobenzenearsonic acids gave sparse precipitates on heating; all other compounds

TABLE I

ARSONIC ACIDS STUDIED



R =

H	*p*-$NHCOCH_3$
o-,*m*,*p*-NO_2	*p*-AsO_3H_2
o-,*m*,*p*-Cl	*p*-$NHCH_2COOCH_3$
o-,*p*-Br	*p*-$NHCOC_6H_4CH_3$-*p*′
o-,*p*-CH_3	2-NO_2-6-CH_3
m-,*p*-SO_2NH_2	2-NO_2-3-COOH
m-COOH	3-NO_2-4-NH_2
p-$COOCH_3$	3-NO_2-4-OH
o-C_6H_5	3-NO_2-4-COOH
p-NH_2	3-NH_2-4-$(CH_2)_3COOH$
p-OH	

(1) L. D. Freedman and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 6221 (1955); see also *Chem. Revs.*, **57**, 479 (1957).

(2) W. M. Dehn, *Am. Chem. J.*, **33**, 101 (1905).

(3) "Atoxyl" is a trivial name for the sodium salt of arsanilic acid. It was first prepared by A. Bechamp, *Compt. rend.*, **56**, 1172 (1863), and was originally believed to be an anilide of arsenic acid.

(4) P. Ehrlich and A. Bertheim, *Ber.*, **40**, 3292 (1907).

(5) L. Benda, *J. prakt. Chem.*, **95**, 75 (1917), reported that several anthraquinonearsonic acids yield precipitates with magnesia mixture in the cold. H. Schmidt, *Ann.*, **421**, 159 (1920), found that *o*-nitrobenzenearsonic acid does not give any precipitate on boiling with magnesia mixture, the magnesium salt separating only on prolonged standing at room temperature. G. O. Doak, H. Eagle, and H. G. Steinman, *J. Am. Chem. Soc.*, **64**, 1064 (1942), state that certain diarsonic acids give insoluble magnesium salts in the cold, whereas the magnesium salts of monoarsonic acids usually precipitate only on heating.

containing *ortho* substituents did not form insoluble magnesium salts. (3) With three exceptions, compounds lacking *ortho* substituents gave copious precipitates on heating. The exceptions, *m*-carboxybenzenearsonic acid, *m*-sulfamylbenzenearsonic acid and (2-amino-4-arsonophenyl)butyric acid, failed to give precipitates with magnesia mixtures. It is probably significant that the exceptions are acid substituted benzenearsonic acids.

The above results are similar to those previously obtained with arylphosphonic acids. In both types of acids the presence of *ortho* substituents seems to inhibit the formation of insoluble magnesium salts. This effect may often be useful in separating *ortho* isomers from mixtures of isomeric acids. In the work described below, the magnesium salt technique was used in the investigation of the products formed in the nitration of benzenearsonic acid.

The Nitration of Benzenearsonic Acid. Michaelis and Lösner[6] were the first to attempt the nitration of benzenearsonic acid. They found that it was unaffected by fuming nitric acid even at 100° but that it could be nitrated with 100% nitric acid. The nitrobenzenearsonic acid obtained was believed to be a single isomer, but no information about the position of the nitro group was obtained. The constitution of the acid was established by Bertheim and Benda,[7] who showed that it is *m*-nitrobenzenearsonic acid. Isomeric compounds could not be detected in the reaction mixture.

We confirmed the observation of Michaelis and Lösner that benzenearsonic acid is remarkably difficult to nitrate. Although phenylphosphonic acid can be nitrated at room temperature with fuming nitric acid to give a virtually quantitative yield of mononitrated phenylphosphonic acid, this procedure is without effect on benzenearsonic acid. The use of anhydrous nitric acid at the boiling point was, however, quite satisfactory. From the reaction mixture an 83% yield of a nitrobenzenearsonic acid was obtained. This material was shown to be pure *m*-nitrobenzenearsonic acid by comparison with an authentic sample prepared from *m*-nitrobenzenediazonium fluoborate.[8] Using the magnesium salt procedure, we isolated also a small yield (1.6%) of a different nitrobenzenearsonic acid, which was shown to be the pure *o*-isomer by comparison with a commercial sample (Eastman Kodak White Label). It is clear, then, that the nitration of benzenearsonic acid does not yield only a single product.

The fact that benzenearsonic acid is much more difficult to nitrate than phenylphosphonic acid requires explanation. A possible reason may be associated with a difference in the base strengths of the two acids, *i.e.*, the relative ease with which they are protonated. Although the appropriate dissociation constants have not been reported, the *acid* dissociation constants of benzenearsonic[9] and phenylphosphonic[10] acids are well-known. And if we assume that the acid dissociation constants of the species $C_6H_5MO_3H_3^+$ (where M is either P or As) are in the ratio $1:10^{-5}:10^{-10}$, then the first pK_a of $C_6H_5AsO_3H_3^+$ is about -1, while the first pK_a of $C_6H_5PO_3H_3^+$ is about -3.[11] The acidity function (H_0) of fuming nitric acid has not been determined, but it seems probable that benzenearsonic acid is almost completely protonated in this solvent because the acidity function of 9.5 M nitric acid is -2.[12] The difficulty in nitrating benzenearsonic acid is caused, then, by the deactivating effect of the positively charged arsono group. We can not be sure as to what extent phenylphosphonic acid is protonated in fuming nitric acid, but it is possible that the phosphonic acid exists to a considerable degree in this solvent as an uncharged molecule, which we would expect to be readily nitrated.

EXPERIMENTAL[13]

The nitration of benzenearsonic acid. Benzenearsonic acid (50 g.) was nitrated with 270 ml. of anhydrous nitric acid (Baker and Adamson) under conditions similar to those described in ref. 6. The reaction mixture was diluted with 375 ml. of water and cooled, whereupon 45.9 g. of pure *m*-nitrobenzenearsonic acid, m.p. 177–180°, crystallized from solution. A second crop (4.9 g.) of *m*-nitrobenzenearsonic acid was obtained by evaporating the mother liquor to incipient crystallization. Both crops were identified by analysis, by mixed m.p. with an authentic sample and by ultraviolet absorption (λ_{max} = 252.5 mμ, ϵ_{max} = 7,800).

The filtrate from the second crop of *m*-nitrobenzenearsonic acid was evaporated to dryness, and the residue was dissolved in 50 ml. of 10% aqueous ammonia. When the resulting solution was mixed with 200 ml. of 0.27*M* magnesium chloride solution, a precipitate formed immediately. This precipitate must consist of a magnesium salt of inorganic arsenic acid, as neither benzenearsonic acid nor the isomeric nitrobenzenearsonic acids give insoluble magnesium salts in the cold. The precipitate, after being washed with 3% aqueous ammonia and dried at 100° for an hour, weighed 2.56 g. and contained 34.9% arsenic. This result indicates that about 5% of the benzenearsonic acid used had been converted to inorganic arsenic during the course of the nitration.

The filtrate and washings from the magnesium arsenate were combined and boiled to precipitate the magnesium salt

(6) A. Michaelis and H. Lösner, *Ber.*, **27**, 263 (1894).

(7) A. Bertheim and L. Benda, *Ber.*, **44**, 3297 (1911).

(8) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5656 (1951).

(9) D. Pressman and D. H. Brown, *J. Am. Chem. Soc.*, **65**, 540 (1943), report for $C_6H_5AsO_3H_2$, $K_1 = 3.4 \times 10^{-4}$, $K_2 = 3.3 \times 10^{-9}$.

(10) H. H. Jaffé, L. D. Freedman, and G. O. Doak, *J. Am. Chem. Soc.*, **75**, 2209 (1953), report for $C_6H_5PO_3H_2$, $pK_1 = 1.83$, $pK_2 = 7.07$.

(11) L. Pauling, *General Chemistry*, W. H. Freeman and Co., San Francisco, Calif., 1954, p. 453.

(12) L. P. Hammett and M. A. Paul, *J. Am. Chem. Soc.*, **56**, 827 (1934).

(13) Melting points were determined by the method of J. F. Morgan and C. S. Hamilton, *J. Am. Chem. Soc.*, **66**, 874 (1944). The ultraviolet absorption spectra were determined in 95% ethanol according to the procedure described by H. H. Jaffé and L. D. Freedman, *J. Am. Chem. Soc.*, **74**, 1069 (1952).

of any *m*-nitrobenzenearsonic acid still remaining in solution. The precipitate, after being washed with hot water and dried *in vacuo* over sulfuric acid, weighed 3.94 g. It was not further investigated.

The filtrate from the above precipitate was evaporated to dryness, and the residue was dissolved in 500 ml. of water and treated with 160 g. of Dowex-50 (hydrogen ion form). The resin was removed, and the resulting solution evaporated to dryness. Recrystallization of the residue from water yielded 1.0 g. of pure *o*-nitrobenzenearsonic acid, m.p. 225–229°. This was identified by analysis, by mixed m.p. with an authentic sample, and by ultraviolet absorption (λ_{max} = 262 mμ, ϵ_{max} = 5740).

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Synthesis of Vinyl *N,N*-Dialkyldithiocarbamates

J. C. SAUER

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Saturated esters of dithiocarbamic acids are well known, generally being prepared by the reaction of an amine, carbon disulfide, and an alkyl halide.[1] Vinyl esters of the dithiocarbamic acids have not been reported. Now it has been found that vinyl *N,N*-dialkyldithiocarbamates can be readily prepared by the interaction of a dialkylamine, carbon disulfide, and acetylene. The vinylations were carried out at applied acetylene pressures of 13–18 atm. and a temperature of 130°. Tetrahydrofuran was the best solvent investigated, being superior to dimethylformamide or water. Catalytic amounts of potassium hydroxide gave slightly improved yields of product, but the catalyst was not otherwise essential. Yields of vinyl esters ranged from 52 to 60%.

$$R_2NH + CS_2 + C_2H_2 \longrightarrow R_2N{-}\overset{\overset{S}{\|}}{C}{-}SCH{=}CH_2$$

The characterization of these new vinyl monomers included elemental and spectral analyses and identification of acetaldehyde as a product of hydrolysis. Added characterization consisted in vinyl polymerization with free radical initiators.

EXPERIMENTAL

Reaction of diethylamine, carbon disulfide, and acetylene.[2] Diethylamine (43.8 g.) was added to 100 ml. of tetrahydrofuran containing carbon disulfide (45.7 g.) with cooling and shaking. Potassium hydroxide (1 g.) was added to the dithiocarbamic acid, and the mixture was transferred to a 500-ml. stainless steel rocker bomb which previously had been flushed with nitrogen. The bomb was pressure tested with nitrogen at 36 atm. pressure, then cooled in a solid carbon dioxide/methanol cooling bath and evacuated to about 10 mm. pressure. The equipment was installed behind a heavy barricade, and all operations with acetylene were controlled from the outside. With the bomb temperature slightly under room temperature, acetylene was introduced to 13 atm., and the reaction mixture was heated to 130°. This temperature was maintained for 6 hr., and the pressure was kept at 13–17 atm. by periodic repressuring with acetylene. The bomb was next cooled to room temperature, the pressure released, and the contents were removed. The reaction mixture was distilled, and the fraction distilling at 92–93°/2 mm. weighed 55 g. (52.4% yield), n_D^{25} 1.5942.

Anal. Calcd. for $C_7H_{13}NS_2$: C, 48.0; H, 7.4; S, 36.5; N, 8.1. Found: C, 48.1; H, 7.5; S, 36.3; N, 7.9.

The infrared spectrum showed absorption at 3.25μ and 3.3μ for double bond CH; 3.4μ, 3.42μ, and 3.5μ for saturated CH; 6.3μ for S—C=C<; and 6.75μ for —N—C=S. Hydrogen deformation bands for S—CH=CH_2 compounds have not been assigned (see Fig. 1).

Vinyl *N,N*-diethyldithiocarbamate (4 g.), ethanol (17.5 ml.), and concentrated hydrochloric acid (25 ml.) were heated in an 18-inch still equipped with variable take-off. The distillate was slowly removed during 1.5 hr. and dropped into excess dinitrophenylhydrazine reagent. The dinitrophenylhydrazone, after recrystallization from ethyl acetate, weighed 2.1 g. (41%), m.p. 147–148°. The infrared spectrum was identical to that of an authentic sample of the dinitrophenylhydrazone of acetaldehyde.

Reaction of dibutylamine, carbon disulfide, and acetylene. A mixture of di-*n*-butylamine (64.5 g.) and carbon disulfide (38 g.) in tetrahydrofuran (100 ml.) containing potassium hydroxide (1 g.) was treated with acetylene under a gauge pressure of 15–17 atm. during 8.5 hr. at 135°. The reaction mixture was worked up as described previously, and 75 g. of the vinyl ester distilling at 131–138°/3 mm. (59.6% yield), n_D^{25} 1.5543, was obtained. On redistillation, most of this fraction distilled at 144–147°/4–5 mm., n_D^{25} 1.5550.

Anal. Calcd. for $C_{11}H_{21}NS_2$: C, 57.2; H, 9.1; S, 27.7. Found: C, 57.3; H, 9.3; S, 27.4.

This vinyl ester (4 g.) containing α,α′-azobis(α,γ-dimethylvaleronitrile) (0.008 g.) was heated to 95–98° for 3 hr. The resulting homopolymer was extremely viscous at room temperature. Polymerization of this vinyl monomer (4.3 g.) with α,α′-azobis(α-isobutyronitrile) initiator (0.08 g.) at 80° and 8000 atm. pressure in benzene (4.3 g.) gave a homopolymer which could be pressed into a film at 50°. At room temperature the film was clear, limp, and slightly tacky.

Quantitative hydrogenation with platinum catalyst at room temperature and atmospheric pressure in dioxane solvent gave values varying from 0.0032 to 0.0073 g. of hydrogen/g. of sample (theory—0.009 g. of hydrogen/g. of sample). It is likely that the hydrogenation was incomplete and erratic because of catalyst poisoning by this sulfur-containing compound.

Reaction of dipropylamine, carbon disulfide, and acetylene. A mixture of di-*n*-propylamine (60.7 g.), carbon disulfide (45.7 g.), and potassium hydroxide (1 g.) in tetrahydrofuran (100 ml.) was treated with acetylene under a gauge pressure of 13–18 atm. during 9 hr. at 110–150°. The reaction mixture was worked up as described previously, and 68 g. of the vinyl ester distilling at 123–124°/8 mm. (55.6% yield), n_D^{25} 1.5721, was obtained.

Anal. Calcd. for $C_9H_{17}NS_2$: C, 53.2; H, 8.3. Found: C, 53.2; H, 8.0.

(1) M. Delephine, *Compt. rend.*, **134**, 715 (1902).

(2) C. T. Handy and J. C. Sauer, U. S. Patent **2,579,384**, December 18, 1951.

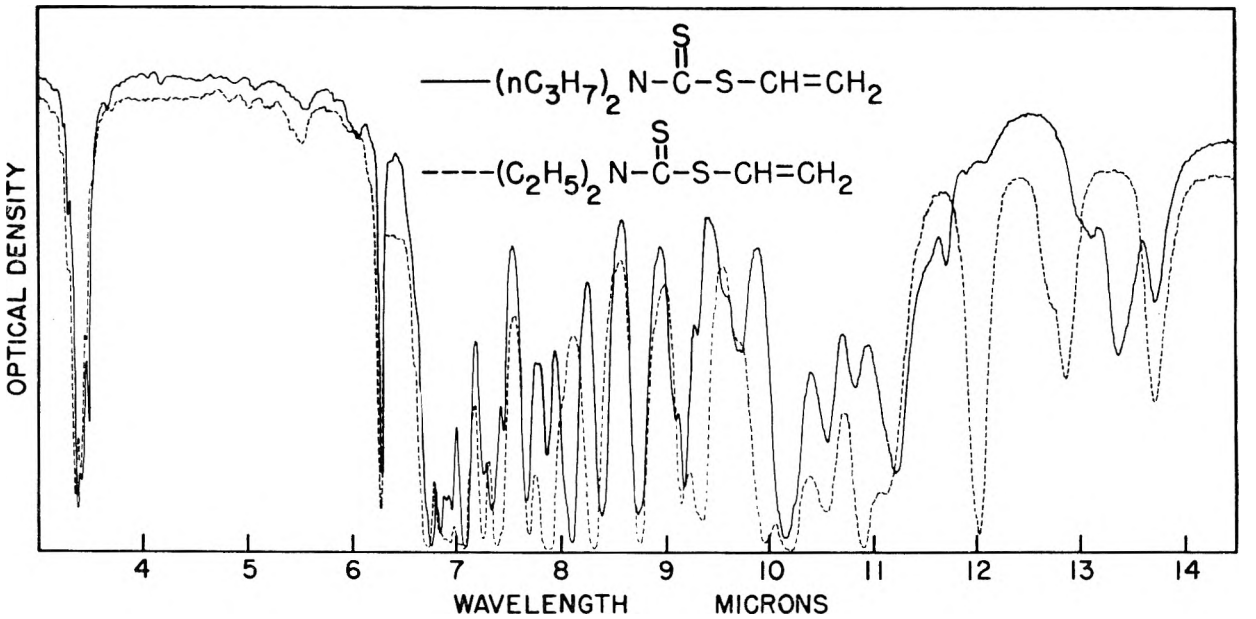

Figure 1

The infrared spectrum is very similar to that obtained for the *N,N*-diethyl analog (see Fig. 1).

Commercial-grade acetylene was purified according to a previously described procedure.[3] The amines were obtained from commercial sources and purified by distillation. The infrared spectra were determined on a Perkin-Elmer 21 double-beam spectrometer.

Acknowledgment. The author is pleased to express his gratitude for the valuable suggestions of Dr. C. T. Handy.

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(3) J. C. Sauer, *J. Am. Chem. Soc.*, **79**, 5314 (1957).

Reaction of 3-Phenyl-3-acetoxypropanoyl Chloride with Ethyl Sodioacetoacetate

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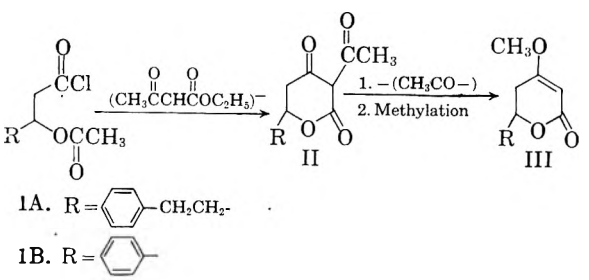
Anschütz[1] prepared 3-acetyl-4-hydroxycoumarin by treating acetylsalicyl chloride with sodioacetoacetic ester. This unique method of preparing β-ketolactones appeared promising as a method of preparing dihydrokavain, IIIA and the following reaction sequence was proposed:



The study of this synthetic route was undertaken using 3-phenyl-3-acetoxypropanoyl chloride, IB, as the model compound.

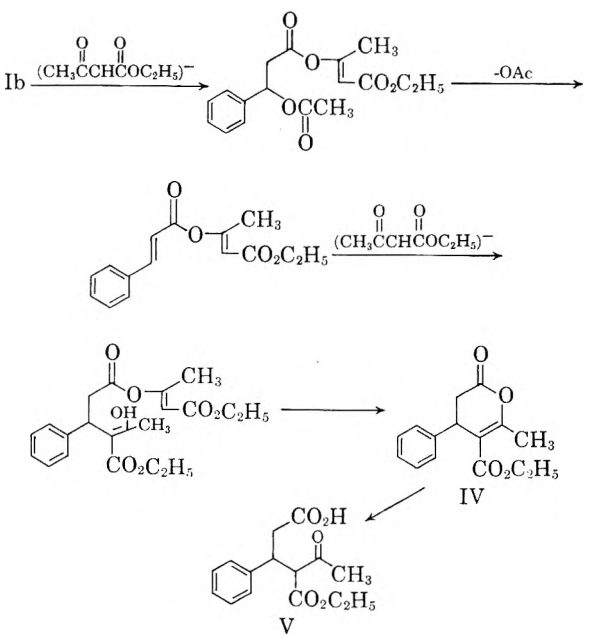
Two crystalline products were obtained from the reaction of ethyl sodioacetoacetate with 3-phenyl-3-acetoxypropanoyl chloride. Both products gave positive ferric chloride tests and were soluble in sodium hydroxide, but only one was soluble in sodium bicarbonate. On alkaline hydrolysis both compounds gave 3-phenyl-5-ketocaproic acid. The infrared spectrum of the sodium bicarbonate soluble material was in good agreement with the structure of 3-phenyl-4-carboethoxy-5-ketocaproic acid V; a 5.80 μ band being ascribed to the ester carbonyl groups (3-phenyl-5-ketocaproic acid has one sharp band 5.91 μ). This material had an ultraviolet absorption spectra of λ_{max}^{EtOH} 258 mμ, ε 336, however in alcoholic potassium hydroxide a shift to λ_{max} 283 mμ, ε 12,440 was observed after one hour.

An independent synthesis of 3-phenyl-4-carbethoxy-5-ketocaproic acid, V, was undertaken and on mixed melting point with the sodium bicarbonate soluble product no depression was observed. The infrared spectrum of the sodium bicarbonate insoluble product differed greatly from V, however

(1) R. Anschütz, *Ann.*, **367**, 193 (1909).

the difference in molecular formulas was one molecule of water. The infrared spectrum suggested an enol lactone structure and 4-phenyl-5-carboethoxy-6-methyl 3,4-dihydro-2-pyrone, IV, was commensurate with the analytical data. Additional evidence for the enol lactone structure was obtained from the ultraviolet spectrum, λ_{max}^{EtOH} 240, ϵ 8,883. The absorption maxima was immediately shifted to 283 mμ in alcoholic potassium hydroxide and after one hour the molecular extinction coefficient was 12,160 which is in agreement with that found when 3-phenyl-4-carbethoxy-5-ketocaproic acid, V, was treated with base.

The enol lactone, IV, was prepared from 3-phenyl-4-carbethoxy-5-ketocaproic acid by treating it with acetic anhydride and anhydrous sodium acetate. The formation of these two products, IV and V, can be rationalized in the following manner:



EXPERIMENTAL

3-Phenyl-3-hydroxypropanoic acid. The method of Hauser and Breslow[2] was used to prepare ethyl 3-phenyl-3-hydroxypropanoate. From 83.5 g. (0.50 mole) ethyl bromoacetate, 65.0 g. (0.61 mole) benzaldehyde, and 40.0 g. (0.60 g.-atom) zinc was obtained 101.0 g. of crude hydroxyester. On hydrolysis 58.8 g. (70.7%) of 3-phenyl-3-hydroxypropanoic acid, m.p. 96–97° (lit. m.p. 100°) was isolated.

3-Phenyl-3-acetoxypropanoic acid. To 6.0 g. (0.0361 mole) 3-hydroxy-3-hydroxypropanoic acid was added 17.8 g. (0.175 mole) acetic anhydride. The mixture was heated and stirred constantly at 90° for 2 hr. Water was added to the cooled reaction mixture. The solution was concentrated and cooled until crystallization occurred. This material was chromatographed on a silicic acid–chloroform column. The first fraction eluted was cinnamic acid. Further elution gave 3.29 g. (43.8%) of 3 phenyl-3-acetoxypropanoic acid, m.p. 102–104; neutral equivalent: calcd. 208.3; found 211.4. λ_{max}^{EtOH} 258 mμ, ϵ 242.

(2) C. R. Hauser and D. Breslow, *Org. Syntheses*, Coll. Vol. III, 408.

3-Phenyl-3-acetoxypropanoyl chloride. 3-Phenyl-3-acetoxypropanoic acid was heated at 70° with a two-fold excess of thionyl chloride for 0.5 hour. The excess thionyl chloride was removed *in vacuo*. Anhydrous ether was added and the evaporation procedure repeated twice. The resulting acid chloride, $\lambda_{max}^{Et_2O}$ mμ, ϵ 960, formed a *p*-bromoanilide, m.p. 145.2–147.2.

Anal. Calcd. for $C_{17}H_{16}O_3$ NBr: C, 56.37; H, 4.45. Found: C, 56.51; H, 4.06.

The reaction of 3-phenyl-3-propanoyl chloride and ethyl sodioacetoacetate. To 4.0 g. (0.0307 mole) ethyl acetoacetate in 200 ml. of ether was added 0.667 g. (0.029 g.-atom) sodium. The reaction mixture was allowed to stir until the sodium metal was completely consumed. To the suspension of ethyl sodioacetate was added an ether solution of 3-phenyl-3-acetoxypropanoyl chloride prepared from 1.781 g. (0.00856 mole) 3 phenyl-3-acetoxypropanoic acid. After addition was complete the mixture was refluxed 18 hr. The reaction mixture was decomposed with dilute hydrochloric acid and the ether solution washed with water and dried over magnesium sulfate. The ether was removed and the remaining liquid carefully chromatographed on a silicic acid–chloroform column. Two crystalline fractions were obtained. The first and more plentiful, 4-phenyl-5-carboethoxy-6-methyl-3,4-dihydro-2-pyrone, was recrystallized from high boiling petroleum ether, m.p. 83.0–84.0°. λ_{max}^{EtOH} 240 mμ, ϵ 8.883. The λ_{max} was immediately shifted to 283 mμ in 0.382*N* ethanolic potassium hydroxide, the ϵ value having a hyperchromic shift to 12,160 in 1 hr. in base.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.06. Found: C, 69.21, 69.52; H, 6.32, 6.17.

The second crystalline fraction, 3-phenyl-4-carboethoxy-5-ketoeaproic acid, was recrystallized from carbon tetrachloride–chloroform, m.p. 128.0–130.6°; neutral equivalent: calcd. 278; found 266; λ_{max}^{EtOH} 258 mμ, ϵ 336, in 0.382*N* ethanolic potassium hydroxide λ_{max} was immediately shifted to 283 mμ, ϵ 12,440 after 1 hr. in base.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.74, 64.86; H, 6.43, 6.52.

Hydrolysis of 4-phenyl-5-carboethoxy-6-methyl-3,4-dihydro-2-pyrone. To 10 ml. of 0.191*N* potassium hydroxide was added 0.123 g. (0.473 Millimole) of 4-phenyl-5-carboethoxy-6-methyl-3,4-dihydro-2-pyrone. The mixture was refluxed for 3 hr. After concentration, the mixture was acidified and extracted with several portions of ether. The ether extracts yielded 0.095 g. (97.5%) of 3-phenyl-5-ketocaproic acid, m.p. 84.1–85.3° from benzene/pet. ether (lit. m.p. 85°) neutral equivalent: calcd. 207, found 212. 3-Phenyl-5-ketocaproic acid semicarbazone, m.p. 166.0–168.0° from water (lit. m.p. 171.5°).[3] Final identification was obtained by converting the semicarbazone to its methyl ester (diazomethane) m.p. 122.0–125.0° (lit. m.p. 121–124°).[4] A mixed melting point with authentic sample gave no depression of melting point.

3-Phenyl 4-carbethoxy-5-ketocaproic acid. Approximately 100 mg. of freshly cut sodium, 10.7 g. (0.066 mole) methyl cinnamate, and 8.6 g. (0.066 mole) ethyl acetoacetate were heated at 100° with stirring for 6 hr. The mixture was dissolved in ether and decomposed with dilute hydrochloric acid. The dried organic phase was distilled *in vacuo* to remove the starting material (61% of methyl cinnamate was recovered). The residue was dissolved in ether and extracted with three 15-ml. portions of 5% sodium hydroxide. Acidification of the alkaline phase, followed by ether extraction, yielded an oil which slowly crystallized when dissolved in warm *n*-butyl ether. The small quantity of 3-phenyl-4-carbethoxy-5-ketocaproic acid thus obtained was recrystallized from *n*-butyl ether, m.p. 123.0–124.0°. Mixed melt with previously isolated material gave no depression.

(3) M. Qudrate-I-Khada, *J. Indian Chem. Soc.*, 8, 215 (1931).

(4) S. M. McElvain, E. Degginger, and J. Behiam, *J. Am. Chem. Soc.*, 76, 5736 (1954).

4-Phenyl-5-carboethoxy-6-methyl-3,4-dihydro-2-pyrone. A trace of anhydrous sodium acetate, 6.0 ml. of acetic anhydride, and 0.057 g. (0.205 millimole) 3-phenyl-4-carboethoxy-5-ketocaproic acid were refluxed for 4 hr. under an atmosphere of dry nitrogen. After removal of the acetic anhydride the residue was dissolved in 25 ml. of ether and washed with 2–10 portions of water. The dried ether solution on evaporation yielded 0.051 g. (95.6%) of crystalline 4-phenyl-5-carboethoxy-6-methyl-3,4-dihydro-2-pyrone, m.p. 81.0–81.3 from high boiling petroleum ether.

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Infrared Spectra of Some Cyclic Anhydrides

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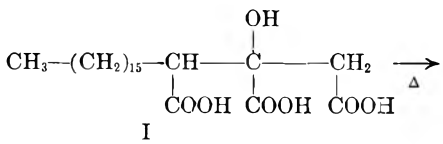
The infrared spectrum of an acid anhydride is characterized by a doublet in the 1750–1850 cm.$^{-1}$ region[2] and this doublet most likely arises from their coupling between the carbonyl vibrations in inphase and out of phase modes.[3] In general, the 2 bands fall into characteristic regions: The open chain or relatively unstrained cyclic glutaric anhydrides possess the doublet in the 1740–1760 cm.$^{-1}$ and 1800–1825 cm.$^{-1}$ regions, and the more strained cyclic succinic anhydrides possess the doublet in the 1770–1790 cm.$^{-1}$ and 1850–1870 cm.$^{-1}$ regions. Furthermore, when this latter series of compounds possesses a conjugated olefinic linkage, the bands shift 20–40 cm.$^{-1}$ towards lower frequency. As has been pointed out by Bellamy,[2] this latter shift places conjugated strained anhydrides in the same region of absorption as unstrained saturated anhydrides and makes structural diagnosis on the basis of infrared absorptions somewhat indefinite.

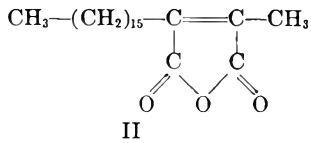
Jones[3] has called attention to the fact that the two bands need not be of equal intensity, but little attention has been paid to the intensity relationship of the two bands in anhydride absorption. Listed in Table I are the results of a limited study of this feature of the spectrum. It is apparent that the intensity features of the bands are of useful diagnostic value. The ratio of the intensities is expressed in terms of optical density (R = D low frequency band/D high frequency band) and, except for the acyclic materials, this rough measure of intensity is a fair approximation of the more exact integrated intensity values.

As seen from the data in Table I, the intensities of the two bands do not differ greatly in the acyclic anhydrides. In the unstrained glutaric anhydride, the intensity of the lower frequency band remains about the same, but the intensity of the higher band is greatly diminished and the ratio of intensities increases. In all of the succinic anhydrides, the intensity of the lower frequency band is greater and the intensity of the other band remains about the same order of magnitude as in glutaric anhydride. The ratio of intensities in the succinic series of all of the materials is about the same. For the maleic anhydrides, smaller changes in both bands are found, but the ratio of the intensities increases.

The most striking case is that of methyl hexadecylmaleic anhydride (II), the last entry in the table. This material is a degradation product of the fungal metabolite *agaric acid*, 2-hexadecylcitric acid (I).[4]



I



II

The high value of 11.1 for relative band intensities makes it imperitive to utilize a very concentrated solution for, otherwise, only the 1757 cm.$^{-1}$ band is seen and the presence of a lactone grouping might be indicated. In the case of the two disubstituted maleic anhydrides, a third band of very low intensity lies about 30 cm.$^{-1}$ higher than the 1808–1812 cm.$^{-1}$ band; perhaps this band is concerned with the anhydride absorption and accounts for the low intensity of the higher frequency band. However, on the basis of the intensity ratio of the maleic anhydrides, a clear differentiation can be made between them and the unstrained cyclic anhydrides absorbing in the same region.

In the succinic and maleic anhydride series, the different effect of substitution is of interest. The band positions in the succinic anhydride series are practically independent of substitution, even though the anhydride is part of a highly strained ring system such as cyclopropane and cyclobutane. Such is not the case in the maleic anhydride series, for the less intense bands shift about 30 cm.$^{-1}$ to lower frequency.

As mentioned above, the doublet in the anhydride absorption most likely arises from coupling between carbonyl vibrations. In cyclic anhydrides, the constraint produced by ring closure should increase the angle between the two carbonyl groups, approaching as a limit a colinear arrangement. As this limit is approached, there would be a progressive decrease in intensity of the phase motion because of

(1) United States Rubber Company Fellow in Chemistry, 1957–1958.

(2) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, J. Wiley and Sons, Inc., New York, 1956, p. 110.

(3) R. N. Jones and C. Sandor, *Techniques of Organic Chemistry*, A. Weissberger, Editor, Interscience Publishing Co., Inc., New York, 1956, Vol. IX, p. 495.

(4) H. Thoms and F. Vogelsang, *Ann.*, **357**, 145 (1907).

TABLE I

INFRARED SPECTRAL DATA FOR ACID ANHYDRIDE

Compound	Band Positions in cm.$^{-1}$		D_H[a]	D_L[a]	D_L/D_H
Acetic anhydride	1825	1754	0.150	0.140	0.93
Propionic anhydride	1818	1745	0.190	0.154	0.81
Glutaric anhydride	1812	1764	0.065	0.174	2.7
Succinic anhydride	1866	1792	0.054	0.367	6.8
Cyclobutane-1,2-dicarboxylic acid anhydride	1859	1786	0.042	0.264	6.3
cis-Endomethylenetetrahydrophthalic anhydride	1855	1783	0.048	0.362	7.6
Cyclopropane-1,2-dicarboxylic acid anhydride	1862	1799	0.048	0.402	8.4
Maleic anhydride	1835	1770	0.030	0.268	9.0
2-Methylmaleic anhydride	1832	1764	0.043	0.342	8.0
2,3-Dimethylmaleic anhydride	1812 (1845)	1757	0.050	0.460	9.2
2-Methyl-3-hexadecylmaleic Anhydride	1808 (1835)	1757	0.034	0.378	11.1

[a] D_L is optical density of lower frequency band and D_H is optical density of higher frequency band.

the cancellation of dipole charges. This decrease should be accompanied by an increase in intensity of the out-of-phase motion. Because such a relationship in intensities is found, the higher frequency band of the doublet can be assigned to inphase vibrations.

The spectra were obtained employing a Baird Associates Double Beam Infrared Spectrophotometer using 1.0 mm. sodium chloride cells. All spectra were obtained with 3.0×10^{-3} *M* solutions in carbon tetrachloride.

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Lithium Aluminum Hydride Reduction of Methylcyclohexanones

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In an earlier study,[2] the composition of the products obtained by lithium aluminum hydride reduction of the isomeric cyclohexanols and of the equilibrium mixture was reported. In this work the ratio of isomers was determined by the density method. Subsequently, Wicker[3] and Hückel[4] have reinvestigated this same problem and have found results which differ from those first reported. This problem has now been restudied utilizing Vapor Phase Chromatography as the method for analysis and the results obtained together with those reported previously by other workers are given in Table I.

TABLE I

ISOMER COMPOSITION OF METHYLCYCLOHEXANOLS

Compound	% *trans* from $LiAlH_4$	% *trans* at Equilibrium
2-Methylcyclohexanol	70[a] (64,[b] 82[c] 60,[d] 59[e])	85[a] (95,[f] 99[c] 83,[e] ~94[g])
3-Methylcyclohexanol	13[a] (18,[b] 7,[e] <15[g])	— (22[g])
4-Methylcyclohexanol	84[a] (81,[b] 82[c] 75,[d] 80[g])	71[a] (88,[c] 70[g])

[a] Present work. [b] D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **72**, 5743 (1950). [c] See Reference (2). [d] See Reference (3). [e] See Reference (4). [f] R. Cornubert, M. Lafont-Lemoine, and N. Nadjme-Abadi, *Compt. rend.*, **237**, 469 (1953). [g] E. E. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

First with regard to the product obtained in the lithium aluminum hydride reduction, the composition of the 4-methylcyclohexanols and the 3-methylcyclohexanols agrees well with that found in all studies. With the 2-methylcyclohexanols where the largest discrepancy existed, the present result is just between the two extremes. In all the results obtained by VPC, two peaks, cleanly separated, were obtained and there was no indication of any other components. Re-examination of some of the samples obtained in our earlier study showed the presence of a third component but it could not be ascertained whether this impurity was actually present in the original mixture or was formed on storage. If, indeed, the former was the case, analysis by density measurement could have readily been affected and yet not detected.

The equilibrium mixtures of the 4-methyl and the 2-methyl-cyclohexanols also were examined with VPC and here again quite different results

(1) Procter & Gamble Fellow, 1958–1959.
(2) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
(3) K. D. Hardy and R. J. Wicker, *J. Am. Chem. Soc.*, **80**, 640 (1958).
(4) W. Hückel and A. Hubele, *Ann.*, **613**, 27 (1958).

from those originally found by us were obtained. With the 4-methyl material, excellent agreement with the recently reported result of Eliel and Ro[5] was obtained. With the 2-methyl material, agreement with the value reported by Hückel[4] last year was obtained and these two values were lower in *trans* content than other reports. Thus, these results with VPC clearly demonstrate that high values of the percentage of the isomer with the lower density were obtained in our earlier work.

It is of interest to look at the present results in terms of the concepts of "product development control" and "steric approach control" in the lithium aluminum hydride reduction.[2] In the case of the 3- and 4-methylcyclohexanols, the amount of stable isomer formed in the reduction is in excess of that found in the equilibrium mixture. As has been pointed out,[2] the relative contributions of the axial and the equatorial approaches in the case of the unhindered ketone (product development control) will depend upon the different energies of the two transition states involved. Since the relative energetics of the two aluminum coordinated species are not known, the equilibrium composition of the alcohols, themselves, serves as a first approximation of the energy difference. However, as already pointed out by Eliel and Ro,[5] in these two cases, this approximation must be on the low side as far as the stable isomer is concerned since any increase in bulk of the oxygen function will serve to increase the amount of the more stable isomer. Thus, the results obtained are in line with expectations derivable from this simplified concept. With regard to the composition of the 2-methylcyclohexanols obtained upon reduction, the presence of more of the less stable isomer than is found in the equilibrium mixture is to be expected on the basis of concurrent functioning of both steric approach control and product development control.

EXPERIMENTAL

The reductions were performed as described earlier.[2] The equilibrations also were conducted as previously[2] and approached from each side of the equilibrium mixture. The analyses were performed using an Aerograph Master A-100 Apparatus (Wilkens Instrument and Research, Inc., Walnut Creek, Calif.), equipped with a 10-inch column of 30% glycerol on Chromosorb.[6] The separations were performed at a temperature of 80 ± 5° with a helium flow rate of 90 ± 10 ml./min. Percentage compositions were obtained from planimeter-determined areas under the separate peaks and the values were reproducible to 1%. Retention times quoted below are taken from the time of injection of sample.

2-Methylcyclohexanols. At 88° and 90 ml./min. flow rate, the retention time for the *cis* isomer was 8.0 min. and for the *trans*-isomer was 15.4 min. The retention time for starting ketone at 80° and 100 ml./min. flow rate was 4.5 min.

3-Methylcyclohexanols. At 81° and 92 ml./min. flow rate, the retention times were 14.0 min. for the *trans* and 20.2 min. for the *cis*. Under ketone conditions, the starting material had an 8 min. retention time.

4-Methylcyclohexanols. Under the conditions used for the 3-methyl isomer, the retention time for the *cis* isomer was 14.6 min. and for the *trans* isomer was 21.3 min.

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(5) E. E. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

(6) The use of glycerol columns for separation of isomeric cyclohexanols was reported by R. Komers, K. Kochloefl, and V. Bazant, *Chem. & Ind. (London)*, 1405 (1958).

5-Amino-3-chloropyridazine[1]

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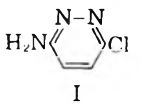
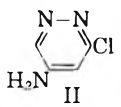
Received May 11, 1959

3,6-Dichloropyridazine undergoes reaction with ammonia to produce I, 6-amino-3-chloropyridazine (m.p. 213–214° dec.), as is well known.[3,4] It was of interest to determine whether the same compound resulted when sodium amide was caused to act on the dichloro compound. Rearrangements have frequently occurred when sodium amide has been used (*cf.*, *inter alia*, refs. 5,6). The aminochloro compound which was obtained in 64% yield melted at 141.5–142°, and was clearly not I. This has been assigned the structure of the rearrangement product, II, *viz.*, 5-amino-3-chloropyridazine. Present circumstances have precluded dehalogenation of II to 4-aminopyridazine, which was prepared by Kuraishi[7] subsequent to the completion of this work.



I



II

EXPERIMENTAL

A vigorously stirred solution of 14.9 g. (0.1 mole) of 3,6-dichloropyridazine in 150 ml. of xylene was treated with 12.0 g. (0.3 mole) of sodium amide and refluxed for 10 hr. To the brown mixture there was added an excess of aqueous hydrochloric acid. The layers were filtered and separated. The organic layer was extracted further with 6*N* hydrochloric acid, and the acidic extracts were concentrated prior to basification. A light tan solid (9.5 g., m.p. 135–138°) was obtained; four crystallizations from benzene-hexane mixture

(1) Pyridazines IV. Previous contribution: E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, 76, 4454 (1954).

(2) Present address: McNeil Laboratories, Philadelphia, Pa.

(3) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, 76, 3225 (1954).

(4) J. Druey, Kd. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(5) R. Levine and W. C. Fernelius, *Chem. Revs.*, **54**, 483 (1954).

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

(7) T. Kuraishi, *Pharmaceutical Bulletin (Japan)*, **4**, 137 (1956).

gave 8.3 g. (64% yield) of jagged blades, m.p. 141.5–142°. This was assigned structure II as 5-amino-3-chloropyridazine on the basis that it caused marked depression of the melting point of I when admixed with it, and that sodium amide is known to cause rearrangements.

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.08; H, 3.11; Cl, 27.57. Found: C, 37.40; H, 3.13; Cl, 27.51.

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Synthesis of Mercaptophenols and Alkyl Derivatives

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Received May 12, 1959

We were interested in studying the behavior of mercaptophenols, containing both phenolic and aromatic mercaptan groups, in free radical processes. The use of a number of thiohydroquinones as polymerization inhibitors has been described by us in a recent patent.[1] A review of the literature indicated relatively few mercaptophenols having a thiocatechol or thiohydroquinone configuration have been described.[2-6] These compounds were usually prepared by reduction of the corresponding sulfonyl chloride.

A synthetic procedure is described in this report based on sulfurization of a phenol with sulfur monochloride. The crude sulfurization product, containing a mixture of monosulfide, disulfide, and polysulfide, is subjected to pressure hydrogenation using supported MoS_2 as a catalyst. The disulfides and polysulfides are reduced to the corresponding thiol.

A study was made of the sulfurization reaction using 2,6-xylenol as a prototype, aimed at maximizing the yield of thiol. The preferred sulfurization procedure was applied to phenol. Thiohydroquinone was recovered. Since thiocatechol was not detected, it was assumed that sulfurization occurred exclusively in the para position. The thiol derived from *o*-cresol was assigned a thiohydroquinone structure. The thiols of 2,4-xylenol, 4-*t*-butyl-*o*-cresol, 6-*t*-butyl-*o*-cresol, 2-*t*-butyl-*p*-cresol, 2-*t*-amylphenol, 2,6-diisopropylphenol, and 2,6-di-*t*-butylphenol were produced by the sulfurization-hydrogenation procedure. All the resulting mercaptophenols except the mercaptans derived from phenol and 2,6-xylenol are new compounds.

(1) U. S. Patent **2,810,765**, M. B. Neuworth and E. B. Hotelling, October 22, 1957.

(2) R. Leuckart, *J. prakt. Chem.*, (2), **41**, 179 (1870).

(3) G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1176 (1934).

(4) T. Zincke and K. Arnold, *Ber.*, **50**, 116 (1917).

(5) P. Karrer and P. Leiser, *Helv. Chim. Acta*, **27**, 678 (1934).

(6) E. Katscher and H. Lehr, *Monatsh.*, **64**, 236 (1934).

EXPERIMENTAL

Starting materials. 2,6-Xylenol and 2,4-xylenol were purchased from Reilly Tar and Chemical Co. Both materials were redistilled and shown to be pure by infrared analysis. 2-*t*-Amylphenol was obtained from Sharples Chemicals, Inc., and used without further purification. 2,6-Diisopropylphenol and 2,6-di-*t*-butylphenol were purchased from Aldrich Chemical Co., and used without further purification.

6-*t*-Butyl-*o*-cresol and 4-*t*-butyl-*o*-cresol were synthesized by sulfuric acid–catalyzed butylation of *o*-cresol with isobutylene. 6-*t*-Butyl-*o*-cresol was obtained by fractionation of the crude butylation mixture, boiling point 118° (20 mm.). 4-*t*-Butyl-*o*-cresol, the higher boiling isomer, was similarly recovered, boiling point 132° (20 mm.). 2-*t*-Butyl-*p*-cresol was formed by sulfuric acid–catalyzed butylation of excess *p*-cresol with isobutylene. The desired product distilled at 125–126° (20 mm.) and had a melting point of 51°.

Sulfurization-hydrogenation procedure. The preferred sulfurization-hydrogenation procedure was carried out as follows:

The apparatus consisted of a 1-l., 4-neck round-bottom flask equipped with heating mantle, stirrer, thermometer well, gas inlet tube, and dropping funnel with pressure equalizer, a reflux condenser and drying tube. One mole of 2,6-xylenol was dissolved in 500 ml. of carbon tetrachloride, containing 1 g. of sulfur. Dry nitrogen gas was bubbled slowly through the apparatus. Seventy-four g. (0.55 mole, 10% excess) of sulfur monochloride (Matheson technical) is dissolved in 200 ml. of carbon tetrachloride. Toluene may be used as the solvent instead of carbon tetrachloride with no loss in yield. The sulfur monochloride solution is added slowly through the dropping funnel with continued efficient stirring and nitrogen sweeping, and at such a rate that the reaction temperature does not exceed 30°. This addition generally requires 1 hr. When it is complete the solution is heated to reflux, held at this temperature for 30 min., and then allowed to cool to room temperature with continued stirring and nitrogen sweeping.

The crude disulfide is freed of solvent by distillation under low vacuum to a pot temperature of 120°/50 mm. (A water aspirator is the only practical source of vacuum, due to the exceedingly corrosive nature of the vapors.) The dark viscous residue is dissolved in toluene while still hot. It is then charged into a hydrogenation bomb constructed of Type 316 stainless steel, treated with 10% by weight of molybdenum disulfide (supported on alumina pellets; Davison Catalyst TS-55-3668), and hydrogenated at 140° (cold hydrogen pressure 1800 p.s.i.) until no further gas uptake is observed.

The hydrogenation product, after cooling to room temperature, is filtered to remove catalyst. The filtrate is distilled on a $^3/_4 \times 24$ in. Vigreaux column; approximately 15% of the 2,6-xylenol is recovered. The yield of 4-mercapto-2,6-xylenol, based on xylenol consumed, is 49%; it is accompanied by a 5% yield of 4-chloro-2,6-xylenol. The remainder of the product is high-boiling yellow oil, presumably mostly 4,4′-thiobis-(2,6-xylenol), plus an intractable tarry residue.

Discussion of results. The preferred sulfurization conditions were applied to phenol followed by hydrogenation of the crude sulfurization mixture. Thiohydroquinone,[7] a solid, melting point 32–35°, was recovered in 19% yield. The lower boiling analog, thiocatechol, could not be detected, indicating sulfurization occurs exclusively in the para position. Sulfurization-hydrogenation of *o*-cresol yielded a crystalline thiol,[8] m.p. 39–42°, in 28% yield. This com-

(7) Boiling point 149–150° (25 mm.). *Anal.* Calcd. for C_6H_6OS: C, 57.11; H, 4.79; S, 25.41. Found: C, 56.90; H, 4.95; S, 24.95. Ref. (4) reports the synthesis of thiohydroquinone, m.p. 29–30°, b.p. 144–146° (20 mm.).

(8) Calcd. for C_7H_8OS: C, 59.98; H, 5.75; S, 22.87. Found: C, 59.65; H, 5.75; S, 23.22.

TABLE I

SYNTHESIS OF ALKYL MERCAPTOPHENOLS, YIELDS AND PROPERTIES

Starting Phenol	Mercaptan	Yield	M.P.[a]	B.P. (mm.)	Formula	Analysis	
						Calculated	Found
2,4-Xylenol	6-Mercapto	48	37–39[b]	99–100 (6.5)	$C_8H_{10}OS$	C, 62.30; H, 6.53; S, 20.79	C, 62.59; H, 6.65; S, 20.20
2,6-Xylenol	4-Mercapto	49	85–87[c]	137–138 (10)	$C_8H_{10}OS$	C, 62.30; H, 6.53; S, 20.79	C, 62.48; H, 6.40; S, 20.21
6-*t*-Butyl-*o*-cresol	4-Mercapto	42	Oil	134–135 (5)	$C_{11}H_{16}OS$	C, 67.29; H, 8.22; S, 16.33	C, 67.26; H, 8.21; S, 16.34
4-*t*-Butyl-*o*-cresol	6-Mercapto	40	Oil	124–125 (5)	$C_{11}H_{16}OS$	C, 67.29; H, 8.22; S, 16.33	C, 67.33; H, 8.20; S, 15.80
2-*t*-Butyl-*p*-cresol	6-Mercapto	41	40–42	118–118.5 (5.5)	$C_{11}H_{16}OS$	C, 67.29; H, 8.22; S, 16.33	C, 67.21; H, 8.40; S, 15.75
2-*t*-Amylphenol	4-Mercapto	40	Oil	140–141 (5)	$C_{11}H_{16}OS$	C, 67.29; H, 8.22; S, 16.33	C, 67.16; H, 8.33; S, 15.93
2,6-Di-isopropylphenol	4-Mercapto	30	Oil	82–90 (0.2)	$C_{12}H_{18}OS$	C, 68.57; H, 8.64	C, 68.51; H, 8.43
2,6-Di-*t*-butylphenol	4-Mercapto	31	65–69	85–97 (0.2)	$C_{14}H_{18}OS$	C, 70.54; H, 9.31	C, 71.13; H, 9.44

[a] All melting points corrected. [b] Reported[6] erroneously to melt at 91–93°C. This is probably the monosulfide. The monosulfide was recovered from the residue m.p. 95–98°C. Calcd. for $C_{16}H_{18}O_2S$: C, 70.03; H, 6.61; S, 11.68. Found: C, 70.02; H, 6.79; S, 11.57. [c] Reported[5] m.p. is 86°.

TABLE II

DERIVATIVES OF THE ALKYL MERCAPTOPHENOLS

Mercaptophenol	Derivative	M.P.[a]	Formula	Analysis	
				Calculated	Found
6-Mercapto-2,4-xylenol	1-(Oxyacetic acid)-6-thioacetic acid[9]	132 (dec.)	$C_{12}H_{14}O_5S$	C, 53.31; H, 5.22; eq. wt. 135	C, 53.23; H, 5.34; eq. wt. 132
	6-(2′,4′-Dinitrophenyl[10] thioether)	154–156	$C_{14}H_{12}O_5N_2S$	C, 52.49; H, 3.78	C, 52.15; H, 3.94
	6-(β-Thiopropionic[11] acid)	78–80	$C_{11}H_{14}O_3S$	C, 58.38; H, 6.23	C, 58.32; H, 6.32
4-Mercapto-2,6-xylenol	1-(Oxyacetic acid)-4-(thioacetic acid)	171–172 (dec.)	$C_{12}H_{14}O_5S$	C, 53.31; H, 5.22; eq. wt. 135	C, 53.42; H, 5.29; eq. wt. 136
	4-(2′,4′-Dinitrophenyl thioether)	191–193	$C_{14}H_{12}O_5N_2S$	C, 52.49; H, 3.78	C, 52.54; H, 4.00
	4-(β-Thiopropionic acid)	106–108	$C_{11}H_{14}O_3S$	C, 58.38; H, 6.23	C, 58.71; H, 6.14
6-Mercapto-4-*t*-butyl-*o*-cresol	6-(2′,4′-Dinitrophenyl thioether)	185–186	$C_{17}H_{18}O_8N_2S$	C, 56.34; H, 5.00; S, 8.85	C, 56.69; H, 5.16; S, 8.78
4-Mercapto-6-*t*-butyl-*o*-cresol	1-(Oxyacetic acid)-4-(thioacetic acid)	118–120 (dec.)	$C_{15}H_{20}O_5S$	C, 57.66; H, 6.45; S, 10.27	C, 58.01; H, 6.97; S, 10.08
6-Mercapto-2-*t*-butyl-*p*-cresol	1-(Oxyacetic acid)-6-(thioacetic acid)	140–141 (dec.)	$C_{15}H_{20}O_5S$	C, 57.66; H, 6.45; S, 10.27	C, 57.50; H, 6.79

[a] All melting points corrected.

pound is assigned a thiohydroquinone structure. The infrared spectrum of this compound, in the 5- to 6-micron region, corresponded to a benzene derivative with a 1,2,4 configuration.

This procedure was then applied to eight alkylphenols. The yields and properties of the resulting thiols are shown in Table I. Characterizing thiol derivatives of five of these thiols were prepared. Their melting points and analyses are presented in Table II.

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(9) Made by reaction of the disodium salt with bromoacetic acid.

(10) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

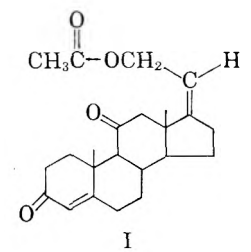
(11) E. A. Bartkus, E. B. Hotelling, and M. B. Neuworth, *J. Org. Chem.*, **22**, 1185 (1957).

11-Alkylated Steroids. III. Two Syntheses of 11-Methylhydrocortisone[1]

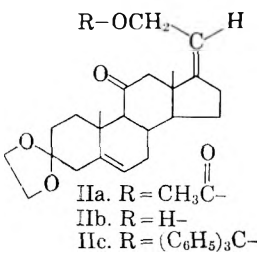
GUNTHER S. FONKEN, JOHN A. HOGG, AND A. VERN MCINTOSH, JR.

Received May 14, 1959

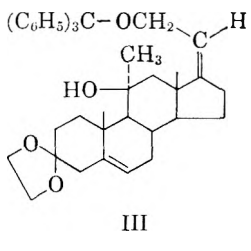
In our earlier report[1] of a synthesis of 11-methylhydrocortisone acetate (XIIa), we outlined the conversion of the known 21-hydroxypregna-4,17(20)-[*cis*]-diene-3,11-dione acetate[2] (I) to its ketal, 21-hydroxypregna-5,17(20)-[*cis*]-diene-3,11-dione 3-ethylene acetal acetate (IIa), which was hydrolyzed with aqueous methanolic potassium bicarbonate to the corresponding free alcohol (IIb). Treatment of the alcohol (IIb) with triphenylmethyl chloride in dry pyridine afforded the 21-trityl ether (IIc), which, on treatment with excess ethereal methyllithium, was converted to 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[*cis*]-dien-3-one ethylene acetal (III). Efforts to substitute methyl Grignard reagent for methyllithium were unsuccessful, only unchanged IIc being recovered. Similarly, treatment of either the alcohol IIb or its acetate IIa with either methyl Grignard reagent or methyllithium gave only the alcohol IIb, with no evidence of addition to the 11-oxo group being observed. A consideration of the molecular model of IIb suggests that an initially formed 21-oxy anion, by virtue of its proximity to the 12β-hydrogen, facilitates enolization of the 11-oxo group. That the 5,6-double bond might also be implicated in some way in the mechanism of unreactivity was suggested by the failure of another 11-oxopregn-5-ene, namely pregn-5-ene-3,11,20-trione 3,20-bis(ethylene acetal)[3] (VI), to add methyllithium (see below). However, in the present case,



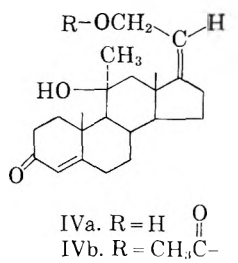
I



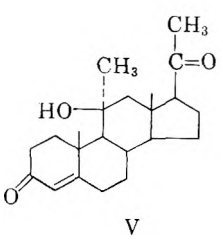
IIa. R = $CH_3C(=O)$–
IIb. R = H–
IIc. R = $(C_6H_5)_3C$–



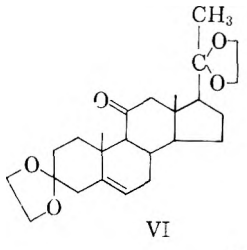
III



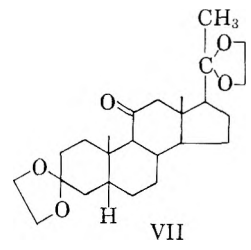
IVa. R = H
IVb. R = $CH_3C(=O)$–



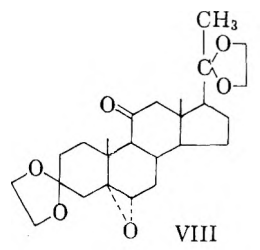
V



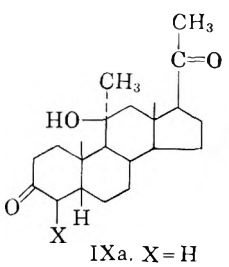
VI



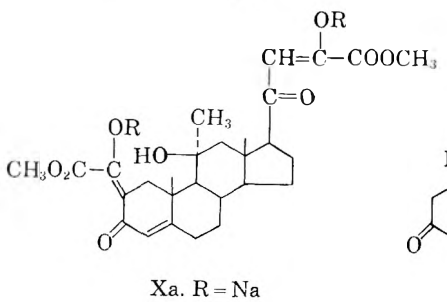
VII



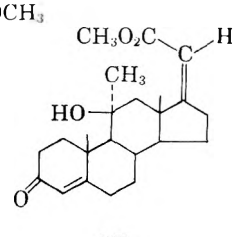
VIII



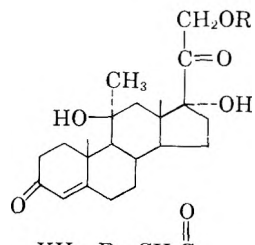
IXa. X = H
IXb. X = Cl



Xa. R = Na
Xb. R = H



XI



XIIa. R = $CH_3C(=O)$–
XIIb. R = H

(1) Part of the material of this paper has appeared as a Preliminary Communication [G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365 (1958)]. Preceding paper in this series: see ref. (8).

(2) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

the 5,6 double bond is also present in IIc, which does undergo addition to the 11-oxo group.

Hydrolysis of 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[*cis*]-dien-3-one ethylene acetal (III) with dilute methanolic hydrochloric acid at room temperature removed the ketal and trityl groups, giving 11β,21-dihydroxy-11-methylpregna-4,17(20)-[*cis*]-dien-3-one (IVa). Acetylation of the 21-hydroxy group occurred in acetic anhydride–pyridine, and the resulting acetate (IVb), when treated with *N*-methylmorpholine *N*-oxide peroxide in *t*-butyl alcohol–pyridine containing a catalytic amount of osmium tetroxide,[4] afforded 11β,17α,21 - trihydroxy - 11 - methylpregn - 4-ene-3,20-dione 21-acetate (11-methylhydrocortisone acetate; XIIa), together with a highly polar material that was not characterized. Hydrolysis of XIIa with aqueous potassium bicarbonate afforded the free alcohol XIIb.

It is of interest to note that although 11-methylhydrocortisone acetate gives a positive test with Tollens (ammoniacal silver oxide) reagent, the time required for the silver deposit to appear is much longer than for hydrocortisone acetate, which gives an almost instantaneous precipitate. This observation, together with some anomalies in the rotatory dispersion spectra of compounds of the 11-methyl series,[5] suggests that the interaction of the 11-methyl group with the steroid side chain is greater than would be predicted on the basis of a consideration of molecular models.

For several reasons, including the sensitive nature of several of the intermediates (particularly of the trityl ether IIc) and certain technical problems in the later steps, we felt that it would be advisable to devise an alternate synthesis of 11-methylhydrocortisone. The general synthetic scheme previously reported from these laboratories[2] seemed suitable, provided that 11β-hydroxy-11-methylpregn-4-ene-3,20-dione (V) could be prepared. Unfortunately, all attempts to prepare this compound by the direct addition of methyllithium or of methyl Grignard reagent to pregn-5-ene-3,11,-20-trione 3,20-bis(ethylene acetal)[3] (VI) were uniformly unsuccessful, only the 11-oxo steroid being recovered. Although no attempt was made to carry out an accurate measurement, a rough determination of evolved methane indicated that enolization was the exclusive reaction of VI with excess ethereal methyllithium. By contrast, a similar rough measurement with 5β-pregnane-3,11,20 - trione 3,20 - bis(ethylene acetal)[6] (VII) showed only about 20% enolization. Similarly, and somewhat surprisingly, 5α,6α-epoxypregnane-3,11,-20-trione 3,20-bis(ethylene acetal)[7] (VIII) underwent only about 3% enolization.

Fortunately, 11β - hydroxy - 11 - methyl - 5β-pregnane-dione[8] (IXa) was readily available and could be converted to 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb) by treatment with *t*-butyl hypochlorite in *t*-butyl alcohol containing hydrochloric acid.[9] Dehydrohalogenation of IXb with semicarbazide-pyruvic acid[10] or with lithium chloride-*N*,*N*-dimethylformamide[11] gave difficultly separable mixtures from which, by repeated crystallization and chromatography, the desired V could be obtained. (In the dehydrohalogenation reaction we again observed a marked difference in reaction rate, the 11-methyl steroid being more sluggish than was expected from experience with a steroid having no 11-methyl group.)

Although the reaction of V with ethyl oxalate in methanolic sodium methoxide was considerably slower than for the corresponding 11 - oxo compound,[12] it afforded the sodium salt of 11β-hydroxy-2,21 - bis(methoxyoxalyl) - 11 - methylpregn-4-ene-3,20-dione (Xa) which, when treated with acid, gave the corresponding free enol Xb. Treatment of Xb successively with methanolic sodium acetate, bromine, methanolic sodium methoxide, acetic acid, and zinc dust[12] afforded methyl 11β-hydroxy-11-methyl-3-oxopregna-4,17(20)-[*cis*]-dien-21-oate[13] (XI). Reaction of XI with pyrrolidine and *p*-toluenesulfonic acid essentially as described by Heyl and Herr[14] gave a crystalline 3-enamine that was not characterized but was reduced with lithium aluminum hydride and hydrolyzed with alkali to give 11β, 21-dihydroxy-11-methylpregna-4,17(20)-[*cis*]-dien-3-one (IVa), whose acetate IVb differed only in crystal form from that prepared by the 21-trityl ether route described earlier.[1] This acetate IVb afforded 11-methylhydrocortisone acetate XIIa identical to that obtained by the alternate route.

(3) J. M. Constantin, A. C. Haven, Jr., and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 1716 (1953).

(4) W. P. Schneider and A. R. Hanze, U. S. Patent 2,769,823 (Nov. 6, 1956).

(5) Extensive measurements on 11-methyl steroids have been carried out in these laboratories by Mr. W. A. Struck and associates. These studies will be published elsewhere.

(6) E. P. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, 75, 486 (1953).

(7) From unpublished studies by G. B. Spero of these laboratories.

(8) G. S. Fonken, *J. Org. Chem.*, 23, 1075 (1958).

(9) R. H. Levin, B. J. Magerlein, A. V. McIntosh, Jr., A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scheri, and E. S. Gutsell, *J. Am. Chem. Soc.*, 76, 546 (1954).

(10) B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *J. Am. Chem. Soc.*, 71, 3262 (1949). See also V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, 70, 882 (1948), and E. B. Hershberg, *J. Org. Chem.*, 13, 542 (1948).

(11) R. P. Holysz, *J. Am. Chem. Soc.*, 75, 4432 (1953).

(12) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal, and J. Korman, *J. Am. Chem. Soc.*, 77, 4438 (1955).

(13) This compound (and IVa derived therefrom) is assigned the *cis* configuration at the 17(20)-double bond on the basis of analogy to the structure proof in the series described in ref. (2).

(14) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, 75, 1918 (1953).

EXPERIMENTAL[15]

21-Hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal acetate (IIa). 21-Hydroxypregna-4,17(20)-[cis]-diene-3,11-dione acetate[2] (I, 0.50 g., 1.35 millimole) was refluxed for 6 hr. with 2 ml. of ethylene glycol and 10 mg. of *p*-toluenesulfonic acid monohydrate in 100 ml. of benzene, the return solvent being passed through a bed of calcium carbide in order to remove water as formed in the reaction. The reaction mixture was cooled, washed with aqueous 4% bicarbonate and with water, and dried over anhydrous sodium sulfate. The desiccant was filtered off and the filtrate concentrated at reduced pressure to a yellow oil which soon crystallized. Recrystallization from ethyl acetate–Skellysolve B gave 0.27 g. of IIa, m.p. 149–154°. Further recrystallization gave an analytical sample, m.p. 160–162°.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.11; H, 8.44.

21-Hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal (IIb). To a solution of 10.0 g. (24.1 millimole) of 21-hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal 21-acetate (IIa) in 1500 ml. of absolute methanol, maintained in a nitrogen atmosphere, was added a solution of 10 g. (100 millimole) of potassium bicarbonate in 100 ml. of water. After being stirred for about 1 hr., the reaction mixture became homogeneous. It was allowed to stand at room temperature overnight, and then the volume reduced greatly by distillation at reduced pressure (bath temperature: 55–60°). Addition of 500 ml. of water with stirring precipitated the product, which was removed by filtration, washed well with water and dried *in vacuo*. The yield of good quality IIb was 8.46 g. (94.2% of the theoretical amount), m.p. 109–111.5°. Recrystallization from 50% aqueous methanol afforded long needles, m.p. 113.5–115°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.05; H, 8.95.

21-Triphenylmethoxypregna-5,17(20)-[cis]-diene-3,11-dione, 3-ethylene acetal (IIc). A solution of 5.38 g. (14.4 millimole) of 21-hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal (IIb) and 4.4 g. (15.8 millimoles) of triphenylmethyl chloride in 70 ml. of carefully dried pyridine was allowed to stand at room temperature for 52 hr. The solution was poured into ice and water, and the product recovered by extraction, first with 200 ml. of ether-benzene (1:1), then with three 100-ml. portions of ether. The combined extracts were washed several times with water, filtered through anhydrous potassium carbonate, and evaporated. The residual glass was crystallized from methanol to give 6.19 g. of nearly pure IIc, m.p. 195–198° with prior softening from 192° on. For analysis a small sample was recrystallized from ether-methanol (*ca.* 1:1) to give chunky crystal clusters, m.p. 201–203°.

Anal. Calcd. for $C_{42}H_{46}O_4$: C, 82.05; H, 7.54. Found: C, 81.99; H, 7.47.

11β-Hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[cis]-dien-3-one ethylene acetal (III). To a solution of 300 mg. (0.488 millimole) of 21-triphenylmethoxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal (IIc) in 5 ml. of dry benzene, maintained in a nitrogen atmosphere, was added 10 ml. of 0.33*M* ethereal methyllithium. The resultant clear colorless solution was kept at room temperature for 3 days, then was diluted with benzene, treated with 6 ml. of acetic acid–water (1:5), and washed several times with water. Filtration through anhydrous sodium acetate followed by evaporation to dryness gave the crude product, contaminated (according to the infrared spectrum) with some carbonyl compound. Chromatography over 30 g. of Florosil concentrated the product in the 5% acetone–Skellysolve B eluates. The weight of residue in these fractions totalled 294 mg. (95.5% of the theoretical amount). A similar reaction, carried out at reflux for 51 hr., gave an eluate residue of 257 mg. (83.5%). Recrystallization from ethyl acetate (or trituration with methanol) gave crystalline III, m.p. 182–184°. The analytical sample was recrystallized from methanol–ethyl acetate (1:1). There was no evidence of carbonyl absorption in the infrared spectrum: γ_{max}^{Nujol} 3480 (OH); 1672 (Δ^5); 1094, 1002 (C—O); 1596, 1492, 714, 698 (C_6H_5).

Anal. Calcd. for $C_{43}H_{50}O_4$: C, 81.87; H, 7.93. Found: C, 81.90; H, 7.95.

11β,21-Hydroxy-11-methylpregna-4,17(20)-[cis]-dien-3-one (IVa). A suspension of 200 mg. of 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[cis]-diene-3-ethylene acetal (III) in 20 ml. of methanol containing 1 ml. of *N* hydrochloric acid was stirred at room temperature for about 44 hr. (The mixture became homogeneous after about 24 hr.) After addition of 15 ml. of aqueous 1.3% sodium bicarbonate, the mixture was evaporated to dryness. The residue was triturated with 30 ml. of benzene, and the organic solution resulting was decanted and chromatographed over 30 g. of Florisil. Elution with Skellysolve B gave triphenylmethyl methyl ether, with 5% acetone in Skellysolve B triphenyl carbinol, with 10% acetone–Skellysolve B a small amount of unidentified steroidal material, and with 25% acetone–Skellysolve B 88 mg. of crude IVa, which was recrystallized thrice from ethyl acetate to m.p. 188–192°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.35; H, 9.33.

Conversion to the corresponding acetate IVb was effected by dissolving crude IVa (160 mg.) in a mixture of 5 ml. of pyridine and 3 ml. of acetic anhydride. After a day at room temperature the mixture was poured into ice water, and the precipitate was collected, dried, and chromatographed over 30 g. of Florisil. On elution with Skellysolve B containing 7% acetone, 108 mg. of crystalline fractions were obtained. Crystallization from acetone-water gave 73 mg. of the acetate, m.p. 109–112°, $[\alpha]_D$ +120°; λ_{max}^{EtOH} 244 mμ, a_M 16,075.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.66; H, 8.97.

11β,17α,21-Trihydroxy-11-methylpregn-4-ene-3,20-dione 21-acetate (XIIa). To a stirred solution of 1.86 g. (5.0 millimoles) of 11α,21-dihydroxy-11-methylpregna-4,17(20)-[cis]-dien-3-one 21-acetate (IVb) in 65 ml. of *t*-butyl alcohol were added, sequentially, 12.5 millimoles of *N*-methylmorpholine oxide peroxide (as 9.4 ml. of *t*-butyl alcohol solution) 2.5 ml. of pyridine, and 30 mg. of osmium tetroxide in 13.8 ml. of *t*-butyl alcohol. After 3 hr., the mixture was diluted with 50 ml. of water and concentrated *in vacuo* to about 50 ml. volume, whereupon an oil precipitated. This oil was reprecipitated from aqueous methanol, giving 0.563 g. of crude XIIa which was combined with similar crops from several other experiments to make 1.77 g., was recrystallized from ethyl acetate–Skellysolve B (1:2) to give 1.416 g. of XIIa, m.p. 191–197°. Treatment of this material with Magnesol in *N*,*N*-dimethylformamide (DMF), followed by recrystallization from aqueous DMF, gave 1.315 g. of pure XIIa, m.p. 202–204°.

A sample not subjected to the Magnesol–DMF purification, but instead recrystallized repeatedly from ethyl acetate, had m.p. 191–195°; λ_{max}^{EtOH} 243 mμ, a_M 16,350; λ_{max}^{Nujol} 3400, 3345 (OH); 1744, 1724 (C=O); 1631 (Conj. C=O); 1606 (Δ^4); 1232 (C—O acetate). This sample was used for combustion analysis.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.85; H, 8.22.

[Extraction of the aqueous filtrates from the precipitation of XIIa with methylene chloride afforded an additional 0.958 g. of material that was chromatographed over 100 g. of Florisil. Elution with 17.5% acetone–Skellysolve B afforded an additional 162 mg. of XIIa, while elution with

(15) Infrared spectra were measured using a Perkin-Elmer Model 21 Spectrophotometer. Maxima are expressed in cm.$^{-1}$ Rotations were determined in chloroform ($c \sim 1\%$). Melting points, determined on a Fisher-Johns block, are uncorrected.

22.5% acetone–Skellysolve B gave 418 mg. of a more polar steroidal material that was not characterized.]

11β,17α,21-Trihydroxy-11-methylpregn-4-ene-3,20-dione (XIIb). A solution of 103 mg. of the acetate XIIa in 7.5 ml. of methanol was stirred at reduced pressure for several minutes to remove dissolved air, and then was blanketed with nitrogen. Following addition of 0.5 ml. of aqueous 20% (w./w.) potassium bicarbonate (nitrogen was bubbled through the water before dissolving the bicarbonate) the mixture was stirred in a sealed vessel under nitrogen at room temperature for 2 days. The mixture was acidified with 2 ml. of *N* hydrochloric acid and evaporated to dryness at reduced pressure, maintaining a bath temperature less than 35°. Trituration of the resultant crystal mass with water, followed by filtration, afforded 79 mg. of XIIb, m.p. 196–198.5°. A mixture m.p. with XIIa was depressed to 180–195°.

The analytical sample crystallized from aqueous acetone as a hemihydrate, m.p. 199–203°.

Anal. Calcd. for $C_{22}H_{32}O_5 \cdot {}^1/_2H_2O$: C, 68.54; H, 8.63. Found: C, 68.06; H, 8.57.

Rough enolization determinations. Into a closed system consisting of a glass reaction vessel attached to a gas-measuring burette filled with saturated sodium chloride solution was placed 0.42 g. (1 millimole) of carefully dried 5β-pregnane-3,11,20-trione 3,20-bis(ethylene acetal)[6] (VII) and 5 ml. of dry benzene. The bottle was placed in a water bath at 15–20°, the contents stirred magnetically, and 5 ml. (excess) of 0.4*M* ethereal methyllithium was introduced slowly through a rubber stopple, using a hypodermic syringe. The observed volume of evolved gas, corrected for the volume of liquid introduced and for the change measured in a blank (no steroid) experiment, was 5.2 ml. (21% of the theoretical amount for 1 mole of methane per mole of steroid).

In a similar manner, using 0.43 g. (1.03 millimole) of pregn-5-ene-3,11,20-trione 3,20-bis(ethylene acetal)[3] (VI), there was obtained 26.4 ml. (corrected volume) of methane, corresponding to 110% of the theoretical amount for 1 mole of methane per mole of steroid. When 432 mg. (1 millimole) 5α,6α-epoxypregnane-3,11,20-trione 3,20-bis(ethylene acetal)[7] (VIII) was substituted for VI, the corrected gas volume was 0.7 ml., corresponding to about 3% of the theoretical.

4-Chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb). A solution of 20.0 g. (0.058 mole) of 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXa) was dissolved in 700 ml. of *t*-butyl alcohol by heating and stirring. The solution was cooled to 23° and protected from light, then 6.9 ml. (1.1 equiv.) of *t*-butyl hypochlorite and 6.0 ml. of concentrated hydrochloric acid in 30 ml. of water were added. The mixture was stirred 18 hr. at room temperature, then was cooled to 14° for several hours. The white precipitate of 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb) was removed by filtration and washed with water; wt. 12.12 g., m.p. 197–200°.

A sample was chromatographed over 120 g. of Merck acid–washed alumina, the product being eluted with 1% acetone–methylene chloride. Crystallization from aqueous acetone and then from methylene chloride–Skellysolve B afforded an analytical sample of IXb, m.p. 226–230°, $[\alpha]_D$ +111°.

Anal. Calcd. for $C_{22}H_{33}ClO_3$: C, 69.36; H, 8.73; Cl, 9.30. Found: C, 69.04; H, 8.76; Cl, 9.07.

11β-Hydroxy-11-methylpregn-4-ene-3,20-dione (V). A. *Lithium chloride procedure.*[11] A solution of 1.8 g. (5 millimoles) of 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb), m.p. 185–195°, and 1.0 g. of dry lithium chloride in 50 ml. of DMF under nitrogen was heated to 130° for 20 min. The reaction mixture was then allowed to cool and poured into 500 ml. of water. The precipitate was separated by filtration and the filtrate was extracted with methylene chloride. The residue from the extract was combined with the precipitate (total 1.64 g.) chromatographed over 150 g. of Merck acid–washed alumina. Fractions 7–12, eluted with methylene chloride and 0.5–1% acetone, contained halogen and weighed 711 mg. Fractions 13–18, 501 mg., were eluted with 2–4% acetone in methylene chloride and consisted of the 4-pregnene (V) melting above 160°. After two crystallizations from acetone-water a sample melting at 174–175°, 177–178° (double m.p.), $[\alpha]_D$ +181° was obtained; λ_{max}^{EtOH} 245 mμ, a_M 13,400.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.75; H, 9.49.

B. *Semicarbazide procedure.*[10] A solution of 1.90 g. of 4-chloro-11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (IXb), m.p. 206–213°, in 40 ml. of redistilled DMF was stirred under nitrogen and a solution of 2.0 g. of semicarbazide hydrochloride and 1.50 g. of anhydrous sodium acetate was added. The temperature rose rapidly from 26° to 37°. A mixture of 5 ml. of redistilled pyruvic acid and 5 ml. of water was added and the temperature was raised to 60° for 2.5 hr. The reaction mixture was poured over 200 g. of crushed ice and diluted with water to 800 ml. The mixture was placed in the refrigerator overnight, then was filtered to give 1.07 g. of precipitate. An additional 0.676 g. was recovered by methylene chloride extraction. The entire yield was chromatographed over Florisil and eluted with methylene chloride–acetone. The higher melting fractions were combined and crystallized from acetone-water to give 0.949 g. of 11β-hydroxy-11-methylpregn-4-ene-3,20-dione (V), m.p. 169–172°.

11β-Hydroxy-2,21-bis(methoxyoxalyl)-11-methylpregn-4-ene-3,20-dione (Xb). A solution of 10.7 g. of 11β-hydroxy-11-methylpregn-4-ene-3,20-dione (V) and 25 ml. of ethyl oxalate in 125 ml. of *t*-butyl alcohol was stirred at room temperature under nitrogen as 25 ml. of 25% (wt./wt.) sodium methoxide in methanol was added. A yellow precipitate formed rapidly. The reaction mixture was stirred 17 hr., then 200 ml. of dry ether was added and stirring was continued for 1 hr. The yellow precipitate was separated by filtration and washed with 300 ml. of dry ether, then dried *in vacuo* to give 22.0 g. of sodium salt (Xa). This was dissolved in 125 ml. of 0.01*N* aqueous sodium hydroxide and made acid with 100 ml. of 1*N* aqueous hydrochloric acid to give the free enol Xb as an amorphous precipitate, wt. 14.7 g. Two recrystallizations from aqueous acetic acid gave 4.93 g. of Xb, m.p. 172–175°, $[\alpha]_D$ +172°, λ_{max}^{EtOH} 289 mμ, a_M 14,400.

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.10; H, 7.03. Found: C, 64.37; H, 6.98.

Methyl 11β-hydroxy-11-methyl-3-oxopregna-4,17(20)-[cis]-dien-21-oate (XI). A suspension of 5.45 g. (0.01 mole) of 11β-hydroxy-2,21-bis(methoxyoxalyl)-11-methyl-pregn-4-ene-3,20-dione in 60 ml. of methanol was stirred under nitrogen at room temperature. A solution of 3.0 g. (0.0365 mole) of anhydrous sodium acetate in 40 ml. of methanol was added immediately. The solution was cooled in an ice bath and held at 0–5° while 24 ml. of a solution of 2.0 ml. of bromine in 33 ml. of methanol (precooled in a dry ice–acetone bath) was added over a 15 min. period, when the mixture became nearly colorless. This corresponded to 2.8 equivalents of bromine. The mixture was stirred 5 min., then 15 ml. of 25% (wt./wt.) sodium methoxide in methanol (6.4 equivalents) was added. The reaction mixture was stirred 2 hr. at room temperature, then 15 ml. of glacial acetic acid was added, followed by 6 g. of zinc dust added in portions during 1 hr. The mixture was stirred 30 min. longer and the excess zinc was separated by filtration.

The filtrate was poured into 1500 ml. of ice water and placed in the refrigerator overnight, giving 3.514 g. of precipitate. The aqueous filtrate was extracted with methylene chloride to give 0.471 g. of gum. This was combined with the precipitate (total, 3.98 g.) and chromatographed over 200 g. of Florisil. Elution with Skellysolve B and 5–7% acetone–Skellysolve B gave crystalline fractions which were recrystallized from methanol-water to give 1.76 g. of methyl 11β-hydroxy-11-methyl-3-oxopregna-4,17(20)-[*cis*]-dien-21-

oate (XI), m.p. 187–195°. Crystallization from methylene chloride–Skellysolve B mixture gave an analytical sample, m.p. 194–197°, $[\alpha]_D$ +147°; λ_{max}^{EtOH} 238 mμ, a_M 23,100.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.19; H, 8.74.

11β,21-Dihydroxy-11-methylpregna-4,17(20)-[cis]-dien-3-one (IVa). A mixture of 3.19 g. of methyl 11β-hydroxy-11-oxopregna-4,17(20)-[*cis*]-dien-21-oate, 40 mg. of *p*-toluenesulfonic acid monohydrate, and 3 ml. of redistilled pyrrolidine in 75 ml. of benzene was heated under reflux, with a water take-off, for 1.5 hr. Then 65 ml. of benzene was removed by distillation and the remaining solvent was removed by distillation *in vacuo* below 45°. The crystalline residue of the 3-pyrrolidyl amine was dissolved in 40 ml. of benzene and added to a stirred suspension of 2.0 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was stirred 1.5 hr., then 20 ml. of ethyl acetate was added slowly, followed by 20 ml. of water. The remaining ether was removed by distillation *in vacuo*, then 120 ml. of methanol was added and the mixture was stirred 20 min. at 45°. After addition of 30 ml. of 5% aqueous sodium hydroxide, stirring was continued 15 min. at 50°, then 8 ml. of glacial acetic acid was added and the methanol was removed *in vacuo*. A solution of 10 ml. of concentrated sulfuric acid in 200 ml. of water was added and the mixture was placed in the refrigerator overnight, giving 2.893 g. of IVa, m.p. 195–202°. Crystallization from methanol-water gave 2.258 g., m.p. 200–208°. A sample was crystallized from aqueous pyridine, aqueous acetic acid, and ethyl acetate, and melted at 205–211°.

The acetate (IVb), prepared as described above, had m.p. 112–115°, $[\alpha]_D$ + 119°. The infrared spectra (Nujol mull) of samples of IVb prepared by the two routes were different, but chloroform solution spectra were identical, indicating that the samples were polymorphic. The same is true of the two samples of IVa having such different melting points.

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The Chemistry of the Aliphatic Esters of Phosphorodithioic Acids. IV. *O,O,S*-Trialkyl Phosphorodithioates by the Reaction of *O,O*-Dialkyl Hydrogen Phosphorodithioates with Their Salts[1]

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The preparation of trialkyl phosphates by the disproportionation of a mixture of a dialkyl hydrogen phosphate and its sodium salt at 300° has been reported.[2]

In the presence of acid, the zinc salts of *O,O*-dialkyl phosphorodithioates have been reported to decompose into mixtures of olefins, hydrogen sulfide and meta-thiophosphate polymers at 130–180°.[3]

The present investigation has shown that the *O,O*-dialkyl hydrogen phosphorodithioates react with their amine salts to yield *O,O,S*-trialkyl phosphorodithioates. The reaction proceeds smoothly at temperatures above 70° in benzene and dioxane, and appears to be general for the alkyl esters. In agreement with the equation shown below, only one alkyl group was transferred from the alkylating moiety in the reactions studied, and H_2S was evolved simultaneously. The yields were in the range of 40–97% based on this equation.

$$(RO)_2PSSH + (RO)_2PSS^-B^+ \longrightarrow (RO)_2PSSR + H_2S + (ROPOS)B$$

The reaction rate was followed readily by titration of the unreacted acid in the reaction mixture. Table I shows the reaction rates, expressed as the time required for 50% reaction, for the reaction of *O,O*-diethyl hydrogen phosphorodithioate with its salts in refluxing benzene solution. The results indicated that the reaction rate increased with the increasing base strength of the unhindered amines; but the rates decreased with increasing substitution around the nitrogen atom of the amine.

TABLE I

REACTION RATES OF *O,O*-DIETHYL HYDROGEN PHOSPHORODITHIOATE WITH ITS AMINE SALTS

Salt	Hours required for 50% reaction
Triethylamine	1.8
Piperidine	2.4
Pyridine	3.8
α-Picoline	7.2
Aniline	7.8
2,6-Lutidine	11.6

The diaryl hydrogen phosphorodithioates do not undergo this reaction as shown by the fact that *O,O*-diphenyl hydrogen phosphorodithioate with its triethylamine salt gave no decrease in acidity after 5 hr. reflux in benzene.

Table II shows the reaction rates of several *O,O*-dialkyl hydrogen phosphorodithioates with their triethylamine salts in benzene solution, expressed as the time required for 50% reaction. In the group tested, the acids prepared from primary alcohols reacted faster than those prepared from secondary alcohols. Within each series the reaction rates decreased with increasing molecular weight.

(1) For preceding article in this series, see W. E. Bacon and W. M. LeSuer, *J. Am. Chem. Soc.*, **76**, 670 (1954).

(2) G. M. Kosolapoff, "Organo-phosphorus Compounds," John Wiley & Sons, New York, 1950, p. 231.

(3) G. W. Kennerly, G. L. M. Christopher, and C. M. Judson, Abstracts of Papers, 122nd Annual Meeting, American Chemical Society, Atlantic City, N. J., Sept. 14–19, 1952, p. 31M.

TABLE II

REACTION RATES OF *O,O*-DIALKYL HYDROGEN PHOSPHORODITHIOATES WITH THEIR TRIETHYLAMINE SALTS

$(RO)_2PSSH$ R =	Hours required for 50% reaction
Ethyl	1.8
n-Propyl	2.6
n-Butyl	2.6
n-Hexyl	3.4
2-Ethylhexyl	14.5
i-Propyl	15.2
s-Butyl	17.5
4-Methyl-2-pentyl	39.5

TABLE III

O,O,S-TRIALKYL PHOSPHORODITHIOATES $(RO)_2PSSR$

R	Amine	Mole Ratio[a]	Solvent	Time (hrs.)	Yield of Ester (%)[b]
C_2H_5	C_5H_5N	1	A	38.5	58
C_2H_5	C_5H_5N	2	B	4	91
C_2H_5	C_5H_5N	5	A	21	84
C_2H_5	C_5H_5N	5	B	8	63
C_2H_5	$(C_2H_5)_3N$	1	B	5	0
C_2H_5	$(C_2H_5)_3N$	2	B	6	41
C_2H_5	$(C_2H_5)_3N$	2.5	B	5	76
C_2H_5	$(C_2H_5)_3N$	5	A	21	84
C_2H_5	$(C_2H_5)_3N$	15	A	21	56
C_2H_5	$C_5H_{11}N$	3	B	4	69
C_2H_5	$C_6H_{11}N$	2	B	3	57
n-C_3H_7	$C_6H_{11}N$	3	B	7	83
i-C_3H_7	C_5H_5N	2	B	6	86
i-C_3H_7	$(C_2H_5)_3N$	3	B	9	69
n-C_4H_9	$(C_2H_5)_3N$	2	A	6	56
s-C_4H_9	$(C_2H_5)_3N$	2	A	17.5	59
m-C_6H_{13}	$(C_2H_5)_3N$	2	A	12.5	58
C_6H_5	$(C_2H_5)_3N$	2	A	5	0

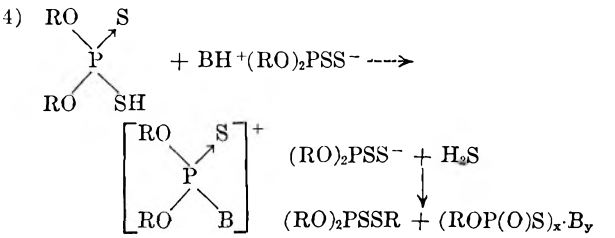
Solvent A = benzene; Solvent B = dioxane. [a] Ratio of *O,O*-dialkyl hydrogen phosphorodithioate to amine. [b] Esters were identified by elemental analysis, and refractive index.

The amine appeared to act catalytically when the aminephosphenothionate complex was soluble in the solvent used for the reaction. This was shown by the reaction of 1 mole of triethylamine with 15 moles of *O,O*-diethyl hydrogen phosphorodithioate. In this reaction a 56% yield of distilled ester was obtained. When pyridine was used, the pyridine–ethyl phosphenothionate complex separated as a benzene-insoluble gum and the reaction stopped when all of the amine had been precipitated. The dialkyl hydrogen phosphorodithioates are strong acids and are capable of removing the base from the amine-phosphenothionate initially formed, provided it does not escape by settling out.

A weak amine salt of the acid should also undergo the reaction, as some free acid would be present in the equilibrium mixture. Thus, the pyridine salt of *O,O*-diethyl hydrogen phosphorothioate yielded 58% of the *O,O,S*-triethyl phosphorodithioate when refluxed in benzene. No reaction occurred when the triethylamine salt was refluxed in dioxane.

In general the amine-phosphenothionates were gummy impure materials—only the pyridine complex was obtained in a pure enough form to obtain satisfactory analyses.

The following sequence is suggested as a possible course for the reaction:



The electron shift which results when the ammonium ion approaches the phosphorus atom of the acid molecule culminates in the ejection of H_2S and the simultaneous formation of a carbonium ion which reacts with the *O,O*-dialkyl hydrogen phosphorodithioate ion. The rate determining step would be the approach of the ammonium ion to the phosphorus atom. This would explain the steric factors involved in the reaction rates discussed above.

EXPERIMENTAL

Reactions in benzene. The procedure followed for the reaction of the *O,O*-dialkyl hydrogen phosphorodithioates and their salts in benzene was in general as follows: The *O,O*-dialkyl hydrogen phosphorodithioate was dissolved in benzene and the amine was added slowly with stirring. The solution was heated at the reflux temperature for the period necessary to complete the reaction. Samples were removed at intervals and titrated in order that the course of the reaction might be followed. In some cases a gum-like layer separated from the solution, in which case the benzene layer was decanted from it. The benzene layer was washed successively with water, 5% hydrochloric acid solution, and water. It was dried over anhydrous sodium carbonate, the benzene was removed by distillation, and the residual ester was distilled through a 7-inch Vigreaux column.

Reactions in dioxane were carried out in the same manner as above.

TABLE IV

ANALYSES OF *O,O,S*-TRIALKYLPHOSPHORODITHIOATES $(RO)_2PSSR$

R	B.P.	n_D^{25}	Calculated P	Calculated S	Found P	Found S
n-C_3H_7	87° at 0.3 mm.	1.4945	12.1	25.0	11.9	24.8
i-C_3H_7	61.8° at 0.1 mm.	1.4851	12.1	25.0	12.1	25.6
n-C_4H_9	96° at 0.06 mm.	1.4892	10.38	21.49	10.30	21.48
s-C_4H_9	90° at 0.2 mm.	1.4862	10.38	21.49	10.50	21.50
n-C_5H_{13}	Decd.[a]	1.4852	8.10	16.76	8.02	16.95

[a] Sample was purified by extraction with 5% KOH, followed by two H_2O washes and dried to 100° at 0.1 mm.

O,O-Diethyl hydrogen phosphorodithioate and its amine salts. Pyridine Salt-Mole Ratio 1:1. Pyridine (19.0 g., 0.25 mole) and 95 g. (0.5 mole) of the acid-ester[4] in 100 ml. of benzene were refluxed for 6 hr. This reaction yielded 52.2 g. (97%) of O,O,S-triethyl phosphorodithioate, b.p. 56–48° at 0.2 mm., n_D^{25} 1.5038.

Anal. Calcd. for $C_6H_{15}O_2S_2P$: P, 14.46; S, 29.93. Found: P, 14.60; S, 29.90.

The gum-like product that separated from the reaction mixture weighed 39 g. It dissolved in water with decomposition and was soluble in ethyl acetate but insoluble in acetone, petroleum ether (30–60°) and benzene.

Anal. Calcd. for $EtOPOS.C_5H_5N$: P, 15.20; S, 15.75. Found: P, 15.28; S, 15.77.

The yields obtained with other amines, and with the various acid-amine ratios employed, are shown in Table III.

Typical analyses of the esters obtained are shown in Table IV.

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Pyridyloxazolidinediones and Related Compounds

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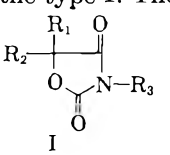
In extension of our work with the pyridylethylated oxazolidinediones[1,2] and in view of recent interest in pyridyl hydantoins,[3] we have investigated the preparation of pyridyl, picolyl, quinolyl, pyrimidyl, and imidazolinylethyl oxazolidinediones of the type I. The compounds prepared have been described in Table I. In addition to the free bases, a number of methiodides of variants of I have been prepared.



I

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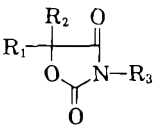
TABLE I. 3-PYRIDYL-OXAZOLIDINEDIONES AND RELATED COMPOUNDS



No.	R_1[a,b]	M.P.,[c] B.P. (Mm.), R_1 = CH_3, R_2 = H	R.S.[d]	Yield,[e] %	Formula	Analyses, %[f] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[g]	2-Py	134 (0.2)		62	$C_9H_8N_2O_3$	56.3	56.3	4.2	4.4	14.6	14.4
2[h]	3-Py	119–120	A	33	$C_9H_8N_2O_3$	56.3	56.4	4.2	4.3	14.6	14.4
3	[b]	164–166	B	65	$C_{10}H_{11}IN_2O_3$	36.0	35.6	3.2	3.5	8.4	8.1
4	3-CH_3-2-Py	126–130 (0.2)		45	$C_{10}H_{10}N_2O_3$	58.3	58.2	4.9	5.5	13.6	13.9
5[i]	4-CH_3-2-Py	88–89	A	32	$C_{10}H_{10}N_2O_3$	58.3	57.8	4.9	4.8	13.6	13.6
6	6-CH_3-2-Py	95–96	A	28	$C_{10}H_{10}N_2O_3$	58.3	58.5	4.9	4.9	13.6	13.6
7[j]	2-Pc	104–108 (0.02)		54	$C_{10}H_{10}N_2O_3$	58.3	57.8	4.9	5.1	13.6	13.2
8	[b]	178–180	B	52	$C_{11}H_{13}IN_2O_3$	37.9	37.9	3.8	3.9	8.0	8.4
9	3-Pc	125–128 (0.12)		73	$C_{10}H_{10}N_2O_3$	58.3	58.5	4.9	5.2		
10	[b]	151–153	B	88	$C_{11}H_{13}IN_2O_3$	37.9	38.3	3.8	3.9	8.0	8.3
11	4-Pc	112–113	A	58	$C_{10}H_{10}N_2O_3$	58.3	57.9	4.9	4.9		
12	[b]	168–171	B	86	$C_{11}H_{13}IN_2O_3$	37.9	38.2	3.8	3.7	8.0	8.3
13[k]	Im	152–154 (0.4) R_1=CH_3=R_2		46	$C_{10}H_{15}N_3O_2$	53.3	53.4	6.7	7.2		
14	2-Py	118–119	A	76	$C_{10}H_{10}N_2O_3$	58.3	58.8	4.9	5.2	13.6	13.9
15	[b]	163–164	B	10	$C_{10}H_{13}IN_2O_3$	37.9	38.3	3.8	3.7	8.0	7.7
16	3-Py	147–148	A	77	$C_{10}H_{10}N_2O_3$	58.3	58.1	4.9	4.7		
17	[b]	201–202	B	84	$C_{11}H_{13}IN_2O_3$	37.9	38.2	3.8	3.8	8.0	8.2
18	4-Py	133–134	A	52	$C_{10}H_{10}N_2O_3$	58.3	58.3	4.9	5.0	13.6	13.9
19	[b]	241–244	B	93	$C_{11}H_{13}IN_2O_3$	37.9	38.2	3.8	3.9	8.0	8.4
20	4-CH_3-2-Py	178–179	A	76	$C_{11}H_{12}N_2O_3$	60.0	60.1	5.5	5.3	12.7	12.7
21[l]	2-Pc	59–60	C	44	$C_{11}H_{12}N_2O_3$	60.0	60.4	5.5	5.7	12.7	12.6
22	3-Pc	117–120 (0.05)		86	$C_{11}H_{12}N_2O_3$	60.0	60.8	5.5	5.7	12.7	12.3
23	4-Pc	94–95	A	64	$C_{11}H_{12}N_2O_3$	60.0	60.2	5.5	5.6	12.7	12.7
24	Qn	164–166	A	71	$C_{14}H_{12}N_2O_3$	65.6	65.7	4.7	4.9	10.9	10.7
25	[b]	217–218	B	72	$C_{15}H_{15}IN_2O_3$	45.3	45.8	3.8	4.0	7.0	7.0
26	Pm	94–95	C	18	$C_{11}H_{13}N_3O_3$	56.2	56.2	5.6	5.3	17.9	17.8

The synthetic procedure used was the direct synthesis[4] of the oxazolidinedione from the amine, the α-hydroxy ester in an excess of the reactant, and diethyl carbonate under sodium alkoxide catalysis. Unlike our previous series,[4] the amines herein evaluated, on occasion gave incomplete conversion to the required dione I, with isolation of the intermediate ethyl urethane derived from reaction of the ethyl carbonate with the hetero amine. In one instance (compound 5) the symmetrical bis-urea was also isolated and may have resulted from transient formation of the pyridyl isocyanate,[5,6] followed by reaction with the reactant amine.

Selected compounds in this series proved to be mildly effective as anti-inflammatory agents[7] (compounds 1, 2, 5, 9, 20, 22, 23, and 24). Compounds 9-11, and 23 were effective potentiators of Evipal sleeping time.[8]

(4) S. L. Shapiro, I. M. Rose and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3083 (1959).

(5) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).

(6) J. W. Baker and D. M. Bailey, *J. Chem. Soc.*, 4652, 4663 (1957).

(7) See S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., (Sci. Ed.)*, **46**, 333 (1957), for method of testing.

←— Footnotes to Table I

[a] The following abbreviations are used for the heterocyclic substituent: Py = pyridyl; Pc = picolyl; Im = 2-[1-(2-methyl-2-imidazolinyl)]ethyl; Qn = 3-quinolyl; Pm = 2,6-dimethyl-4-pyrimidyl. [b] The compounds so marked are methiodides of the compounds immediately above. [c] The melting points are uncorrected and were established on a Fisher-Johns melting point block. [d] R.S. = recrystallizing solvent; A = ethyl acetate–hexane; B = ethanol; C = hexane. [e] Yields are based on recrystallized or distilled product. [f] Analyses are by Weiler and Strauss, Oxford, England. [g] After the removal of the formed ethanol of reaction a 13% yield of the ethyl urethane of 2-aminopyridine precipitated, m.p. 105–106°, not depressing the melting point of the authentic urethane prepared from 2-aminopyridine and ethyl chloroformate [R. L. Shriner and R. G. Child, *J. Am. Chem. Soc.*, **74**, 549 (1952), report m.p. 104–105°]. [h] When the mother liquor obtained after filtration of the product was evaporated and the residue recrystallized (hexane) there was obtained 5% yield of the ethyl urethane of 3-aminopyridine, m.p. 90–92° [*J. Am. Chem. Soc.*, **74**, 549 (1952) report m.p. 91–92°]. [i] After the removal of the formed ethanol of reaction 4.2 g. of a mixture of solids, m.p. 120–210° precipitated and was treated with boiling hexane. The hexane insoluble portion proved to be bis(4-methyl-2-pyridyl)urea m.p. 225°. An authentic sample prepared from 2-amino-4-methylpyridine and ethyl chloroformate melted at 228.5° (ethyl acetate). *Anal.* Calcd. for $C_{13}H_{14}N_4O$: C, 64.4; H, 5.8; N, 23.1. Found: C, 64.5; H, 5.1; N, 23.3. The hexane solution on standing gave the ethyl urethane of 2-amino-4-methylpyridine m.p. 128–131°, not depressing the melting point of the authentic urethane (prepared from 2-amino-4-methylpyridine and ethyl chloroformate), m.p. 130–131° (hexane). *Anal.* Calcd. for $C_9H_{12}N_2O_2$: N, 15.6. Found: N, 15.7. [j] A forerun in the distillation 1.6 g. (9%), b.p. 95–97 (0.02 mm.), n_D^{20} 1.5140 gave analyses indicative of impure ethyl urethane of 2-picolylamine. [k] The required initial reactant 2-[1-(2-methyl-2-imidazolinyl)] ethylamine was obtained from the National Aluminate Corp., Chicago, Ill., and was purified by distillation, b.p. 62–80° (0.04 mm.), n_D^{20} 1.5119. [l] A forerun in the distillation, 3.37 g. (19%), b.p. 98–100° (0.08 mm.), n_D^{20} 1.5162 gave analyses indicative of impure ethyl urethane of 2-picolylamine. The oxazolidinedione product boiled 103–104° (0.05 mm.), n_D^{20} 1.5183, and crystallized on standing.

EXPERIMENTAL

General procedure (Table I). A solution of 0.2 g. of sodium in 4 ml. of ethanol was added to a solution of 0.1 mole of the amine, 0.1 mole of the ethyl α-hydroxy ester and 37 ml. of diethyl carbonate, and the stirred mixture was heated under reflux. When the internal temperature had dropped approximately 20°, the formed ethanol was removed and measured. If the quantity of ethanol was substantially less than theoretical, an additional charge of catalyst was added and the reflux and removal of formed ethanol were repeated as described above. Upon standing, or after removal of most of the diethyl carbonate, the product crystallized and was separated. Liquid products were distilled.

The methiodides were prepared by treating 0.01 mole of the free base with 2 ml. of methyl iodide in 40 ml. of ethanol and were obtained after the reaction mixture had been stored at room temperature for 7 to 10 days.

2-[N-(4-Methyl-2-pyridyl)carbamoyloxy]propionic acid. Alkaline hydrolysis of compound 5 and work-up as previously described[2] afforded the title compound in 68% yield, m.p. 144–148° (ethanol).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.9; H, 5.6; N, 12.8.

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(8) See ref. (1) for method of testing.

Antihypertensive Agents. II. Tropine Quaternaries[1]

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A series of tropine quaternaries (Table I) have been prepared for pharmacological screening. Synthesis was effected by treating a mixture of the quaternizing halide with tropine in a polar solvent such as acetonitrile.[2]

Whereas bis-tropinium salts (compounds 9–12) formed readily, methylene iodide yielded the iodomethyltropinium iodide, suggesting that steric factors prevent two tropinium nitrogens from being linked by a single methylene unit.[3,4]

(1) For Paper I of this series, see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(2) C. J. Cavallito, A. P. Gray and E. E. Spinner, *J. Am. Chem. Soc.*, **76**, 1862 (1954).

(3) For a related work see W. C. Davies, E. B. Evans and F. L. Hulbert, *J. Chem. Soc.*, 412 (1939).

(4) The failure for the conversion to the bis-quaternary may be associated with the "neopentyl-like" structure of the iodomethyl quaternary and its relative inactivity in S_N2 reactions, see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1956, page 157.

TABLE I

QUATERNARY SALTS OF TROPINE[a]

No.	R	X	M.p., °C.[b]	Rs[c]	Yield,[d] %	Formula	Analyses,[e] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	n-$C_{12}H_{25}$—	Br	211–213	A–B	58	$C_{20}H_{40}BrNO$					3.6	3.8
2	C_8H_{15}—[f]	Br	182–185	B–C	49	$C_{16}H_{30}BrNO$	57.8	57.9	9.1	8.9		
3	$C_6H_5(CH_2)_3$—	Br	217–220	A	84	$C_{17}H_{26}BrNO$	60.0	60.4	7.7	7.8	4.1	3.8
4	$(C_6H_5)_2CH$—	Cl	195–197	A	9	$C_{21}H_{26}ClNO$	73.3	73.4	7.6	7.7	4.1	4.1
5	$HC{\equiv}CCH_2$—	Br	243–245	A	57	$C_{11}H_{18}BrNO$	50.8	51.0	7.0	7.2	5.4	5.3
6	ICH_2—	I	203–206	D	31	$C_9H_{17}I_2NO$[g]	26.4	26.2	4.2	4.1	3.4	3.4
7	$IC{=}CCH_2$—[h]	Cl	212	A	12	$C_{11}H_{17}ClINO$					4.1	4.1
8	[i]	Cl	>300	A	32	$C_{14}H_{32}Cl_2N_2O$	53.3	53.4	10.2	10.4	8.9	9.2
9	$—CH_2CH{=}CHCH_2—$[j]	2Cl	>300	D	37	$C_{20}H_{36}Cl_2N_2O_2$	59.0	59.1	8.9	8.9	6.9	6.9
10	$—CH_2C{\equiv}CCH_2—$[j]	2Cl	260–263	A	21	$C_{20}H_{34}Cl_2N_2O_2$[k]					6.9	6.9
11	$—(CH_2)_5—$[j]	2Br	>300	D	30	$C_{21}H_{40}Br_2N_2O_2$	49.2	49.2	7.9	7.7	5.5	5.9
12	$—(CH_2)_6—$[j]	2Br	282–285	B–D	22	$C_{22}H_{42}Br_2N_2O_2$	50.2	49.8	8.0	7.9	5.3	5.5
13	CH_3COCH_2—	Cl	246–247	C	47	$C_{11}H_{20}ClNO_2$	56.5	56.5	8.6	8.5	6.0	6.1
14	$C_6H_5COCH_2$—	Cl	220–223	C	41	$C_{16}H_{22}ClNO_2$	65.0	65.2	7.5	7.8	4.7	4.8
15[n]	H	H Cl	258–260	A	58	$C_{10}H_{19}ClN_2O_2$	51.2	51.2	8.2	8.1	11.9	11.8
16[n]	CH_3—	CH_3— Br	242–243	E	57	$C_{12}H_{23}BrN_2O_2$	46.9	47.2	7.5	7.0	9.1	9.2
17[n]	$—(CH_2)_4—$	Br	241	A	61	$C_{14}H_{25}BrN_2O_2$	50.5	50.5	7.6	7.4	8.4	8.2
18[n]	i-C_5H_{11}—	H Cl	183–184	G	33	$C_{15}H_{29}ClN_2O_2$	59.1	59.2	9.6	9.1	9.2	9.6
19[n]	[l]	H Br	246–248	C–F	52	$C_{18}H_{31}BrN_2O_2$	55.8	55.6	8.1	7.9	7.2	7.4
20[n]	$C_6H_5CH_2$—	H Cl	196–197	E	32	$C_{17}H_{25}ClN_2O_2$	62.9	62.8	7.8	7.7	8.6	8.7
22[n]	$C_6H_5CHCH_3$—	H Br	198–199	C–F	47	$C_{18}H_{27}BrN_2O_2$					7.3	7.4
23[n]	C_6H_5CH—	i-C_3H_7— Br	169–172	F–G	35	$C_{20}H_{31}BrN_2O_2$	58.4	58.3	7.6	7.2	6.8	7.3
24[n]	$C_6H_5CH_2CHCH_3$—[m]	H Cl	204–207	H	49	$C_{19}H_{29}ClN_2O_2$	64.7	64.7	8.3	8.2	7.9	7.6
25[n]	C_6H_5—	H Cl	175–178	C	39	$C_{16}H_{23}ClN_2O_2$	61.8	61.8	7.5	7.4	9.0	9.2
26[n]	p-Cl—C_6H_4—	H Cl	247–248	C	44	$C_{16}H_{22}Cl_2N_2O_2$	55.7	56.0	6.4	6.4	8.1	7.9

[a] The formula for the tropine base has been shown as TrN. [b] Melting points are uncorrected and have been taken on a Fisher-Johns melting point block. [c] Recrystallization solvent: A—ethanol; B—isopropyl ether; C—isopropyl alcohol; D—methanol; E—acetonitrile; F—hexane; G—ether; H—ethyl acetate. [d] Yields are based on recrystallized product. [e] Analyses were performed by Weiler and Strauss, Oxford, England. [f] C_8H_{15}— is 2-cyclohexylethyl-. [g] Calcd.: I, 62.1. Found: I, 62.4. [h] The reactant 3-chloro-1-iodopropyne-1 was obtained from the Dow Chemical Company. [i] R = $—CH_2CH_2N(C_2H_5)_2 \cdot HCl$. [j] Ditropinium quaternary salt. [k] An acceptable CH analysis was not obtained. [l] R_1 = (2,5-endomethylenecyclohexyl)methyl. [m] Derived from d-α-methylphenethylamine. [n] R = $R_1R_2NCOCH_2$—; R_1 and R_2 shown under R column.

Pharmacology. All of the compounds were evaluated for hypotensive response following procedures previously described.[5] A 3+ response was noted on administration of compounds 14, 15, 20 and 25, while compounds 3, 24 and 26 showed 2+ hypotension. Each of the 3+ compounds also showed a potentiating effect on adrenalin and complete ganglionic block. Compound 26 inhibited adrenalin and showed a ganglionic block, compound 3 resembled the 3+ responders, and compound 24 was without effect on adrenalin.

In the carbamido series (compounds 15–26) it is of interest that hypotensive activity was associated with the compounds R_1, R_2 = H, and R_1 = aralkyl or aryl and R_2 = H. Other structural modifications such as those found in compounds 16, 17, 18, 19, 22 and 23 were associated with loss of hypotensive activity.

EXPERIMENTAL[6]

N-(Iodomethyl) tropinium iodide (Compound 6, Table I). Tropine (5.6 g., 0.04 mole) and 5.3 g. (0.02 mole) of diiodomethane were dissolved in 30 ml. of acetonitrile and maintained at 20° for 5 days.

The formed crystals were separated to give 5.0 g. (62%), m.p. 198–202°.

The same compound was obtained from 1:1 molar ratios of the reactants at 20°, or when the reaction mixture above was heated for 0.5 hour under reflux. The reaction of tropine with penta-erythrityl tetrabromide failed with no evidence of quaternization after 50 hr. under reflux in acetonitrile.

N-(Carbamidomethyl)tropinium chloride (Compound 15, Table I). A solution of 4.2 g. (0.03 mole) of tropine, 5.6 g. (0.06 mole) of α-chloroacetamide and 60 ml. of acetonitrile was maintained at 20° for 5 days. Filtration yielded 4.7 g. of product, m.p. 232–237°. An additional 1.4 g. was obtained by addition of ether to the filtrate.

N-Methyl-α-chloroacetanilide.[7] The following preparation is typical of the synthesis of compounds of the α-haloacetamides.

A solution of 11.8 g. (0.11 mole) of *N*-methylaniline in 75 ml. of acetonitrile was slowly added to a cooled solution of 5.7 g. (0.05 mole) of chloroacetyl chloride in 25 ml. of acetonitrile. After 48 hr. at 20°, the *N*-methylaniline hydrochloride was separated and the filtrate evaporated. Trituration of the residue with ether gave 8.8 g. (96%) of crude product, which recrystallized (hexane) melted 69–70°.

The constants of most of the α-haloacetamides were in substantial agreement with values reported in the literature. The following amides have not been previously reported: *N*-benzyl-*N*-*i*-propyl-bromacetamide, b.p. 124–136° (0.2 mm.); *N*-α-phenethyl-bromacetamide, m.p. 82–83° (hexane); *N*-(2,5-endomethylenecyclohexyl)methyl-bromacetamide, b.p. 104–130° (0.04 mm.).

Analyses were N Calcd./N Found, respectively, 5.2/5.1, 5.8/6.0, 5.7/5.6.

(5) (a) For evaluation of hypotensive effect see Ref. 1; (b) for evaluation of effect on adrenalin and ganglionic block see S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959).

(6) Data given in the tables are not reproduced in this section. Representative examples of the synthetic work are given.

(7) Reported by W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 105 (1915), m.p. 70°.

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Bis(5-hydroxymethyl-1-naphthyl)disulfide

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Although preparations of bis(hydroxyalkyl-aryl) disulfides, including those of bis(2-hydroxymethylphenyl)disulfide,[1a,b,c] bis(4-hydroxylmethyl phenyl) disulfide,[1c] and bis(4-β-hydroxyethyl-1-naphthyl) disulfide[2] have been reported previously, an example of a bis(hydroxymethyl-naphthyl)disulfide was hitherto unknown. Since the aforementioned known disulfides have been evaluated as chain transfer agents for free radical polymerization systems,[1b,1c,2] it seemed worthwhile to evaluate a compound of the latter type in such a system.

This paper reports the preparation of such a disulfide, namely bis(5-hydroxymethyl-1-naphthyl)-disulfide (VI) by the following procedure: A sample of 5-acetoxymethyl-1-nitronaphthalene (II) was prepared in two steps from 1-nitronaphthalene by the method of Short and Wang[3] *via* chloromethylation and acetolysis, and hydrolyzed to the known carbinol (III) (99%) with alcoholic alkali. The overall yield of III obtained from 5-chloromethyl-1-nitronaphthalene (I) by this two step method was much greater (65%) than that which we obtained by hydrolyzing the chloride directly to the carbinol with aqueous sodium carbonate by Short's procedure[3] (12%). Compound III was catalytically reduced to 5-hydroxymethyl-1-naphthylamine (IV), an orange compound, m.p. 107.2–108.4° (94%) with Raney nickel, converted to a crude form of 5-hydroxymethyl-1-thionaphthol (V) *via* the xanthate method, and oxidized to the corresponding disulfide (VI), a tan compound, m.p. 196.1–197.1°.

EXPERIMENTAL[4]

5-Hydroxymethyl-1-nitronaphthalene (III). This compound was prepared by alkaline hydrolysis of 5-acetoxymethyl-

(1) (a) A. Reichert and K. Crämer, *Ber.*, **61**, 2555 (1928); (b) A. J. Costanza, R. J. Coleman, R. M. Pierson, C. S. Marvel, and C. King, *J. Polymer Sci.*, **17**, 319 (1955); (c) R. M. Pierson, A. J. Costanza, and A. H. Weinstein, *J. Polymer Sci.*, **17**, 221 (1955).

(2) A. H. Weinstein, R. M. Pierson, B. Wargotz, and T. F. Yen, *J. Org. Chem.*, **23**, 363 (1958).

(3) W. F. Short and H. Wang, *J. Chem. Soc.*, 991 (1950).

(4) All melting points are corrected.

1-nitronaphthalene (II), m.p. 90.2–91.2°, which was prepared in turn (70%) from 5-chloromethyl-1-nitronaphthalene (I)[3] by an acetolysis procedure described by Short and Wang.[3]

A 4.90 g. (0.0200 mole) portion of II was suspended in 45 ml. of 0.44*N* alcoholic potassium hydroxide, and the mixture refluxed for 3 hr. By concentrating the resultant solution *in vacuo*, and adding water to it, a brown precipitate was formed. By collecting this precipitate, washing it with water, then with *n*-hexane, and desiccating it, 4.02 g. (99%) of III, m.p. 128–129°, was obtained. The product was recrystallized from hot 1:1 chloroform/cyclohexane to pale yellow needles, m.p. 130.4–131.2°. (Compare with m.p. 128–129° reported for III by Short and Wang[3] as prepared by hydrolysis of I with aqueous sodium carbonate)

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.01; H, 4.46; N, 6.89. Found: C, 65.27; H, 4.37; N, 6.79, 6.83.

5-Hydroxymethyl-1-naphthylamine (IV). A 10.16 g. (0.0500 mole) quantity of III, m.p. 128–129°, was dissolved in 200 ml. of warm absolute ethanol, and the solution poured into a 375 ml. Parr hydrogenation pressure bottle, and allowed to cool. Water-wet, active Raney nickel catalyst (2.9 g.) was added to the bottle, which was connected to a Parr low pressure hydrogenation apparatus. The system was swept with hydrogen and reduced with hydrogen at an initial pressure of three atmospheres, at 25° with mechanical shaking, for 4 hr. (to constant pressure value of gas reservoir). Then the solution was exposed to the system for another hour at 75° (during which time no further drop in hydrogen pressure occurred). After filtering the catalyst from the hot solution (quickly flushing the pyrophoric residue into the sink), the ethanol solution was evaporated *in vacuo*. In this way, 8.13 g. (93.6%) of fairly pure IV was obtained as a brown solid m.p. 106.4–107.4°. On recrystallizing the product from hot 7:1 toluene/ethanol solution, orange-brown crystals, m.p. 107.2–108.4°, with an equivalent weight of amine of 175 (on basis of titration with perchloric acid in acetic acid with methyl violet indicator), as compared with a theoretical equivalent weight of 173 for $C_{11}H_{11}NO$, were obtained.

Bis(5-hydroxymethyl-1-naphthyl) disulfide (VI). (A) Formation of crude 5-hydroxymethyl-1-thionaphthol (V). A 3.98 g. (0.0230 mole) quantity of IV was mixed with 5.76 ml. of concentrated hydrochloric acid and 15 ml. of water. To this yellow-green slurry, cooled to −5°, was added an ice-chilled solution of 1.59 g. of sodium nitrite in 5 ml. of water, gradually with stirring, along with some ice. This brown diazonium salt suspension was added, dropwise, with stirring to a solution of 5.60 g. (0.0350 mole) of potassium ethyl xanthate in 10 ml. of water, maintaining the latter system at 50°, and the former at 0°. After mixing, the system was maintained at 50° for an additional hour, with continued stirring, and allowed to cool. After acidification with 1:1 concentrated sulfuric acid/water in the hood, the system was extracted with ether and the solvent removed. The resultant 5.30 g. of crude 5-hydroxymethyl-1-naphthyl ethyl xanthate was hydrolyzed by treating with a solution containing 3.46 g. potassium hydroxide, 1 ml. of water, and 5 ml. of ethanol at reflux for 1 hr. After removal of ethanol *in vacuo*, the residue was extracted with 100 ml. of water, and the aqueous extract acidified with 6*N* sulfuric acid. The brown precipitate which formed was collected, washed with water, then with hexane, and air dried. This crude 2.68 g. of thiol (V), m.p. 73–76°, was obtained in 61% yield of product of 58% thiol activity (on the basis of potentiometric titration of an ammoniacal solution of V in isopropanol with standardized silver nitrate).

(B) Disulfide formation. A 1.96 g. quantity of V (containing 0.00600 mole of active V) was dissolved in 30 ml. of ethanol, and treated with a solution of 0.76 g. (0.0060 gram atoms) of iodine in aqueous potassium iodide solution. By collecting, washing, and drying the resultant yellow precipitate, 1.34 g. of solid, m.p. 178–185°, was obtained. On recrystallizing this product from 60 ml. of 4:2:1 toluene/ethanol/nitrobenzene solution, 0.56 g. of VI, m.p. 193–194°, was isolated. This was recrystallized from 5:1 ethanol/nitrobenzene to tan crystals, m.p. 196–197°. The latter substance gave a negative test for mercaptan with silver nitrate reagent, but did form the silver mercaptide after being reduced with aqueous sodium sulfite (the latter test confirms presence of the disulfide function).

Anal. Calcd. for $(C_{11}H_9OS)_2$: C, 69.85; H, 4.80; S, 16.95. Found: C, 69.18, 69.30; H, 4.57, 4.68; S, 17.38, 17.46.

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Resolution of DL-β-Hydroxybutyric Acid

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The resolution of racemic β-hydroxybutyric acid, described in 1902 by McKenzie[2] and repeated by Levene and Haller,[3] depends primarily on inoculation of an aqueous solution of the quinine salts with a crystalline sample of the salt of the L acid obtained from diabetic urine.

In the procedure here described advantage is taken of the hitherto unrecorded great difference in the solubility in acetone of the two quinine salts, the D variety of which requires nearly ten times as much of the solvent as the L isomer for solution. The relationships are illustrated in Table I.

TABLE I

Approximate Percentage Concentration of Saturated Solutions of the Quinine Salts of D- and L-β-Hydroxybutyric Acids in Acetone and in Water at Various Temperatures

Acetone		Water	
D	L	D	L
0.49/1°	4.4/1°	3.5/0°	2.6/0°
1.33/21°	13.2/25°	4.0/25°	5.8/25°
		10/60°	10/36°

EXPERIMENTAL

To a hot solution of 200 meq. of DL-β-hydroxybutyric acid (91.3% by titration) in 500 ml. of acetone, 65 g. (200 mmoles) of anhydrous quinine base was gradually added. When solution was complete the mixture was chilled at 0–1° for 24 hr.; the crystalline salt was collected with suction, washed with 50 ml. of ice cold acetone, and then digested with 300 ml. of boiling acetone for 30 min. The suspension was cooled, held at 0–1° overnight, and filtered with suction; the crystals were washed with 30 ml. of cold acetone, digested as before with 150 ml. of boiling acetone, and dried in air. The yield was 36 g. (81 mmoles, calculated as monohydrate) of quinine D-β-hydroxybutyrate.

(1) Present address: Department of Biochemistry, Yale University, New Haven, Conn.

(2) A. McKenzie, *J. Chem. Soc.*, 81, 1402 (1902).

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The acetone in the combined filtrates and washings was removed as completely as possible by distillation from a steam bath; the sirupy residue was dissolved in 100 ml. of water, the solution was gently warmed until the odor of acetone was no longer perceptible, and was then chilled at 0–1° for 2 days. The needle crystals of quinine L-β-hydroxybutyrate were collected with suction and washed with 10 ml. of ice water in small portions, and the adhering solution was largely displaced by washing with ether. The product was then recrystallized from 80 ml. of water as before, washed with 10 ml. of ice water and finally with ether.[4] After being dried in air, the crystals, which weighed 31.3 g., were dried *in vacuo* to constant weight, 26.1 g. These values correspond to 62 mmoles of the hydrated (4.5 H_2O) and anhydrous salts, respectively.

The free acids were liberated by the gradual addition of 45-ml. quantities of 45% H_2SO_4 to suspensions of the above products in 100 ml. of water. During this operation, quinine sulfate crystallized at first but later dissolved with the formation of the more soluble acid sulfate. The optically active β-hydroxybutyric acids were extracted in a continuous apparatus by a rapid current of ether during 8 hr. and after the removal of solvent the residues were dissolved in water. The solutions were cleared with Norit and aliquots taken for titration and measurement of rotation. The 81 mmoles of D salt yielded 75 mmoles of D acid, $[\alpha]_D^{25} = +23.9°$. The 62 mmoles of L salt yielded 58 mmoles of L acid, $[\alpha]_D^{25} = -24.5°$.

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(4) The yields of both salts could no doubt be materially increased by evaporation of the aqueous filtrates to dryness and repetition of the crystallizations from acetone and water.

α-Alkyloximino Aldehydes[1]

DOMINICK A. COVIELLO[2] AND WALTER H. HARTUNG

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Certain α-oximino acids, R—C(=NOH)—COOH, and α-alkyloximino acids, R—C(=NOR$_1$)—COOH, inhibit incorporation of glycine into tumor tissue and exhibit slight antitumor activity.[3] This activity, in experimental animals, even though not pronounced, suggests that modifications in the structure of these compounds be made for pharmacological testing.

Aldehydes are not only versatile intermediates for further syntheses but are frequently very active biologically. Accordingly, the preparation of two α-alkyloximino aldehydes, R—C(=NOCH$_2$C$_6$H$_5$)—CHO, namely R = CH_3— and R = $C_6H_5CH_2$—, is described.

The most promising route appeared to depend on the reduction of the corresponding acid chlorides. To accomplish this, it was necessary to avoid reagents or conditions that would also attack the sensitive alkyloximino groups. Since it is impossible to obtain the chlorides of α-oximino acids, R—C(=NOH)—COCl, by conventional procedures[4] the oxime intermediate is not available for this type of study. The reduction was accomplished with tri-*t*-butyl-oxyaluminohydride according to the procedure of Brown and McFarlin.[5] The yields of aldehydes were very low and because of comparative instability were characterized by reoxidation to the carboxylic acid and a derivative. Insufficient material was obtained to permit biological screening.

EXPERIMENTAL

The preparation of α-benzyloximino acids and the conversion to the corresponding acid chlorides has been previously described.[6,7] A typical reduction was carried out as follows.

Eighteen and seven-tenths g. (0.089 mole) of α-benzyloximinopropionyl chloride was placed in a 500 ml. three neck flask equipped with magnetic stirrer, dropping funnel, and thermometer. Fifty ml. of dry tetrahydrofuran was added, and the solution was cooled to −78° in an acetone–Dry Ice bath. An equivalent amount of lithium tri-*t*-butoxyaluminohydride prepared in tetrahydrofuran[5] was added through the dropping funnel slowly with stirring and continued cooling so that the temperature never went above −70°. When addition was completed, the reaction mixture was allowed to come to room temperature and poured over crushed ice. Since filtration of the precipitate was difficult, the procedure of Brown and McFarlin[5] which was followed to this point, was modified slightly. The reaction mixture was made acid to litmus with dilute HCl at 0°. The mixture was extracted with five 50-ml. portions of ether. The ether was evaporated and the remaining oil, which gave positive Tollens' and Schiff tests, was treated with sodium bisulfite. A precipitate formed instantly. The addition product was dried in air and repeatedly washed with ether until the washings were clear. A portion of the product was treated with dilute HCl and the liberated aldehyde was extracted with ether, the ether evaporated, and the residual oil used to prepare derivatives and a portion of the aldehyde was oxidized to the parent acid in alkaline permanganate after the procedure outlined in McElvain.[8] Melting point of product 75–76°.

Derivatives of α-benzyloximinopropionaldehyde. Semicarbazone, $CH_{14}N_4O_2$, m.p. 189°. Calcd.: C, 56.31%, H, 5.98%;

(1) Paper number 19 in amino acid series. For number 18 see K. L. Hoy and W. H. Hartung, *J. Org. Chem.*, **23**, 967 (1958).

(2) Mead Johnson Fellow, 1957–58. Address after September 1959, College of Pharmacy, University of Illinois, Chicago, Ill.

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(8) S. M. McElvain, The Characterization of Organic Compounds, The MacMillan Co., New York, N. Y., 1945.

N, 23.93%. Found[9]: C, 56.64, 56.54%; H, 6.01, 6.06%; N, 23.14, 23.30%. 2,4-Dinitrophenylhydrazone, $C_{16}H_{15}N_5O_5$, m.p. 156–158°. Calcd.: C, 53.81%, H, 4.20%, N, 19.88%. Found: C, 53.84, 53.76%; H, 4.44, 4.43%; N, 18.80, 19.03%.[10]

Derivatives of α-benzyloximinohydrocinnamaldehyde. Semicarbazone, $C_{17}H_{18}N_4O_2$, m.p. 180°. Calcd.: C, 65.81%, H, 5.58%, N, 18.06%. Found[10]: C, 65.96, 65.68%; H, 6.27, 6.03%; N, 17.70%.

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(9) Analyses by Micro-Tech Laboratories, Skokie, Ill.

(10) Analyses by Messrs. Weiler and Strauss, Oxford, England.

Ring A Aromatization of a 19-Norsteroid

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The reactions of 4,5-epoxides of 3-ketosteroids have been studied, *inter alia*, by Camerino *et al.*,[1–3] who found that they led to 4-halo, 4-hydroxy, and 2α-hydroxy derivatives of 3-keto-Δ⁴-steroids. During the course of an investigation involving the preparation of some esters of 4-chloro-19-nortestosterone (Table I) in this laboratory, another reaction of such 4,5-epoxides was observed.

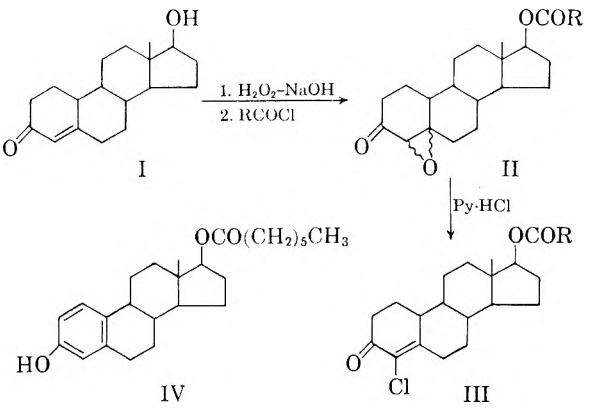
A synthetic scheme similar to that of the Italian workers[3] was employed. 19-Nortestosterone (I) was treated with alkaline peroxide and the oily epoxide was acylated with the appropriate acyl chloride. The crude esters (II) were boiled with pyridinium chloride in chloroform to give the desired 4-chloro compounds (III).

When this sequence was carried out in the case of the heptanoate derivative the expected ester (Table I, No. 1) was obtained as an oil and a second, crystalline, fraction was also isolated. This material had analyses, spectra, and melting point consistent with estradiol 17β-heptanoate (IV).

The mode of formation of IV is unknown. 3-Keto-4β,5-epoxides are known to rearrange under acid conditions to give stable 2α-hydroxy-3-keto-Δ⁴-steroids.[2]

The analogous 2β-hydroxy compounds, which could dehydrate to form a 1,4-diene-3-one, are not obtained under these conditions. The corresponding 4α,5-epoxides do not undergo such a rearrangement.

Apparently, in the case of the present 19-nor system, a rearrangement of the epoxide, perhaps involving C-10, followed by epoxide cleavage, elimination, and tautomerization, gives rise to the aromatic product. It is pertinent to note that 5β,10β-oxido-19-norandrostan-17β-ol-3-one furnishes 10β-hydroxy-19-nortestosterone on treatment with perchloric acid[4] and that the latter compound undergoes acid catalyzed conversion to estradiol.[5] A more detailed formulation of the mechanism cannot be given at this time since the oily intermediates could not be purified and, in particular, because it was necessary to use the oily, mixed 4α,5- and 4β,5-epoxides.



EXPERIMENTAL[6]

Esters of 4-chloro-19-nortestosterone (Table I). To a stirred solution of 5.0 g. (0.018 mole) of 19-nortestosterone[7] in 300 ml. of methanol maintained at −5° to 0° there were added, dropwise and simultaneously during 8–10 min., 10 ml. of 4*N* sodium hydroxide solution and 37.5 ml. of 30% hydrogen peroxide solution. The resulting solution was stirred at 0° for an additional 50 min., treated with 2.5 ml. of glacial acetic acid, and poured into 2 l. of brine. The resulting suspension was extracted with ethyl acetate (5 × 400 ml.) and the united extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to give 6.1–6.6 g. of a gum with no selective ultraviolet absorption.

A stirred solution of the crude epoxide in 55 ml. of dry pyridine was chilled to below −5° and treated with 0.0549–0.0915 mole of the requisite acid chloride. The mixture was allowed to stand at 5–27° for 18 hr., cooled in ice, and then decomposed by cautious addition of 60 ml. of water. The resulting solution was poured into 1 l. of brine and extracted with chloroform (5 × 200 ml.). The combined organic extract was washed with 5% sodium bicarbonate solution and water, and then dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was a brown gum.

A solution of the crude ester in 120 ml. of chloroform containing 21.2 g. (0.183 mole) of distilled pyridinium chloride was refluxed for 18 hr. The cooled brown solution was diluted with 150 ml. of chloroform, washed with 1% hydrochloric acid and then with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by recrystallization or chromatography.

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(6) All melting points are corrected. Microanalyses were performed under the supervision of Mr. W. F. Ellenbogen, Analytical Section. Spectral determinations and interpretations were made by Dr. Walter Thompson.

(7) Purchased from Schering, A. G., m.p. 122.5–123.5°.

TABLE I

ESTERS OF 4-CHLORO-19-NORTESTOSTERONE (III)

No.	R	M.P.	Yield, %[a]	Recryst. Solv.	Formula	Analyses Calcd. C	Calcd. H	Found C	Found H
1	$CH_3(CH_2)_5$	Oil	13	[b]	$C_{25}H_{37}O_3Cl$	71.32	8.86	71.48	9.19
2	$CH_2(CH_2)_3CH—CH_2—CH_2$[c]	88–89	17	Et_2O-PE[d]	$C_{26}H_{37}O_3Cl$	72.11	8.61	72.27	8.70
3	$C_6H_5CH_2CH_2$	127–130	17	Et_2O[e]	$C_{27}H_{33}O_3Cl$	73.53	7.54	73.39	7.77
4	p-$ClC_6H_4OCH_2$[f]	167–168	37	MeCOEt	$C_{26}H_{30}O_4Cl_2$	65.41	6.33	65.28	6.37
5	C_6H_5	192–196	12	Et_2O[g]	$C_{25}H_{29}O_3Cl$	72.71	7.08	72.47	7.37

[a] Yields are of pure product based on 19-nortestosterone. [b] Eluted by benzene and 1:1 benzene-ether. [c] B. Camerino, B. Patelli, and A. Vercellone, *J. Am. Chem. Soc.*, **28**, 3540 (1956) disclosed the biological activity of this compound but not the physical properties. [d] Eluted by 1:1 benzene-ether. [e] Eluted by 1:1 petroleum ether–benzene and benzene. [f] $[\alpha]_D^{25}$ +60.5° (1% in chloroform). [g] Decolorized by passage through alumina in benzene.

4-Chloro-19-nortestosterone-17β-benzoate (Table I, No. 5). The preparation of this substance differed from the other esters in that 19-nortestosterone-17β-benzoate[8] was epoxidized using the same general procedure as for 19-nortestosterone. The remainder of the sequence was unchanged.

Isolation of estradiol 17β-heptanoate. The preparation of 4-chloro-19-nortestosterone-17β-heptanoate, starting from 10.0 g. (0.0366 mole) of 19-nortestosterone was carried out as described above. The total crude final product was chromatographed on 770 g. of ethyl acetate washed alumina. After elution of the desired oily ester with a total of 5000 ml. of petroleum ether, benzene and ether mixtures, the estradiol ester was eluted by 1:1 benzene:ether and ether and recrystallized from ligroin to give 2.35 g. (18% from 19-nortestosterone) of colorless plates, m.p. 94–96° (lit.[9] 96–98°), $\epsilon_{281}^{C_2H_5OH}$ 2000 (shoulder at 286 mμ), μ^{Nujol} 2.9, 5.9, 6.2, 6.3, 6.7, 7.8, 8.1, 8.7, 11.5, 12.3, 12.8.

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44; mol. wt. 384. Found: C, 78.21; H, 9.64; mol. wt. 370 (camphor).

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The Dipole Moment of Norbornylene. Use of the IBM 650 Computer for Dipole Moment Calculations[1]

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Norbornylene (bicyclo[2.2.1]hept-2-ene) is known to contain a "strained" olefinic linkage by the usual chemical test of phenyl azide addition.[2] A comparison of the infrared spectrum of norbornylene[3] with other *cis* olefins[4] showed the olefinic hydrogen stretching band of the former at 3070 cm.$^{-1}$, considerably higher than the usual value (3010 cm.$^{-1}$). It was shown that the corresponding absorption was found at 3000 cm.$^{-1}$ for *trans*-cyclooctene, another strained olefin, which indicated the strain in this case was quite different from that found in norbornylene.[5] The dipole moment of *trans*-cyclooctene was found to have the unusually large value of 0.8 D, and a unique strained geometry about the double bond was proposed[5] to account for this large moment.

TABLE I

INFRARED ABSORPTION MAXIMA, CM.$^{-1}$

	=C—H	C=C
cis-4-Octene	3010	1650
cis-Cyclooctene	3010	1664
trans-Cyclooctene	3000	1658
Cyclohexene	3020	1650
Norbornylene	3070	1575
1-Butyne	3300	—

Norbornylene is strained in quite a different way from *trans*-cyclooctene as is indicated by the infrared spectrum. Some pertinent infrared data are summarized in Table I. In norbornylene, the C—C=C bond angles are reduced below the preferred value of 120° by the geometrical requirements of the ring system. There is a consequent increase in the p character in the C—C bonds of the olefinic system, and a corresponding increase in s character in the olefinic C—H bond. These effects increase the =C—H stretching frequency considerably, and simultaneously reduce the C=C stretching frequency. A quantitative relationship exists[6] between the C—H stretching frequency and the amount of s character in the bond, and from the position of the norbornylene band relative to the corresponding bands in an ordinary *cis* olefin and a terminal acetylene (Table I), the appreciable strain is apparent.

(1) This work was supported by a grant from the Sloan Foundation.

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It was of interest to determine what effect the type of strain present in norbornylene exerted upon the dipole moment. The moment was therefore measured in the customary way in heptane solution, and it was found to have the value of 0.40 D. This value may be compared with those found for the ordinary *cis* olefins cyclooctene[5] (0.43 D) and cyclodecene[7] (0.44 D). Clearly the strain in the norbornylene case, which although considerable in terms of energy,[8] is inconsequential in its effect on the dipole moment.

The calculation of a dipole moment from dielectric constant measurements is a tedious process with a desk calculator. If six or seven experimental measurements are taken, the whole calculation, including rechecking and correcting of errors requires the better part of a day. We have therefore applied automatic computing methods, utilizing an IBM 650 computer, to the solution of this problem. Large digital computers of this general class are now rather generally available, and are ideally suited to solving lengthy problems of this kind. Advances in automatic programming made in the last few years now make it possible for the average chemist to program and use such a computer with much less difficulty than is commonly supposed. The program was first prepared and checked by calculating known moments from available data. To calculate a dipole moment now that the program is available, the experimental data (weights, dielectric constants, *etc.*) are put directly onto punched cards, which takes about 15 min. The computer is then able to read the program and data cards, do the calculations, including the two least squares fittings, and punch out all of the desired data (N_2, $d_{1,2}$, $\epsilon_{1,2}$, $P_{2\infty}$, and μ) in about 3 min.

EXPERIMENTAL

Materials. The norbornylene (obtained from the reaction of ethylene with dicyclopentadiene[9]) was redistilled before use, b.p. 97°, m.p. 44.0–44.5° (sealed capillary). The heptane solvent was purified as described earlier.[6] The apparatus used for the dielectric constant measurements has been described.[10]

Calculations. The general procedure of Halverstadt and Kumler[11] as described earlier[7] was used as the basis for the program. The program was initially written in the RUNCIBLE[12] language. This program was translated by RUNCIBLE into the SOAP[13] input program, which was in turn converted by SOAP to the machine language program in the usual way.[14]

The actual experimental data, the weight of the empty flask, flask plus sample, flask plus sample plus solvent, cell constant, condenser correction, absolute temperature, and so on were placed on punched cards. The program and data were then run into the computer. The program instructed the computer to read the data and calculate N_2, d_{12}, and ϵ_{12} and then calculate from these quantities d_1, ϵ_1, α and β by the method of least squares. After these least squares lines were available, the computer continued by testing the experimental points against the least squares lines and it would have discarded any point which was further from the line than an amount δ.

A new line would then have been calculated omitting these discarded points. The value of δ was introduced into the computer as data, and so may be varied from one calculation to the next. In this particular case the points were all within 0.0002 in mole fraction of the N_2 *vs.* d_{12} line and within 0.0004 in dielectric constant of the ϵ_{12} *vs.* N_2 line, hence none were discarded. The probable error in the moment is estimated at 0.05 D. The computer then continued by calculating A, B, and C, and then $P_{2\infty}$. The molar refractivity, calculated by hand from tables,[15] was inserted into the computer with the data. (Atomic polarization was neglected. In other cases it could be inserted with the molar refractivity if desired.) The moment was then calculated, and all of the desired quantities were punched by the computer as output. The output data are listed in Table II.

TABLE II

DIPOLE MOMENT DATA FOR NORBORNYLENE IN HEPTANE AT 25°C.

N_2	d_{12}	ϵ_{12}
0.0239207	0.680836	1.9141
0.0201392	0.680294	1.9126
0.0144320	0.679471	1.9117
0.0101019	0.678902	1.9099
0.0026978	0.677821	1.9081
0.0000000	0.677423	1.9077
α = 0.26746	β = 0.14122	ϵ_{12} = 1.9075
d_1 = 0.677447	$P_{2\infty}$ = 32.889	μ = 0.398D

Acknowledgment. The authors are indebted to Dr. N. A. LeBel of this Department for supplying the norbornylene used in this work, and to Dr. M. T. Rogers of Michigan State University for the use of his apparatus for the dielectric constant measurements. We would also like to thank Dr. W. Hoffman and Miss E. Horst of the Department of Mathematics for their advice and assistance in the work with the computer.

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Identity of Compound A from Kava Root with 5,6-Dehydrokavain

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We established the structure 4-methoxy-6-(β-styryl)-α-pyrone for a compound isolated from the

wood of *Aniba firmula* (Nees *et* Mart.) Mez (family *Lauraceae*).[1] Simple 6-substituted 4-methoxy-α-pyrones seem to be quite rare in nature. Before our work on South American *Aniba* species[2] only the Polynesian kava root, *Piper methysticum* Forst. (family *Piperaceae*), had been known to contain representatives of this class of compounds.[3] One of them is kavain, 4-methoxy-6-(β-styryl)-5,6-dihydro-α-pyrone, from which we derived the name 5,6-dehydrokavain for the substance isolated from *Aniba firmula*.

Recently Klohs *et al.*[4] re-examined the extractives of kava root and, in addition to the already known constituents, isolated a new, optically inactive substance, m.p. 138–139°, which they designated compound A. The formula $C_{14}H_{12}O_3$ was assigned to it and ultraviolet and infrared spectra were determined. All their data are in exact agreement with those of our substance fron *Aniba firmula*.[1] Direct comparison by mixture melting point and infrared spectral comparison of 5,6-dehydrokavain with a sample of compound A kindly supplied by Dr. M. W. Klohs, Riker Laboratories, Inc., Northridge, Calif., confirmed the identity of the two substances.

It is interesting to recall that this substance, 4-methoxy-6-(β-styryl)-α-pyrone, was synthesized 20 years ago by Macierewicz[5] as a model compound for yangonin. Later, Chmielewska and Cieślak[6] proved the correct structure of yangonin to be its simple derivative 4-methoxy-6-(p-methoxy-β-styryl)-α-pyrone and not a γ-pyrone as previously admitted.[7]

Among the different constituents of kava root, whose pharmacological investigation was undertaken by Klohs *et al.*,[4] yangonin and compound A fall distinctly into a separate class. Contrary to the four other compounds tested, they did not antagonize clonic strychnine convulsions and death in mice, or potentiate sodium pentobarbital-induced sleeping time. The identity of compound A having been established, it becomes among the members of the group the only one which shares with yangonin the true pyrone structure (the others being dihydropyrones). The observed effects on the central nervous system can thus be associated with a definite structural feature of these constituents of kava root.

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Communications TO THE EDITOR

Studies on the Barks of the Family Salicaceae. II. Salireposide from the Bark of *Populus tremuloides*

Sir:

In our recent paper[1] on the structure of the new glucoside, tremuloidin, the presence of the glucoside, populin, in the extract of the bark of *Populus tremuloides* was confirmed. Further investigation of the glucosides of *P. tremuloides* bark with diazotized *p*-nitroaniline spray reagent on paper chromatograms indicated that the glucoside mistakenly identified as populin was in fact salireposide, a glucoside first isolated from the bark of *Salix repens* by Wattiez[2] in 1931. At that time Wattiez showed salireposide to be the benzoate of a phenolic glucoside. Later, Rabaté[3] isolated the aglucone and inferred from its empirical formula that it could be gentisyl alcohol. Sakai, Tsurumi, Eno, and Inukai[4] isolated the same salireposide from a Japanese willow, *Salix purpurea* L. subsp. *angstifolia* Koidz. Still later Fujikawa and Tokuoka[5] obtained salireposide from another willow, *S. koriyanagi* Kimura, proved the aglucone to be gentisyl alcohol and the glucoside linkage to involve the 2-hydroxyl group of the gentisyl alcohol, and assumed the structure of salireposide to be hydroxypopulin.

Re-examination of several crystalline fractions isolated from the bark of *P. tremuloides*[1] by means of paper chromatography indicated that the glucoside originally reported to be populin gave an intense bluish violet spot when sprayed with diazotized *p*-nitroaniline whereas populin and tremuloidin gave no spots whatsoever. One fraction was recrystallized first from water and then from methanol to give colorless crystals shrinking at 154–156° and melting at 205–206°, $[\alpha]_D^{25}$ −35.6° (*c*, 5 in 80% acetone). Acetylation with acetic anhydride in pyridine yielded the penta-acetate melting at 124–126°. These properties are identical with those reported for salireposide.[2–5] Hydrolysis yielded benzoic acid, glucose, and gentisyl alcohol.

A re-investigation of all glucoside fractions obtained from the bark of *P. tremuloides* by means of paper chromatography and the diazotized *p*-nitroaniline spray indicated substantial amounts of salicin, tremuloidin, and salireposide, but no populin. This is the first reported instance of the presence of salireposide in a *Populus* species.

Although populin is not present in the bark of *P. tremuloides*, it is definitely present in the bark and leaves of the two European species *P. tremula* and *P. alba*. Earlier indications of the presence of populin in the bark of *P. tremuloides*[6,7] on the basis of indirect evidence confirm the need for more absolute identification of these glucosides when reporting their presence in plant materials.

Work in our laboratory on the isolation, characterization, and determination of the complete structure of salireposide will be published in future papers.

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(1) I. A. Pearl and S. F. Darling, *J. Org. Chem.*, **24**, 731 (1959).
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(3) J. Rabaté, *Bull. Soc. Chim. Biol.*, **17**, 328 (1935).
(4) S. Sakai, M. Tsurumi, Y. Eno, and F. Inukai, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **22**, 868 (1943).
(5) F. Fujikawa and A. Tokuoka, *J. Pharm. Soc. Japan*, **67**, 121 (1947).
(6) W. Theis, and C. Wehmer in G. Klein, Handbuch der Pflanzenanalyze. Bd. III, 2 Teil, Vienna, 1932, p. 845.
(7) R. L. Hossfeld and F. H. Kaufert, *Forest Prods. J.*, **7**, 437 (1957).

Ring Equivalence and Charge Distribution in Triphenylcarbonium Ion from NMR Spectra

Sir:

We have examined the proton magnetic resonance spectra of triphenylcarbonium and several deuterated and methoxy-substituted triphenylcarbonium ions in order (a) to establish the equivalence or nonequivalence of the three rings, and (b) to ascertain the relative electron densities of the various sites on the phenyl rings. The ions were prepared *via* Grignard reactions from bromobenzene, and subsequent solution of the carbinol in SO_2, sometimes with $SnCl_4$ added. The specifically deuterated bromobenzenes were prepared as follows: 3,5-*d*; from *p*-bromoaniline with D_3PO_4 in D_2O, and reduction with H_3PO_2; 3,4,5-*d*, as with 3,5-*d*, but reduction with D_3PO_2; 2,4,6-*d*, by heating *p*-bromobenzenesulfonic acid with D_3PO_4 in a sealed tube; and 4-*d*, from *p*-bromoaniline with D_3PO_2 reduction. The identity and purity of the deuterated bromobenzenes were readily ascertained from their NMR spectra. An analysis of the bromobenzene NMR spectrum based on these observations will be forthcoming. The NMR spectra were measured on a Varian 4300B spectrometer at 40 mc. and also on a Varian 4300C spectrometer at 60 mc. No measurable concentration dependence was observed for the aromatic ring protons.

The spectra of undeuterated triphenylcarbonium and tri-*p*-methoxyphenylcarbonium were essentially

the same as those recently reported by Moodie, Connor, and Stewart.[1] The ions with all rings similarly deuterated gave the following results: 3,5-*d*, two peaks, intensity 1:2, low intensity at low field; 3,4,5-*d*, one peak with weak trace at low field; 2,4,6-*d*, with traces of undeuterated material, one intense peak, with one weak triplet at low fields, and a weak doublet at high fields very close to the intense peak. We have assigned the low field peaks, in agreement with the work of Moodie, Connor, and Stewart,[1] as belonging to the *para*-protons. The group at highest fields must be due to the *ortho*- protons, and the intermediate absorption, close to the *ortho*- peak, arises from *meta*-protons.

The identity of the three rings is established as follows: The 3,5-*d* spectrum may correspond either to two kinds of rings, with essentially no chemical shift within each kind, or to two kinds of positions, with all three rings equivalent. The single strong peak in the 3,4,5-*d* species shows that the *ortho*- positions of all three rings are equivalent, and so therefore must the other positions be also.

The apparent conflict between these results, which establish ring equivalence and those of Newman and Deno[2] which base nonequivalence on the ultraviolet spectrum, may be resolved by reinterpretation of the origin of the ultraviolet bands. Historically, the virtual identity of the spectra of triarylcarbonium ions with those of related fuchsones has been interpreted as evidence in support of quinoid structure in one (or more) rings. Reconsideration of the nature of the trityl cation chromophore suggests that it should be attributed instead *to the ion as a whole*. Its ground and first excited electronic energy levels, respectively, can be characterized as the totally symmetric (A) and doubly degenerate (E) combinations of one quinoid and two benzenoid structures. The A↔E transition is allowed and is probably the source of the intense color in triphenylcarbonium and other di- and triarylcarbonium ions as well.[3] With only one ring (phenylcarbonium), no such combinations can exist, so no low-frequency absorption takes place.

The shift of the aromatic protons relative to an external water peak is approximately −100 c.p.s., in agreement with Moodie *et al.* The chemical shifts, from audio modulation at 60 mc., give $\delta_{ortho\text{-}para}$ ~31 c.p.s. and $\delta_{meta\text{-}para}$ ~21 c.p.s. Tentative spin coupling values are $J_{ortho\text{-}meta}$ ~1.8 c.p.s. and $J_{meta\text{-}para}$ ~3.0 c.p.s. No *ortho-para* coupling was detected.

The results show that negative charge density is greatest on the *ortho*- positions, slightly less on the *meta*s, and considerably less still on the *para*-positions. This is in excellent agreement with the predictions of self-consistent molecular orbital theory, as carried out by Pople[4]; his calculations give the following charge densities: *ortho*-, 0.95; *meta*-, 0.94, and *para*-, 0.81.[5]

Acknowledgment. The authors would like to express their appreciation to Dr. E. D. Becker of the National Institutes of Health for taking the 60-mc. spectra.

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(1) R. B. Moodie, T. M. Connor, and Ross Stewart, *Canad. J. Chem.*, **37**, 1402 (1959).

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

(3) One of us (RSB) is indebted to Professor W. T. Simpson, The University of Washington, Seattle, for helpful and enlightening discussion of this problem.

(4) J. A. Pople, *J. Phys. Chem.*, **61**, 6 (1957).

(5) Note added in proof: At the suggestion of Professor Newman, we have examined the proton resonance spectrum of tri-*O*-tolyl carbonium ion at 40 mc., under the same conditions as triphenylcarbonium ion. Steric blocking by the methyl groups effectively prohibits coplanarity of the rings. The magnetic resonance spectrum shows a single sharp methyl peak, thus indicating that even in this extreme case the three rings are equivalent on a time scale of 0.1 sec., and suggests that the molecule is propeller-shaped [*cf.* N. C. Deno, P. T. Groves, and G. Saines, *J. Am. Chem. Soc.*, **81**, 5790 (1959)].

16,16-Dimethylprednisone Acetate

Sir:

In view of the enhanced anti-inflammatory activity and elimination of sodium retention brought about by introduction of a 16α-methyl[1] or 16β-methyl[2] group into cortical steroids we undertook the synthesis of a suitable 16,16-dimethyl steroid. In the present communication we describe the preparation of 16,16-dimethylprednisone acetate (IV).

The conjugate addition of methylmagnesium iodide[3] to 3α-acetoxy-16-methyl-16-pregnene-11,-20-dione (I)[2a,b] in the presence of cuprous chloride

(1) (a) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958). (b) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

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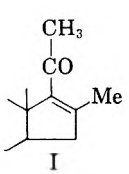
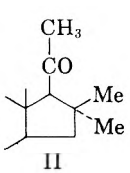
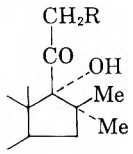
(3) M. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941); R. E. Marker and H. M. Crooks [*J. Am. Chem. Soc.*, **64**, 1280 (1942)] prepared 16α-alkylpregnan-20-ones by conjugate addition of Grignard reagents to 16-unsubstituted-16-pregnene-20-ones.



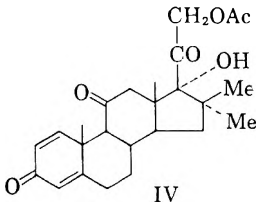
I



II



IIIa. R = H
IIIb. R = OAc



IV

followed by acetylation proceeded in part by 1:4 addition to give 3α-acetoxy-16,16-dimethylpregnane-11,20-dione (II) m.p. 212–217°; $[\alpha]_D^{Chf}$ +77°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.58; H, 9.51 Found: C, 74.80; H, 9.35. Introduction of the 17α-hydroxyl group was achieved by a modification[4] of the method of Hogg and Nathan[5] to give 3α,17α-dihydroxy - 16,16 - dimethylpregnane - 11,20 - dione (IIIa) m.p. 177–182°; λ_{max}^{Chf} 2.75, 2.92, 5.87 μ. *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.40; H, 9.57. Found: C, 73.29; H, 9.44. As a consequence of the high degree of steric hindrance in the vicinity of C-17 and C-20, IIIa was inordinately sensitive to base catalyzed D-homoannulation and conventional alkaline hydrolysis of the intermediate peracid product could not be employed. A new procedure, to be reported subsequently, involving the use of ethylenediamine was developed. Bromination of IIIa at C-21 followed by acetoxylation led to 21-acetoxy-16,16-dimethylpregnane-3α,17α-diol-11,20-dione (IIIb) m.p. 206–208°; λ_{max}^{Chf} 2.72, 2.9 (broad), 5.74, 5.76, 5.85, 8.1 μ.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.90; H, 8.53. Oxidation of IIIb at C-3 by sodium dichromate in aqueous acetic acid led to 21-acetoxy-16,16-dimethylpregnane-17α-ol-3,11,20-trione, m.p. 203–206°; $[\alpha]_D^{Chf}$ +114°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.59; H, 8.48. Dibromination of the 3,11,20-trione followed by dehydrobromination in dimethylformamide-dimethylaniline[6] led to 16,16-dimethylprednisone acetate (IV), m.p. 231–235°; $[\alpha]_D^{Chf}$ +210°; λ_{max}^{MeOH} 238 mμ (14,200); λ_{max}^{Chf} 2.85, 5.73, 5.76, 5.84, 6.00, 6.14, 6.19 sh., 8.06, 11.20 μ.

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.08; H, 7.53. Found: C, 70.02; H, 7.42.

In the rat systemic granuloma and mouse liver glycogen assays compound IV showed respectively no activity and *ca.* one-tenth the activity of hydrocortisone.[7]

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(4) Procedure of M. Sletzinger of these laboratories. We are grateful to Dr. Sletzinger for informing us of his procedure in advance of publication and for several helpful discussions.

(5) J. A. Hogg and A. H. Nathan, U. S Patents 2,740,782, 2,740,783 (1956).

(6) Procedure of J. Day, R. Erickson and R. Pettebone, U. S. Patent 2,873,284 (1959).

(7) We are grateful to Dr. R. H. Silber of the Merck Institute for therapeutic research for the biological assays.

Potential Anticancer Agents.[1] XXIX. Inversion of a Ring Carbon of a Glycoside

Sir:

The low reactivity of secondary sugar sulfonates toward S_N2 displacement by nucleophiles has placed a severe restriction on an otherwise potentially useful reaction for the synthesis of rare sugars. Few nucleophiles are powerful enough to effect this displacement unaided by a neighboring group. Thus, sodium iodide generally fails to react with "isolated" secondary tosylates, and sodium hydroxide or sodium methoxide, when they do react, bring about simple hydrolysis of the sulfonate with retention of configuration.[2]

A useful reaction for the synthesis of amino sugars involves the displacement of an "isolated" secondary tosylate by ammonia, or better, by hydrazine.[3] This reaction, as illustrated by the synthesis of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-allofuranose from 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-D-glucofuranose, proceeds with inversion of configuration.[4] A recent report from these laboratories[5] described the use of sodium benzoate in refluxing *N*,*N*-dimethylformamide to effect the displacement of a side-chain secondary tosylate by benzoate with inversion of configuration. Of paramount interest was the determination whether the use of this reagent could be extended to cover the broad range of sterically more hindered and much less reactive ring sulfonates.

We wish to report the successful displacement of a pyranoside ring tosylate by sodium benzoate to give the sugar benzoate with inverted configuration on the ring carbon.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, in press (1960).

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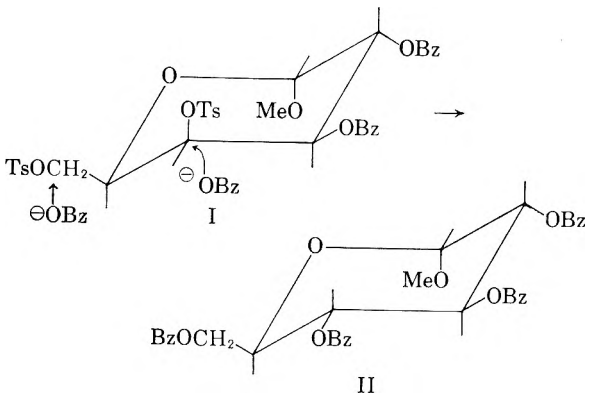

Hydrogenation of methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-galactopyranoside[6] with palladium black in alcohol at 65° gave a quantitative yield of analytically pure methyl 2,3-di-*O*-benzoyl-α-D-galactopyranoside as a glass. Found: C, 62.4; H, 5.60. Tosylation of the dibenzoate gave a 60% yield of crystalline methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-(*p*-tolylsulfonyl)-α-D-*galacto*pyranoside (I),[7] m.p. 128–129°, $[\alpha]_D^{39}$ +150° (1% in chloroform). Found: C, 58.8; H, 4.91; S, 9.11. Treatment of 0.5 g. of I with 0.7 g. of sodium benzoate in 15 ml. of *N*,*N*-dimethylformamide at 140° for 24 hours gave a 49% yield of II, m.p. 104°, $[\alpha]_D^{31}$ +78° (0.5% in chloroform). Found: C, 68.9; H, 5.36. This product was identical with authentic methyl α-D-glucopyranoside tetrabenzoate, as shown by the infrared spectra and mixed melting point behavior. An interesting and important contrast is the reported failure[8] of methyl 4-*O*-(*p*-tolylsulfonyl)-β-D-galactopyranoside, when treated with refluxing methanolic sodium methoxide, to give any evidence for a tosylate displacement.

This successful benzoate displacement lends further credence to the suggestion[5] that sodium benzoate in *N*,*N*-dimethylformamide be placed high on the list of powerful nucleophilic reagents[9] and that the potential of this reagent be investigated further for the synthesis of rare sugars.

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(6) M. Gyr and T. Reichstein, *Helv.*, **28**, 226 (1945).

(7) Examination of models suggested that the galactopyranoside conformation (I) in which the 4-*O*-tosyl is axial should be favored sterically, thus aiding the back-side attack on the 4-position by benzoate.

(8) A. Müller, M. Móricz, and G. Verner, *Ber.*, **72B**, 745 (1939).

(9) Since sodium acetate in acetic anhydride displaced only the primary 5-tosylate, but not the ring 3-tosylate of 1,2-*O*-isopropylidene-3,5-di-*O*-(*p*-tolylsulfonyl)-D-xylofuranose,[10] it would be of interest to investigate whether or not both tosylates could be displaced by sodium benzoate in *N*,*N*-dimethylformamide.

(10) L. Vargha, *Chem. Ber.*, **87**, 1351 (1954).

A New Synthesis of Triptycene

Sir:

We wish to report the synthesis of triptycene[1] by a new, simple, and direct route. When the adduct (I) between anthracene and *p*-benzoquinone was reduced with $LiAlH_4$ or $NaBH_4$, a crude mixture resulted. Although this mixture was not separated and analyzed, its infrared spectrum and subsequent reactions were consistent with the assumption that it contained the diol reduction products. This mixture, when refluxed with ethanolic hydrochloric acid followed by chromatography of the products on acid alumina, gave triptycene in 15% yield based on I. This hydrocarbon had a m.p. 254–256 and an infrared tracing that was superimposable on that of authentic triptycene. *Anal.* Calcd. for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.49; H, 5.78. In addition to the triptycene, a substance identified as anthracene was obtained in 25% yield based on I.

The present synthesis of triptycene is considerably shorter than the elegant classical synthesis by Bartlett, Ryan, and Cohen.[1] Further, it shows promise of being more generally applicable to the synthesis of bridgehead substituted triptycenes than the ingeneous syntheses through benzyne by Wittig and co-workers.[2–4]

The details of the present route and its extension to substituted triptycenes are being investigated.

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(2) G. Wittig and E. Benz, *Ber.*, **91**, 873 (1958).

(3) G. Wittig and R. Ludwig, *Angew. Chem.*, **68**, 40 (1956).

(4) G. Wittig and E. Benz, *Angew. Chem.*, **70**, 166 (1958).

(5) Taken from a dissertion submitted by A. C. Craig to Cornell University for the Ph.D. degree, June 1959.