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Behavior of Triphenylsilane, Triphenylgermane, and Triphenyltin Hydride in the Presence of Olefins[1a]

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The addition of triphenylsilane, triphenylgermane, and triphenyltin hydride to cyclohexene and of triphenylgermane to 1,1-diphenylethylene has been studied. Triphenyltin hydride does not add to octene-1 but gives a redistribution product, tetraphenyltin. Triphenylgermane adds to octene-1 and to cyclohexene when the reaction is initiated by either benzoyl peroxide or ultraviolet irradiation, but peroxide initiation fails to cause its addition to 1,1-diphenylethylene. Triphenylsilane adds to octene-1 when peroxide initiation is used, but not under ultraviolet irradiation. Several addition products were prepared by independent syntheses.

The addition of trichlorosilane to a variety of olefins under the influence of peroxide, ultraviolet irradiation, or heat has been reported[2] in a number of publications. More recently triphenylsilane has been added to the carbon-carbon double bond of 9-undecenoic acid,[3a] ethyl 9-undecenoate[3a] and several olefins,[3b] and a variety of silicon hydrides have been added to double-bonded compounds,[3c] in peroxide-catalyzed reactions. Addition reactions have also been reported for trichlorogermane[3d] and for triphenyl- and tributyltin hydrides.[3e]

A comparison of the behavior of triphenylsilane, triphenylgermane, and triphenyltin hydride towards 1-octene with peroxide and ultraviolet initiation has now been made. Also the reactions of triphenylgermane with 1,1-diphenylethylene and with cyclohexene have been studied.

Both triphenylsilane and triphenylgermane added readily to 1-octene under the influence of peroxide.

$$(C_6H_5)_3GeH + C_6H_{13}CH{=}CH_2 \longrightarrow (C_6H_5)_3GeCH_2CH_2C_6H_{13}$$

Triphenyltin hydride afforded only the redistribution product tetraphenyltin. Triphenylgermane did not react with 1,1-diphenylethylene, but the reaction with cyclohexene produced the expected addition product along with tetraphenylgermane. Ultraviolet irradiation failed to initiate the reaction of triphenylsilane with 1-octene, but successfully initiated the addition of triphenylgermane to 1-octene, the addition of triphenylgermane to cyclohexene accompanied by redistribution, and the redistribution of triphenyltin hydride, about as effectively as did peroxide. Triphenyltin hydride was found to be stable to redistribution in the absence of light and peroxide. The use of phenylazotriphenylmethane, which furnishes radicals at a relatively low temperature, also led to the formation of tetraphenyltin from triphenyltin hydride, rather than to the product of addition.

Authentic samples of the expected addition products were prepared from triphenylchlorosilane, triphenylchlorogermane or triphenyltin chloride

(1a) A preliminary report of this work was presented at the 66th meeting of the Iowa Academy of Sciences held at Iowa State College, April 30 and May 1, 1954.

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(2) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Am. Chem. Soc.*, **69**, 188 (1947); *Ibid.*, **70**, 484 (1948); C. A. Burkhard and R. R. Krieble, *J. Am. Chem. Soc.*, **69**, 2687 (1947); A. J. Barry, L. De Pree, J. Gilkey, and D. E. Hook, *J. Am. Chem Soc.*, **69**, 2916 (1947); R. Calas and E. Frainnet, *Bull. soc. chim. France*, 241 (1952); N. Duffant and R. Calas, *Bull. soc. chim. France*, 241 (1952); R. Calas and N. Duffant, *Bull. soc. chim. France*, 792 (1953); E. Frainnet, *Bull. soc. chim. France*, 792 (1953); R. Calas, E. Frainnet, and J. Valade, *Bull. soc. chim. France*, 793 (1953).

(3a) G. N. Gadsby, *Research (London)*, **3**, 338 (1950). (b) H. Merten and H. Gilman, *J. Am. Chem. Soc.*, **76**, 5798 (1954). (c) J. L. Speier, R. Zimmerman, and J. Webster, *J. Am. Chem. Soc.*, **78**, 2278 (1956). (d) A. K. Fischer, R. C. West, and E. G. Rochow, *J. Am. Chem. Soc.*, **76**, 5878 (1954). (e) G. J. M. Van der Kerk, J. G. A. Luijten, and J. G. Noltes, *Chemistry and Industry*, 352 (1956); G. J. M. Van der Kerk and J. G. A. Luijten, *J. Appl. Chem. London*, **6**, 49, 56, 93 (1956). H. Gilman and J. Eisch, *J. Org. Chem.*, **20**, 763 (1955).

and the appropriate alkyl Grignard or lithium reagent.

$$(C_6H_5)_3SnCl + C_8H_{17}MgBr \longrightarrow (C_6H_5)_3SnC_8H_{17}$$

The structure of each radical-addition product was confirmed by the nondepression of the melting point of an authentic sample of the compound, and by the identity of the infrared absorption spectra.

EXPERIMENTAL[4]

Addition of triphenylsilane to 1-octene with peroxide initiation. A mixture of 20.8 g. (0.08 mole) of triphenylsilane,[5] 25 ml. of petroleum ether (b.p. 60–70°), 1.1 g. (0.01 mole) of 1-octene and 0.30 g. (0.00012 mole) of benzoyl peroxide was placed in a 100-ml. flask. The system was flushed for 5 min. with a brisk stream of nitrogen, and subsequently a positive nitrogen pressure was maintained. The mixture was heated for 48 hr. in an oil bath kept at 75°. Afterwards distillation of the slightly yellow solution through a Vigreux column yielded first, solvent, second, a little biphenyl, third, a factor rich in unchanged triphenylsilane, b.p. 138–182° at 0.5 mm., and finally, triphenyl-1-octylsilane, b.p. 182° at 0.5 mm. to 192° at 0.2 mm. The latter fraction after one recrystallization from ethanol gave 2.0 g. (54%) of crystals, m.p. 64–69°. Two additional recrystallizations afforded 1.4 g. (38%) of material melting at 70.0–71.5°.

An authentic sample of triphenyl-1-octylsilane, m.p. 72.5–73.5°, prepared from triphenylchlorosilane and 1-octylmagnesium bromide, was kindly supplied by Dr. Ronald Meen of this laboratory. A mixture of the two samples melted at 71–73°. The infrared absorption spectra in carbon disulfide solution were identical.

Ultraviolet irradiation of triphenylsilane and 1-octene. A mixture of 20.8 g. (0.08 mole) of triphenylsilane, 25 ml. of *n*-heptane and 1.7 ml. (0.01 mole) of 1-octene was irradiated in a quartz flask for 48 hr. by a 125-watt ultraviolet lamp placed at about 1 cm. below the flask. The contents of the flask were kept below about 40° by a continuous stream of air impinging on the bottom of the flask. The solvent was distilled through a Vigreux column. Some unchanged 1-octene came over with the heptane, and could be detected by the odor and by the instantaneous reduction of permanganate in acetic acid solution. Distillation of the residue yielded triphenylsilane, b.p. 127–134° at 0.25 mm., but no higher boiling material suggestive of triphenyl-1-octylsilane. A brown, tarry residue of less than 0.5 g. remained in the flask.

Preparation of triphenyl-1-octylgermane from triphenylchlorogermane and 1-octyllithium. A solution of 1-octyllithium[6] was prepared from 17.3 ml. (0.10 mole) of 1-bromooctane and 1.53 g. (0.22 g. atom) of lithium wire in ether solution at 0°. The yield determined by the double titration procedure[7] was 67%. To 0.063 mole of the 1-octyllithium solution was added a solution of 5.1 g. (0.015 mole) of triphenylchlorogermane[8] in 100 ml. of ether at room temperature over 0.5 hr. After 1 hr. of stirring, 100 ml. of toluene was added, and solvent was distilled until the vapor temperature reached 105°. Hydrolysis was then effected by the slow addition of 150 ml. of cold water with external ice cooling of the flask. Some petroleum ether was added and the layers were separated. The organic layer was dried over magnesium sulfate. Two recrystallizations from about 50 ml. of ethanol gave 3.9 g. (62%) of triphenyl-1-octylgermane, m.p. 72–73°.

Addition of triphenylgermane to 1-octene with peroxide initiation. The procedure used was similar to that employed with triphenylsilane, 1-octene, and peroxide. In a dry flask were mixed 21.4 g. (0.07 mole) of triphenylgermane,[9] m.p. 45.5–47.0°, 25 ml. of petroleum ether (b.p. 60–70°), 1.7 ml. (0.01 mole) of 1-octene and 0.3 g. of benzoyl peroxide. The mixture was heated in a 75° bath for 24 hr. Distillation afforded unchanged triphenylgermane, b.p. 143–151° at 0.25 mm., and 3.8 g. (91%) of product, b.p. 190–198° at 0.25 mm., m.p. 57–67°. Two recrystallizations from ethanol raised the melting point to 71–72°. A mixture of the latter sample with triphenyl-1-octylgermane (m.p. 72–73°) melted at 71.5–72.0°. The identity of the two materials was confirmed by the infrared spectra.

Anal.[10] Calcd. for $C_{26}H_{32}Ge$: Ge, 17.4. Found: Ge, 17.5, 17.7.

Addition of triphenylgermane to 1-octene with ultraviolet initiation. A mixture of 0.045 mole of triphenylgermane, 0.006 mole of 1-octene and 25 ml. of heptane in a quartz flask was irradiated for 48 hr. The solid material which distilled at 170–195° at 0.15 mm. and was recrystallized from ethanol weighed 2.0 g. (80%), and melted at 69–70.5°. A mixture with authentic triphenyl-1-octylgermane (m.p. 72–73°) melted at 72–73°. A white, ethanol-insoluble residue was recovered from the recrystallization of this triphenyl-1-octylgermane. Recrystallization of the residue from a benzene (2/3)-ethanol (1/3) mixture gave 0.4 g. of solid, m.p. 232–234°. A mixture of this material with authentic tetraphenylgermane (m.p. 227.5–230.0°) melted at 228.0–232.5°.

Preparation of triphenylcyclohexylgermane from triphenylchlorogermane and cyclohexylmagnesium bromide. Cyclohexylmagnesium bromide was prepared by the dropwise addition of a solution of 24.6 ml. (0.20 mole) of bromocyclohexane in 50 ml. of ether to a mixture of 5.0 g. (0.205 g. atom) of magnesium turnings in 150 ml. of ether. The mixture was refluxed for 3 hr., was allowed to stand overnight, and was filtered through glass wool. Then a solution of 10.2 g. (0.03 mole) of triphenylchlorogermane[9] in 100 ml. of benzene was added dropwise to the black Grignard solution. The mixture was refluxed for 4 hr. and was allowed to stand overnight. Water was added dropwise with ice cooling. The organic layer was separated and dried over magnesium sulfate. Most of the benzene was distilled, and the residue was recrystallized from ethanol. The product weighed 3.6 g. (31%) and melted at 137–145°. Further recrystallization was not a very effective means of purification, so a distillation was tried, and the material boiling at 162–193° at 0.2 mm. was collected. After recrystallization from ethanol (4/5)-isopropyl ether (1/5) mixture, including filtration of the hot solution, 1.6 g. (14%) of slightly impure triphenylcyclohexylgermane was obtained, m.p. 143–146°.

Anal. Calcd. for $C_{24}H_{26}Ge$: Ge, 18.8. Found: Ge, 19.3, 19.3.

Reaction of triphenylgermane with cyclohexene. Two separate experiments were carried out with 15.2 g. (0.05 mole) of triphenylgermane, 1.0 ml. (0.01 mole) of cyclohexene and 25 ml. of heptane. One reaction was initiated by the addition of 0.3 g. of benzoyl peroxide to the mixture which

(4) All reactions were carried out under dry, oxygen-free nitrogen.

(5) Triphenylsilane was prepared by the lithium aluminum hydride reduction of commercial triphenylchlorosilane by Mr. Leonard Moore following the unpublished procedure of J. Curtice.

(6) This procedure was used for the preparation of other alkyllithium compounds by H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(7) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

(8) Triphenylchlorogermane was prepared from phenylmagnesium bromide and germanium tetrachloride according to the unpublished procedure of Mr. Clare Gerow.

(9) O. H. Johnson and W. H. Nebergall, *J. Am. Chem. Soc.*, **71**, 1720 (1949).

(10) Germanium analyses were done by the method of H. Gilman and C. Gerow, *J. Am. Chem. Soc.*, **77**, 5740 (1955).

was then heated in a 75° bath for 48 hr. A second mixture was irradiated for 48 hr. using an ultraviolet lamp. The following isolation procedure was used on the mixture which had been irradiated. A similar procedure was used for the peroxide-catalyzed reaction product, with like results. Distillation gave, in addition to solvent and unchanged triphenylgermane, 3.0 g. of a solid, b.p. 175–180° at 0.06 mm., which, after recrystallization from a mixture of 150 ml. of absolute ethanol and 50 ml. of isopropyl ether, melted at approximately 150–190°. This latter mixture was lixiviated with hot 80% aqueous ethanol and cooled. The crystals which were deposited melted at 147.0–149.5°, and a mixture with triphenylcyclohexylgermane (m.p. 143–146°) melted at 146.5–148.5°. The infrared absorption spectra confirmed the identity of the two samples. Another portion of the crude solid (m.p. 150–190°) was recrystallized twice from heptane and once from benzene-heptane mixture. The product, which melted at 228–232°, when mixed with authentic tetraphenylgermane (m.p. 232–234°), melted at 231–233°.

Reaction of triphenylgermane with 1,1-diphenylethylene and peroxide. The benzoyl peroxide initiation procedure used with cyclohexene was employed with the substitution of 1.1 ml. (0.0063 mole) of freshly distilled 1,1-diphenylethylene (b.p. 136–140° at 12 mm.) for the cyclohexene. The mixture was heated for 48 hr., and the unchanged triphenylgermane was distilled leaving behind a yellow oil which could not be crystallized with or without the aid of solvents. The oil appeared to be an olefin polymer. The desired product, triphenyl-2,2-diphenylethylgermane, or an isomer, which has been prepared by the addition[11] of triphenylgermylpotassium to 1,1-diphenylethylene, is a readily crystallizable solid which melts at 99.0–99.5°.

Preparation of triphenyl-1-octyltin from triphenyltin chloride and 1-octylmagnesium bromide. 1-Octylmagnesium bromide was prepared from 1.22 g. (0.05 g. atom) of magnesium and 9.7 g. (0.05 mole) of 1-bromooctane in ether. To the filtered Grignard solution was added dropwise a solution of 7.2 g. (0.02 mole) of triphenyltin chloride[12] in ether. The mixture was refluxed for 2 hr. and then was hydrolyzed by the addition of 125 ml. of cold water. The ether layer was separated and dried over magnesium sulfate. Removal of the solvent left a yellow liquid which was crystallized from 150 ml. of ethanol. The yield was 6.3 g. (68%) of crystals which melted at 54.0–54.6°. Another recrystallization raised the melting point to 54.3–55.0°.

Anal. Calcd. for $C_{26}H_{32}Sn$: Sn, 25.6. Found: Sn, 25.8, 26.0.

Reaction of triphenyltin hydride and 1-octene with benzoyl peroxide, ultraviolet or phenylazotriphenylmethane initiation. Three experiments were run using the three sources of radical initiation. In a typical run 23.8 g. (0.068 mole) of triphenyltin hydride,[13] 1.7 ml. (0.01 mole) of 1-octene, 25 ml. of petroleum ether (b.p. 60–70°), and 0.3 g. of benzoyl peroxide were heated to 75° for 24 hr. Another run used ultraviolet irradiation for 4 days at about room temperature in place of the benzoyl peroxide and heat. The third run used 0.3 g. of phenylazotriphenylmethane[14] at room temperature in the dark. In all three cases a white solid was deposited as the reaction progressed. A solution of triphenyltin hydride in petroleum ether remained clear for 2 days when kept in the dark. The white solid was collected by filtration and extracted with hot ethanol. No dissolved material could be isolated from the ethanol, although triphenyl-1-octyltin is very soluble in the hot solvent. Recrystallization of the white solid from chloroform gave crystals melting at 226.0–228.5°. A mixture with authentic tetraphenyltin (m.p. 228.0–228.5°) melted at 226.5–228.5°.

Solvent was distilled from the filtrate from which the tetraphenyltin had originally been isolated. During the distillation the residue changed to a dark gray solid mass, apparently due to disproportionation. Extraction of the solid with hot ethanol failed to dissolve any material suggestive of triphenyl-1-octyltin. The gray solid dissolved in chloroform except for a small amount of black powder which dissolved in hydrochloric acid and appeared to be metallic tin.

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(11) H. Gilman and C. Gerow, *J. Am. Chem. Soc.*, **79**, 343 (1957).

(12) K. A. Kocheshkov, M. M. Nad, and A. P. Aleksandrov, *Ber.*, **67**, 1348 (1934). The material used in this experiment was kindly supplied by Mr. David Miles of this laboratory.

(13) G. Wittig, F. J. Meyer, and G. Lange, *Ann.*, **571**, 167 (1951).

(14) Kindly supplied by Mr. Chester Hamilton and Professor G. S. Hammond.

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

Stability of an Ether Solution of Methylmagnesium Iodide

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Incidental to studies concerned with the stability of some organometallic compounds, it has been observed that an ether solution of methylmagnesium iodide contained in a sealed glass container is essentially unchanged after a period of twenty years.

In connection with studies on the general reactions of organometallic compounds, the stability of Grignard reagents has long been of interest. Previous work in this laboratory[1] indicated that the normalities of diethyl ether solutions of various Grignard reagents, as determined by acid titration,[2] remained essentially unchanged for four months. It was necessary to adequately protect the Gri-

(1) H. Gilman and C. H. Meyers, *Ind. Eng. Chem.*, **14**, 243 (1922); **15**, 61 (1923).

(2) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923).

gnard reagent solutions from the air, but parallel experiments with ethylmagnesium bromide in the light and in the dark indicated that daylight had little effect on the stability of the solutions. Solutions of methylmagnesium iodide are widely used in analytical methods based on the Tschugaeff-Zerewitinoff[3] analysis for active hydrogen, and as a result their stability has been subjected to some study. A solution of methylmagnesium iodide in di-*n*-amyl ether is reported to be "stable for a month or more."[4] When a diisoamyl ether solution of methylmagnesium iodide, prepared for use in an apparatus designed for analysis with Grignard reagents, was analyzed "immediately after its preparation and after it had remained in its receptacle, exposed to the light for months," the composition of the solution was found to be invariable.[5a] In connection with the stability of solutions of organometallic compounds in general, it is of interest to compare the above reported stability of methylmagnesium iodide in various solvents with the stability of methyllithium. Methyllithium in diethyl ether and in di-*n*-butyl ether[6] has been shown to enjoy certain advantages over methylmagnesium halides in the Tschugaeff-Zerewitinoff analysis, partly because of its stability and partly because of the greater solubility of some —OLi compounds over —OMgX compounds. In studies on a modification of the Tschugaeff-Zerewitinoff determination,[7] a di-*n*-butyl ether solution of methyllithium was stored in a Grignard machine[5b] and the normality of the solution, as determined by gas analysis, was found to have decreased only from 0.777 to 0.764 during four months. The above evidence indicates that a di-*n*-butyl ether solution of methyllithium is sufficiently stable for use as a valuable supplement to solutions of methylmagnesium iodide in carrying out Tschugaeff-Zerewitinoff analyses.

We are reporting further evidence of the stability of methylmagnesium iodide obtained recently when a sealed Carius tube containing 50 ml. of a diethyl ether solution of about 2*N* methylmagnesium iodide was opened after remaining sealed for twenty years. The normality of the solution was determined by both acid titration and gas analysis[2] and was found to be essentially the same as when the solution was first placed in the tube. The results of the gas and acid titration analyses are listed in Table I. Of particular significance is the fact that

TABLE I

COMPARISON OF THE NORMALITY VALUES OF AN ETHER SOLUTION OF METHYLMAGNESIUM IODIDE AS DETERMINED BY ACID TITRATION AND BY GAS ANALYSIS

Sample No.	Volume of Sample (ml.)	Method of Analysis	Normality Found	Variation from Mean Titration Normality (%)[a]
1	2.66	Titration	2.295	−0.1[b]
2	2.66	Titration	2.301	+0.1
3	2.66	Titration	2.328	+1.3
4	2.56	Titration	2.267	−1.4
Mean	—	Titration	2.298	—
5	1.66	Gas	2.287	−0.5
6	1.16	Gas	2.164	−6.2
7	1.26	Gas	2.264	−1.5
Mean	—	Gas	2.239	−2.6

[a] Calculated as per cent of the normality found. [b] + and − indicate higher and lower percentage respectively.

the normality values found by the two different methods of analysis are in close agreement. It has been shown[2] that the normality values obtained by acid titration normally run slightly higher than those obtained by gas analysis, due probably to the presence of basic magnesium compounds formed by means other than hydrolysis of the Grignard reagent such as ether cleavage and the reaction of the Grignard reagent with traces of water and/or oxygen. Any cleavage of the diethyl ether by the methylmagnesium iodide which might have occurred during the twenty years of storage would have been evidenced by an abnormal difference between the normality values found by acid titration and those found by gas analysis. The average difference was found to be 2.6%, well below the reported average difference of 3.9%.[2]

Positive identification of the material as a solution of methylmagnesium iodide was made by preparing acet-α-naphthalide[8] and methylmercuric iodide[9] and checking their properties against those of authentic specimens.

A Color Test I,[10] which was taken immediately after opening the sealed tube, was strongly positive.

It would not be unreasonable to expect variations with other Grignard reagents and variations with other solvents. For example, it is known that methylmetallic compounds may differ appreciably from others.[6,11,12]

(3) (a) L. Tschugaeff, *Ber.*, **35**, 3912 (1902). (b) T. Zerewitinoff, *Ber.*, **40**, 2023 (1907).

(4) S. Siggia, *Quantitative Organic Analysis Via Functional Groups*, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 48.

(5) (a) E. P. Kohler, J. F. Stone, and R. C. Fuson, *J. Am. Chem. Soc.*, **49**, 3181 (1927). (b) E. P. Kohler and N. K. Richtmyer, *J. Am. Chem. Soc.*, **52**, 3736 (1930).

(6) (a) H. Gilman, F. W. Moore, and O. Baine, *J. Am. Chem. Soc.*, **63**, 2479 (1941). (b) H. Gilman, R. A. Benkeser, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 1689 (1950).

(7) Unpublished studies by H. Gilman and R. V. Christian.

(8) H. Gilman and M. Furry, *J. Am. Chem. Soc.*, **50**, 1214 (1928).

(9) C. S. Marvel, C. G. Gauerke, and E. L. Hill, *J. Am. Chem. Soc*, **47**, 3009 (1925).

(10) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(11) H. Gilman, F. W. Moore, and R. G. Jones, *J. Am. Chem. Soc.*, **63**, 2482 (1941).

(12) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

EXPERIMENTAL

The volume of the solution contained in the sealed Carius tube (50 ml.) and the total volume of the tube (140 ml.) were determined by measuring an equivalent volume of water in a tube of comparable size. The volume of the diethyl ether solution of methylmagnesium iodide had not decreased appreciably during the twenty years of storage as the level of the top of the solution prior to opening the tube was even with the top of a blank label which had been placed on the tube to mark the initial volume. The tube had been wrapped in a towel and kept in a shatter-proof container throughout the twenty years it had remained sealed. There was no detectable rush of gas when the tube was opened after having been cooled for 4 hr. in an ice bath. By working promptly in an inert atmosphere according to the usual techniques employed when handling reactive organometallic compounds, all quantitative determinations were completed within 8 hr. after opening the tube. The samples used were removed by a pipette of previously determined volume which had been drawn out long enough to easily reach the solution in the tube and small enough to readily pass through the constricted neck of the tube.

The analytical procedures were essentially those reported earlier from this laboratory,[2] the chief difference being in the size of the sample used. The sulfuric acid in the gas wash bottle used in the gas analysis was replaced with fresh acid between the analyses of samples 6 and 7.

Acet-α-naphthalide (m.p. 159.5–160°) was prepared by the procedure previously reported from this laboratory,[8] and methylmercuric iodide (m.p. 146–147°) was prepared by the procedure of Marvel, Gauerke, and Hill.[9] A mixed melting point of a sample of each derivative with its respective authentic specimen was not depressed.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF WISCONSIN]

Addition of Organometallic Reagents to α,β-Unsaturated Amides

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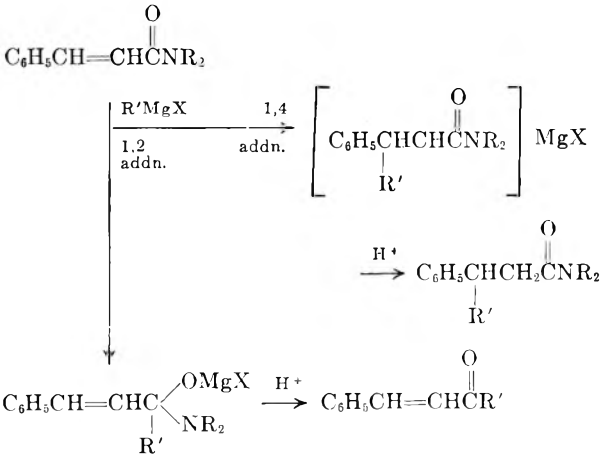
Phenyllithium adds *via* conjugate addition to *N,N*-dicyclohexylcinnamamide with no evidence of 1,2 addition, but adds 1,2 to *N,N*-dimethylcinnamamide.

N,N-Disubstituted α,β-unsaturated amides add phenyl and ethyl Grignard reagents by conjugate addition despite wide variations in the substituents. In contrast, methylmagnesium iodide yields some 1,2 addition and some unchanged starting material. The latter appears to involve a complex which regenerates the amide on hydrolysis. Enolization does not occur to an important extent in the formation of this intermediate.

An organometallic reagent may add to an unsaturated amide by normal addition to form an unsaturated ketone or by conjugate addition to form a saturated amide.



The reaction of phenylmagnesium bromide with *N*-ethylcinnamanilide was reported by Kohler and Heritage[3] to yield conjugate addition products. The investigation was extended by Maxim and Ioanid[4] to the condensation of several cinnamanilides with ethyl- and phenylmagnesium bromides and with methylmagnesium iodide.

In the present work, it was desired to determine the effect of wider variations in the structure of the amide on the course of the condensation. As the study progressed and the conjugate nature of the addition of the Grignard reagents was confirmed, the addition of phenyllithium to α,β-unsaturated amides became a further object of investigation.

The extent of 1,2 addition was found by comparison of the ultraviolet absorption spectrum of the products with a standard curve of the ketone produced. The extent of conjugate addition was determined by isolation of the saturated amide. The results of these and previously reported experiments are summarized in Table I. They illustrate a marked tendency of the unsaturated amides to undergo conjugate addition somewhat like that shown by the unsaturated ketones. For example, the reaction of phenylmagnesium bromide with *N,N*-dimethylcinnamamide yields 93% 1,4 addition[5] while isopropyl styryl ketone, which is almost identical sterically, yields 88% of the conjugate addition product.[6] However, the analogy is not

(1) Applied Research Laboratory, U. S. Steel Corp., Monroeville, Pa., to whom inquiries should be sent.

(2) Rohm & Haas Co., Bridesburg, Philadelphia, Pa.

(3) E. P. Kohler and G. Heritage, *Am. Chem. J.*, **33**, 21 (1905).

(4) N. Maxim and N. Ioanid, *Bul. Soc. Chim. România*, **10**, 29 (1928).

(5) G. Gilbert, *J. Am. Chem. Soc.*, **77**, 4413 (1955).

(6) E. P. Kohler, *Am. Chem. J.*, **38**, 511 (1907).

complete since phenylmagnesium bromide will produce 1,2-addition products with some unsaturated ketones, although none were obtained from the unsaturated amides. Even the relatively unhindered crotonylpiperidine showed no evidence of 1,2-addition with phenylmagnesium bromide. The method thus appears useful for the synthesis of β-substituted propionamides and their derivatives when the unsaturated amide and Grignard reagent are available.

TABLE I

SUMMARY OF ADDITION REACTIONS

Amide	Organometallic Reagent	Products % 1,2	Products % 1,4
N,N-Diphenylcinnamamide	C_6H_5MgBr[a]	0	100
	C_2H_5MgI	0	65
	C_2H_5MgBr[e]	0	100
	CH_3MgI[b]	45	0
Cinnamoyl piperidine	CH_3MgI[c]	10	0
N,N-Dicyclohexylcinnamamide	C_6H_5MgBr	0	97
	CH_3MgI[d]	10	0
	C_6H_5Li	0	68
N,N-Dimethylcinnamamide	C_6H_5MgBr	0	93
	C_6H_5Li	72	0
Crotonylpiperidine	C_6H_5MgBr	0	51

[a] See ref. 4. [b] 42% recovered starting material. [c] 76% recovered starting material. [d] 87% recovered starting material. [e] See ref. 5.

In view of its well-known tendency to add *via* the normal route, phenyllithium was condensed with *N,N*-dimethyl- and *N,N*-dicyclohexylcinnamamide to determine whether it, too, would undergo conjugate addition. The cyclohexyl substituted amide did, indeed, yield 68% of *N,N*-dicyclohexyl-β,β-diphenylpropionamide, the conjugate addition product. There was no indication of benzalacetophenone, the 1,2 addition product, in the ultraviolet absorption spectrum of the crude product, a significant departure from the usual reactions of organolithium compounds. *N,N*-Dimethylcinnamamide yielded 72% benzalacetophenone on condensation with phenyllithium. It seems likely, therefore, that steric hindrance of the amide carbonyl by the bulky cyclohexyl substituents is at least partly responsible for the conjugate addition of phenyllithium.

The behavior of methylmagnesium iodide contrasts significantly with the other organometallic reagents studied. In reactions involving this reagent no 1,4 products, but some normal addition products and some starting material, were recovered. This anomalous behavior is particularly illustrated by comparison with the other alkylmagnesium halides. With *N,N*-diphenylcinnamamide, ethylmagnesium bromide and ethylmagnesium iodide both yielded only 1,4 addition products, while methylmagnesium iodide yielded 42% unchanged starting material and 45% benzalacetone, the product of 1,2 addition. Other investigators have also noted anomalies in the reactions of methylmagnesium iodide as evidenced by an unusual tendency to undergo 1,2 addition with unsaturated ketones. Smith and Hanson[7] added methylmagnesium iodide to benzalpropiophenone in the hope of obtaining 1,4 addition. However, all of the products isolated were those of 1,2 addition. When ethyl- or phenylmagnesium bromide were added to this ketone, only conjugate addition was observed.[6] Similarly, methyl propenyl ketone yields 75% 1,4 addition with methylmagnesium bromide[6] and 80% 1,2 addition with methylmagnesium iodide.[8]

In the reaction of methylmagnesium iodide with *N,N*-dicyclohexylcinnamamide, precipitation occurred on addition of the amide solution, indicating the formation of a stable intermediate. Essentially no gaseous products were evolved during the reaction, eliminating the possibility that an enol salt is the precursor of the recovered starting material. It seems likely, therefore, that methylmagnesium iodide forms a complex with the unsaturated amides which may be hydrolyzed to obtain the starting amide, but which does not undergo addition under the conditions of the reaction.

The coincidence of high yields of 1,2 addition products and the recovery of starting material as exclusive properties of methylmagnesium iodide seems to indicate that these two properties stem from the same difference in behavior with the other Grignard reagents studied here. Relation of this difference to the structure of the Grignard reagents probably must await a detailed explanation of the nature of Grignard reagents in solution and especially of the mechanism of addition of organometallic reagents to conjugated systems. Although considerable effort has been devoted to these ends, no generally accepted theory has as yet been evolved.[9]

EXPERIMENTAL

The organometallic reagents were prepared by the usual procedures in dry ether and brought to room temperature. In order to avoid the formation of complex products[3] the addition of the ethereal amide solution was carried out slowly and only to the point of persistence of the precipitate.

Condensation of ethylmagnesium iodide and N,N-diphenylcinnamamide. To the ethylmagnesium iodide prepared from 4.67 g. (0.03 mole) of ethyl iodide was added 2.9 g. (0.0097 mole) of *N,N*-diphenylcinnamamide, prepared by the method of Bernthsen,[10] in 200 ml. of ether and stirring was continued for 3 hr. After hydrolysis with dilute HCl, the ether solution was dried and the solvent evaporated, yielding 3.8

(7) L. I. Smith and L. I. Hanson, *J. Am. Chem. Soc.*, **57**, 1326 (1935).

(8) L. P. Kyriakides, *J. Am. Chem. Soc.*, **36**, 661 (1914).

(9) See, for example, E. R. Alexander and G. R. Coraor, *J. Am. Chem. Soc.*, **73**, 2721 (1951); R. E. Lutz and W. G. Reveley, *J. Am. Chem. Soc.*, **63**, 3184 (1941); H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, **62**, 1243 (1940); C. G. Swain and L. Kent, *J. Am. Chem. Soc.*, **72**, 518 (1950); E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley and Sons, New York, 1950, p. 190.

(10) A. Bernthsen, *Ber.*, **20**, 1554 (1887).

g. of a viscous yellow oil. Distillation of 3.5 g. yielded 1.9 g. boiling at 195–210° (0.2 mm.), a clear, viscous oil, *N,N,β*-triphenylvaleramide, which could not be crystallized. Refluxing with concentrated HCl for 6 hr. yielded 0.63 g. of β-phenylvaleric acid, m.p. 62–64° from 40–60° petroleum ether. The basic fraction of the hydrolyzate gave a positive nitric acid test for diphenylamine.[11] The ultraviolet absorption spectrum of the crude product showed no maximum in the region in which ethyl styryl ketone would be expected to absorb.

Condensation of methylmagnesium iodide with N,N-diphenylcinnamamide. To a solution of methylmagnesium iodide prepared from 3.55 g. (0.025 mole) of methyl iodide was added 2.48 g. (0.0083 mole) of *N,N*-diphenylcinnamamide in ether and stirring continued for 4 hr. The mixture was hydrolyzed with dilute acid, and the crude product (2.43 g.) isolated as usual. Recovered starting material (1.04 g., 42%) was identified by a mixture melting point with an authentic sample.

The ultraviolet absorption spectrum indicated a yield of 45% of benzalacetone.

Condensation of methylmagnesium iodide with cinnamoylpiperidine. To a solution of methylmagnesium iodide prepared from 1.70 g. (0.012 mole) of methyl iodide was added 1.15 g. (0.0053 mole) of cinnamoylpiperidine in 200 ml. of ether and the mixture was stirred at room temperature for 3.5 hr. After hydrolysis, 1.07 g. of brownish crystalline solid was obtained which yielded 0.18 g. of 94% (by ultraviolet analysis) benzalacetone on steam distillation. The yield of benzalacetone was 23%.

The residue from the steam distillation yielded 0.81 g. (76%) of starting material, identified by a mixture melting point with an authentic sample and hydrolysis with concentrated HCl to cinnamic acid.

N,N-Dicyclohexylcinnamamide. To 19.6 ml. (18.1 g., 0.1 mole) of dicyclohexylamine in 50 ml. of benzene was added 8.4 g. (0.05 mole) of cinnamoyl chloride in 50 ml. of benzene. The mixture was refluxed 2 hr., the precipitated hydrochloride filtered, and the benzene solution extracted with 10% aqueous HCl, 10% aqueous NaOH, and water.

The product obtained on removal of the solvent was recrystallized from 90–100° petroleum ether, m.p. 115–115.5°.

Anal. Calcd. for $C_{21}H_{29}NO$: C, 80.96; H, 9.39. Found: C, 81.20; H, 9.45.

Evolution of gaseous products in the condensation of methylmagnesium iodide with N,N-dicyclohexylcinnamamide. A 100-ml. Erlenmeyer flask with ground-glass joint and side arm was connected by a rubber tube to a 30-ml. bottle. The mouth of the flask was stoppered with a soda lime drying tube. Magnesium (0.06 g., 0.00247 mole) was placed in the flask and converted to methylmagnesium iodide with a slight excess of methyl iodide.

After cooling to room temperature, the flask was attached to a gas measuring apparatus and the bottle was filled with an ethereal solution of the substance to be added. This solution was added to the methylmagnesium iodide through the side arm of the flask while maintaining a closed system and the changes in volume were measured. After stirring for 3 hr., a solution of 1 ml. of ethanol in 18 ml. of ether was added slowly through the side arm and the resulting volume increment was again noted.

Three runs were carried out in this manner. In a blank run, 14% of the total gas was collected before hydrolysis. In the second run, 0.3 g. of *N,N*-dicyclohexylcinnamamide and in the third 0.6 g. of *N,N*-dicyclohexylcinnamamide were added. These yielded 24 and 18% of the evolved gas before hydrolysis. The theoretical amounts expected if methane were a product in the reaction were 0, 39, and 78%, respectively.

Condensation of methylmagnesium iodide with N,N-dicyclohexylcinnamamide. The Grignard reagent was prepared from 3.55 g. (0.025 mole) of methyl iodide. On addition of 3.11 g. (0.01 mole) of *N,N*-dicyclohexylcinnamamide a white precipitate formed. The mixture was stirred for 3 hr. and hydrolyzed with dilute HCl. On removal of the solvent, 2.95 g. of product containing 2.74 g. (87%) of starting material, m.p. 114–115°, was obtained. A mixture melting point with an authentic sample showed no depression. Ultraviolet analysis of the steam distillate indicated a yield of 10% of benzalacetone.

Condensation of phenylmagnesium bromide with N,N-dicyclohexylcinnamamide. To phenylmagnesium bromide, prepared from 2.26 g. (0.0145 mole) of bromobenzene, was added a dilute ethereal solution of 1.5 g. (0.0048 mole) of *N,N*-dicyclohexylcinnamamide and stirring was continued for several hours. On hydrolysis there was obtained 3.22 g. of crude product which yielded 97% of the theoretical quantity of *N,N*-dicyclohexyl-β,β-diphenylpropionamide, m.p. 125.6–127.0°. A mixture melting point with an authentic sample prepared from β,β-diphenylpropionyl chloride and dicyclohexylamine showed no depression.

Anal. Calcd. for $C_{27}H_{35}ON$: C, 83.24; H, 9.06. Found: C, 82.99; H, 9.01.

Condensation of phenyllithium with N,N-dicyclohexylcinnamamide. An ethereal solution of 1.59 g. (0.0051 mole) of *N,N*-dicyclohexylcinnamamide was added slowly to phenyllithium, prepared from 0.14 g. (0.02 mole) of lithium and 1.57 g. (0.01 mole) of bromobenzene, and the mixture was stirred for 3 hr. The intermediate was hydrolyzed with 15 ml. of water.

The product solidified on standing and was recrystallized from alcohol-water, m.p. 124–125.4°. A mixture melting point with an authentic sample of N,N-dicyclohexyl-β,β-diphenylpropionamide showed no depression; yield 1.32 g. (68%).

The ultraviolet absorption spectrum of the crude product showed no peak in the region of 310 mμ.

Condensation of phenyllithium with N,N-dimethylcinnamamide. Phenyllithium was prepared from 0.18 g. (0.026 mole) of lithium and 2.04 g. (0.013 mole) of bromobenzene. A solution of 1.13 g. (0.0065 mole) of *N,N*-dimethylcinnamamide in ether was added, stirring was continued for 3 hr., and 15 ml. of water was added to hydrolyze the lithium salts.

On removal of the solvent 3.75 g. of product was obtained. The method of Iddles *et al.*[12] was used for determination of the benzalacetophenone present. Since the reaction product was not completely soluble in 2*N* HCl, small quantities of alcohol were added. In order to test the effect of the added ethanol, three determinations were carried out on a standard solution of benzalacetophenone by adding 2-, 4- and 6-ml. portions of alcohol. The precipitates represented 96, 97.8, and 98.3% of the expected 2,4-dinitrophenylhydrazone, respectively.

Duplicate ketone determinations on the product obtained above indicated 64 and 67% yield of benzalacetophenone. The dinitrophenylhydrazones were combined, treated with glacial acetic acid, filtered, and allowed to crystallize, m.p. 245–7°. A mixture melting point with an authentic sample of benzalacetophenone 2,4-dinitrophenylhydrazone showed no depression.

A standard ultraviolet absorption curve of benzalacetophenone was prepared and compared with the spectrum of the crude reaction product. The yield calculated by this method was 72%.

Condensation of phenylmagnesium bromide with crotonylpiperidine. Phenylmagnesium bromide prepared from 25.2 g. (0.157 mole) of bromobenzene was treated with 15 g.

(11) S. P. Mulliken, *Identification of Pure Organic Compounds*, John Wiley and Sons, New York, 1916, p. 165.

(12) H. A. Iddles *et al.*, *Ind. Eng. Chem., Anal. Ed.*, **11**, 102 (1939).

(0.098 mole) of crotonylpiperidine[13] in ether and the mixture was stirred for 30 min. Hydrolysis with dilute HCl, followed by fractionation yielded 11.6 g. (51%) of β-phenylbutyryl piperidine, b.p. 145–50° (0.3 mm.), n_D^{25} 1.5399.

(13) H. Staudinger and H. Schneider, *Ber.*, **56**, 699 (1923).

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.16. Found: C, 78.24; H, 8.95.

The ultraviolet absorption spectrum of the crude reaction product showed no peak in the region expected for phenyl propenyl ketone.

MADISON, WIS.

[CONTRIBUTION FROM MATERIALS LABORATORY, WRIGHT AIR DEVELOPMENT CENTER]

Derivatives of Ferrocene. III. The Preparation of Some Acylferrocenes and Alkylferrocenes[1]

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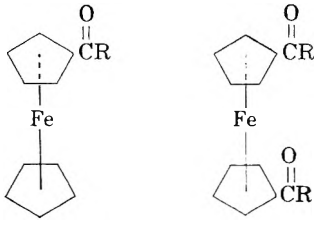
Several new acylferrocenes and 1,1′-diacylferrocenes have been prepared and reduced to the corresponding alkylferrocenes and 1,1′-dialkylferrocenes. Attempts to directly alkylate ferrocene resulted in mixtures of polyalkylated products.

One of the first reactions of ferrocene[2,3] to be investigated was the Friedel-Crafts acylation with acid chlorides and anhydrides in the presence of a suitable Lewis acid catalyst[4] under conditions similar to those used for preparing acylbenzenes. However, at the time of the inception of the present investigation, no successful attempts to directly alkylate ferrocene had been reported in the literature.[5,6]

In order to prepare a series of alkylferrocenes, the direct alkylation of ferrocene was first investigated and found to be an unsatisfactory synthetic method. The acylation of ferrocene and subsequent reduction was then studied and many new acylferrocenes and alkylferrocenes synthesized.

It has been found that both acylferrocenes (I) and 1,1′-diacylferrocenes (II) can be prepared in satisfactory yield by varying the ratio of ferrocene,



I II

acid chloride, and aluminum chloride, and also the mode of addition. Compounds of type I were prepared by the dropwise addition of the acid chloride-aluminum chloride complex to the ferrocene solution, using equimolar amounts of acid chloride, catalyst, and ferrocene. The disubstituted derivatives, II, were prepared by adding the ferrocene solution to the complex, using a molar ratio of both the acid chloride and the aluminum chloride to ferrocene of greater than 2:1.

The preparation of both I and II by these procedures appears to be a very satisfactory synthetic method. Using the appropriate procedure, either was obtained uncontaminated by the other or by unreacted ferrocene. The unaccounted ferrocene was present in the form of tars. If the reaction was carried out at room temperature instead of at reflux, the amount of tar produced was considerably decreased. The yields of the diketones tended to decrease with increasing molecular weight, probably due to steric factors as well as decreased reactivity of the acid chlorides. The properties and analyses of the acylferrocenes and 1,1′-diacylferrocenes are summarized in Table I.

The catalytic hydrogenation of 1,1′-diacetylferrocene to 1,1′-diethylferrocene was successfully carried out by Rosenblum.[7] However, it was not possible to extend this reaction to the higher homologues under similar as well as stronger conditions, although it was possible to duplicate Rosenblum's work. This is in marked contrast to aryl alkyl ketones which in general are readily hydrogenated to hydrocarbons.[8] Consequently, the Clemmensen reduction was used for the reduction of the higher homologs. Recently, Nesmeyanov and Vol'kenau[9] have used this same method for the reduction of

(1) Presented in part at the 131st Meeting of the American Chemical Society, Miami, Fla., April 7 to 12, 1957; see Abstracts of Papers, pp. 47–0.

(2) T. J. Kealy and P. L. Pauson, *Nature*, **168**, 1039 (1951).

(3) S. A. Miller, J. A. Tebboth, and J. F. Tremaine, *J. Chem. Soc.*, 632 (1952).

(4) R. B. Woodward, M. Rosenblum, and M. C. Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).

(5) V. Weinmayr, *J. Am. Chem. Soc.*, **77**, 3009 (1955).

(6) P. L. Pauson, *Quart. Revs.*, **9**, 391 (1955).

(7) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953.

(8) W. H. Hartung and R. Simonoff, *Org. Reactions*, *VII*, 263–326 (1953).

(9) A. N. Nesmeyanov and N. A. Vol'kenau, *Doklady Akad. Nauk SSSR*, **107**, 262 (1956).

TABLE I

ACYLFERROCENES

Ferrocene	M.P., °C.	Yield, %	Analyses Calcd. C	Calcd. H	Calcd. Fe	Found C	Found H	Found Fe
1,1′-Diacetyl-[a]	127.0–127.5	74	62.26	5.22	20.67	61.96, 61.98	5.29, 5.16	20.83, 20.91
1,1′-Dicaprylyl-[b]	54.8–56.0	65	71.23	8.74	12.74	71.55, 71.79	8.80, 8.89	13.00, 12.98
1,1′-Dicapryl-[b]	68.6–69.8	41	72.86	9.38	11.29	73.00, 73.17	9.38, 9.27	11.57, 11.46
1,1′-Dilauroyl-[b]	76.6–77.1	44	74.17	9.88	10.14	74.38, 74.37	9.75, 9.75	10.06, 10.05
1,1′-Ditridecanoyl-[b]	80.0–80.4	15	74.71	10.11	9.65	74.87, 74.77	10.19, 10.07	9.88, 9.84
1,1′-Dipalmitoyl-[c]	82.4–83.4	12	76.10	10.65	8.43	76.29, 76.19	10.30, 10.16	8.79, 9.04
Palmitoyl-[d]	59.0–59.8	46	73.57	9.50	13.16	74.07, 74.07	9.53, 9.36	13.20, 13.27

[a] Red crystalline solid. [b] Red-orange crystalline solid. [c] Salmon-colored solid. [d] Yellow crystalline solid.

TABLE II

ALKYLFERROCENES

Ferrocene	M.P., °C.	B.P., °C.	n_D^{25}	Yield, %	Calcd. C	Calcd. H	Calcd. Fe	Found C	Found H	Found Fe
1,1′-Diethyl-[a]	−35.0[b]	87–89/ 0.15 mm.	1.5761	60	69.45	7.49	23.06	69.12, 69.11	7.36, 7.28	23.10, 22.86
1,1′-Dioctyl-[a]	−16.0[c]	190–193/ 0.15 mm.	1.5214	58	76.07	10.32	13.61	76.30, 76.10	10.27, 10.49	13.09, 13.04
1,1′-Didecyl-[a]	11.5[d]	197–205/ 0.04 mm.	1.5142	50	77.23	10.80	11.97	78.01, 77.78	10.89, 10.69	11.47, 11.43
1,1′-Didodecyl-[e,f]	30.6–30.8			—	78.13	11.19	10.68	77.89, 77.93	11.01, 10.98	10.72, 10.93
1,1′-Ditridecyl-[e]	38.0–39.0			32	78.51	11.35	10.14	78.15, 78.17	11.07, 11.01	10.40, 10.41
1,1′-Dihexadecyl-[e]	41.2–42.4			33	79.45	11.75	8.80	79.59, 79.27	11.56, 11.65	8.82, 9.13
Hexadecyl-[e]	55.0–55.6			77	76.08	10.32	13.61	76.00, 76.26	10.32, 10.20	13.43, 13.65

[a] Dark-red liquid. [b] Melting point value obtained from reference 7. [c] d_4^{25} 1.0076; M.R. 124.12. [d] d_4^{25} 0.9863; M.R. 140.91. [e] Yellow crystalline solid. [f] Two unsaturated compounds, melting points 32.4–33.4° and 37.2–38.8° (uncorr.), were the only products isolated from the initial Clemmensen reduction. Both exhibited strong absorption in the *trans* double-bond region of the infrared (10.3 microns) and both could be hydrogenated to the expected compound. In a repeat experiment, 1,1′-didodecylferrocene was obtained directly.

some lower 1,1′-diacylferrocenes. The properties and analyses of the alkylferrocenes and 1,1′-dialkylferrocenes are summarized in Table II.

1,1′-Diethylferrocene decomposed to a considerable extent after standing for several months, even in the absence of light and air. This is in accord with observations by other workers[7,9] concerning this and other low molecular weight liquid alkylferrocenes. On the other hand, 1,1′-dioctylferrocene and 1,1′-didecylferrocene, both liquids, appeared completely stable to air and light after several months storage.

A point worth noting is the unusual melting point of hexadecylferrocene (55.0–55.6°) compared to those of 1,1′-dioctylferrocene (−16.0°) and 1,1′-dihexadecylferrocene (41.2–42.4°). Hexadecylferrocene would be expected to have a lower melting point than its symmetrical isomer, 1,1′-dioctylferrocene, but it does not. Also, hexadecylferrocene is higher melting than even 1,1′-dihexadecylferrocene, the corresponding disubstituted derivative, which is very unusual among substituted aromatic compounds.

The question arises whether the diacylferrocenes and dialkylferrocenes are symmetrically or unsymmetrically substituted. Since none of these compounds absorb in the infrared in the region of 9.00 or 9.95 microns (peaks in these regions being indicative of unsymmetrical substitution according to the date of Rosenblum[7] and of Pauson[10]), it was concluded that these compounds were symmetrically substituted. The two monosubstituted compounds, palmitoylferrocene and hexadecylferrocene, did absorb in these regions as expected.

Three methods of direct alkylation of ferrocene were attempted; alcohols and 100% phosphoric acid, as successfully used for alkylating biphenyl,[11] alcohols and aluminum chloride, and alkyl halides and aluminum chloride. All were successful to the extent that little or no unreacted ferrocene could be recovered by steam distillation. However, the product was always a mixture of polyalkylated liquid ferrocenes, boiling over a wide range, or undistillable tars. We were unable to obtain any pure fractions upon distillation, and it appeared that the yield of any one product was small. Nesmeyanov

(10) P. L. Pauson, *J. Am. Chem. Soc.*, **76**, 2187 (1954).

(11) I. A. Romadan and V. K. Berzinya, *J. Gen. Chem. USSR*, **25**, 265 (1955).

and Kochetkova[12] have recently reported similar work using alkyl halides and aluminum chloride. They were able to isolate by distillation mono-, di-, and penta-alkylated ferrocenes in very small yields.

EXPERIMENTAL[13]

1,1'-Diacylferrocenes (II). All 1,1'-diacylferrocenes were prepared by the reaction of the appropriate acid chloride with aluminum chloride and ferrocene. As a typical example, 1,1'-dicaprylylferrocene was prepared by adding 120 g. (0.90 mole) of anhydrous aluminum chloride to 350 ml. of methylene chloride (dried over calcium hydride) in a 2-liter, 3-necked flask equipped with stirrer, reflux condenser, and addition funnel. A nitrogen atmosphere and stirring were maintained throughout the reaction. Through the addition funnel, 146.5 g. (0.90 mole) of caprylyl chloride (prepared from caprylic acid and thionyl chloride in 80% yield) was slowly added, dissolving the aluminum chloride. A solution of 65.1 g. (0.35 mole) of ferrocene in 350 ml. of methylene chloride was added dropwise over a period of 2 hrs. Reaction was immediate as evidenced by the evolution of hydrogen chloride and the formation of a dark purple complex. After 70 hr. of stirring, hydrogen chloride evolution had ceased and the reaction mixture was hydrolyzed by pouring it onto 500 g. of ice. The two-phase system, which was badly emulsified, was filtered under vacuum and the phases were separated. The organic phase was washed until neutral and dried over anhydrous calcium sulfate. The methylene chloride solution was filtered free of drying agent and the solvent evaporated under an air stream. The crude product was recrystallized twice from methanol yielding 100.0 g. (65% yield) of orange-red crystals, m.p. 50–52° (uncorr.). An analytical sample was obtained after two additional recrystallizations from methanol, m.p. 54.8–56.0°. See Table I for the analysis.

Palmitoylferrocene. The equipment and procedure used were the same as for the preparation of the 1,1'-diacylferrocenes with the exception that the mode of addition was reversed. A solution of 153.4 g. (0.558 mole) of palmitoyl chloride (prepared in 88% yield from palmitic acid and thionyl chloride) and 77.4 g. (0.558 mole) of aluminum chloride in 200 ml. of anhydrous methylene chloride was added dropwise over a 2.5 hr. period to 103.8 g. (0.558 mole) of ferrocene dissolved in 600 ml. of methylene chloride. After stirring overnight the reaction mixture was worked up and the crude product isolated. One recrystallization from methanol produced 116.4 g. (45.8% yield) of yellow crystals, m.p. 57.0–58.7°. An analytical sample was obtained after one recrystallization from methanol, m.p. 59.0–59.8°. See Table I for the analysis.

Hydrogenation of 1,1'-diacetylferrocene. In a 500-ml hydrogenation bottle were placed 10.8 g. (0.040 mole) of 1,1'-diacetylferrocene dissolved in 300 ml. of methanol and 1 g. of 5% platinum on charcoal. The mixture was placed in a Parr hydrogenation apparatus at a pressure of 50 p.s.i. After 24 hr. the hydrogen uptake had reached the theoretical value. The solution was filtered free of catalyst and the methanol stripped off. Distillation of the crude product at reduced pressure gave 5.7 g. (60% yield) of a dark-red liquid with a strong camphoraceous odor, b.p. 87–89° at 0.15 mm., n_D^{25} 1.5761. Rosenblum reports b.p. 130–131° at 9 mm., n_D^{25} 1.5760.[7]

Attempts to hydrogenate the higher 1,1'-diacylferrocenes under similar conditions and also at elevated temperatures gave starting material as the only isolatable product.

Clemmensen reduction of acyl- and 1,1'-diacylferrocenes. The acyl- and 1,1'-diacylferrocenes were reduced to the corresponding alkyl derivatives by refluxing with dilute hydrochloric acid and amalgamated zinc. In a typical experiment, 200 g. of granular zinc was amalgamated by stirring 5 min. with 15 g. of mercuric chloride, 250 ml. of water, and 10 ml. of concentrated hydrochloric acid in a 1-liter, 3-necked flask equipped with a stirrer and reflux condenser. The aqueous phase was pipetted off and 100 ml. of water, 200 ml. of concentrated hydrochloric acid, 43.8 g. (0.10 mole) of 1,1'-dicaprylylferrocene, and 100 ml. of benzene were added quickly in that order. The mixture was brought to reflux and stirred vigorously so that the amalgam was in contact with both phases. At intervals during the reaction, four 50-ml. portions of concentrated hydrochloric acid were added to maintain the acidity of the solution. After 52 hr. the mixture was brought to room temperature and filtered free of amalgam. The amalgam was washed with ether and the combined organic phase extracted with water to neutrality and dried over anhydrous calcium sulfate. After filtration from the drying agent, the solvent was evaporated under an air stream. The crude product was distilled twice under reduced pressure through a heated 9-inch Vigreux column yielding 23.8 g. (58% yield) of a dark red liquid b.p. 190–193° at 0.15 mm. See Table II for the analysis.

The solid alkyl- and 1,1'-dialkylferrocenes were purified by recrystallization from acetone.

Direct alkylation of ferrocene. As a typical example, 35.8 g. (0.192 mole) of ferrocene, 40.0 g. (0.30 mole) of anhydrous aluminum chloride, and 100 ml. of dry methylene chloride were placed in a 250-ml., 3-necked flask equipped with stirrer, reflux condenser, and addition funnel. Stirring and a nitrogen atmosphere were maintained throughout the reaction. A solution of 17.6 g. (0.20 mole) of *t*-amyl alcohol in 50 ml. of dry methylene chloride was added over a period of 1.5 hr. After 18 hr., the mixture was hydrolyzed with ice water and neutralized with sodium hydroxide solution. A steam distillation failed to produce any unreacted ferrocene. The residue from the steam distillation was extracted with benzene, the benzene solution washed with water, and dried over calcium chloride. After filtration from the drying agent, the solvent was evaporated under an air stream. The crude product was distilled twice under reduced pressure through a 24-inch column packed with 0.25-inch glass helices. The main fraction, a dark-red liquid, weighed 5.0 g., b.p. 62–64° at 0.1 mm., n_D^{25} 1.5683. The elemental analysis was intermediate between those calculated for the mono- and disubstituted derivatives.

Anal. Calcd. for $C_{15}H_{20}Fe$: C, 70.34; H, 7.87; Fe, 21.79. Calcd. for $C_{20}H_{30}Fe$: C, 73.62; H, 9.27; Fe, 17.11. Found: C, 72.17, 72.28; H, 8.19, 8.13; Fe, 19.57, 19.55.

Similarly, ferrocene was alkylated with *n*-decyl alcohol and with *n*-decyl chloride by refluxing several days with excess aluminum chloride in methylene chloride solution. The reaction of ferrocene with either *t*-amyl alcohol or *n*-amyl alcohol for several hours at 110–115° with 100% phosphoric acid as the solvent also produced alkylated derivatives. The products in every case were mixtures of liquid alkylferrocenes, none of which could be readily separated into pure compounds by distillation or by chromatography on alumina.

Acknowledgments. The authors wish to express their appreciation to Mr. F. F. Bentley, and Mrs. N. E. Srp for the infrared spectra, and to Dr. Eric Barthel of the E. I. du Pont de Nemours and Co., Inc. and Dr. Roy Pruett of the Linde Co. for generous samples of ferrocene which have been used in this research program.

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(12) A. N. Nesmeyanov and N. S. Kochetkova, *Doklady Akad. Nauk SSSR*, 109, 543 (1956).

(13) All melting points are corrected unless otherwise noted; boiling points are not corrected. Analyses were made by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, HEBREW UNIVERSITY]

Synthesis of 8-Bromo-1-Methylnaphthalene from o-Bromoacetophenone

JOSEF KLEIN AND ERNST D. BERGMANN

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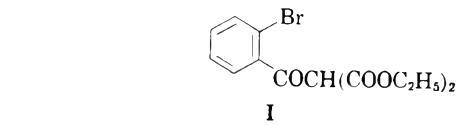
o-Bromoacetophenone, for which a new synthesis is described, has been converted by condensation with ethyl cyanoacetate, hydrogenation, hydrolysis, and decarboxylation into β-(*o*-bromophenyl)butyric acid (VIII). Arndt-Eistert reaction converted this acid into γ-(*o*-bromophenyl)valeric acid (IX) which was cyclized to 4-methyl-5-bromo-1-tetralone (X). From this, 8-bromo-1-methylnaphthalene was prepared.

8-Bromo-1-methylnaphthalene has been synthesized by Fieser and Seligman[1] from 1,8-diaminonaphthalene by a three-step procedure and with an over-all yield of 21%. Another synthesis reported starts with 8-methyl-1-naphthylamine, which is not an easily available substance.[2] In the course of a study of reactions of *o*-bromoacetophenone (II) a new synthesis for the above compound has been elaborated.

For the preparation of the starting material (II), three methods have been described: the Sandmeyer reaction of *o*-aminoacetophenone,[3,4] the reaction of *o*-bromobenzonitrile with methylmagnesium iodide,[5,6] and the reaction of *o*-bromobenzoyl chloride with diazomethane.[7] In the present study, the method used by Walker and Hauser[8] for the preparation of *o*-nitro- and *o*-chloroacetophenones has given advantageous results (92% yield). *o*-Bromobenzoyl chloride was condensed with diethyl malonate and the diethyl *o*-bromobenzoylmalonate (I) hydrolyzed. The condensation of *o*-bromoacetophenone (II) with ethyl cyanoacetate in the presence of ammonium acetate[9] as catalyst gave an 86% yield of ethyl α-cyano-β-(*o*-bromophenyl)crotonate (III), which showed considerable resistance to hydrolysis. Alkali in aqueous Cellosolve eliminated the carbethoxy group and gave a 71% yield of β-(*o*-bromophenyl)-crotononitrile (IV), whilst with hydrobromic acid in glacial acetic acid a 70% yield of the crude dicarboxylic acid (V) was obtained. The purification of this product was accompanied by serious losses of material.



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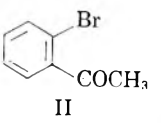

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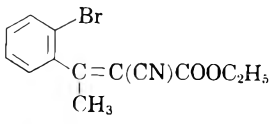

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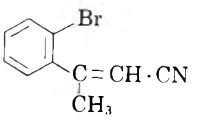

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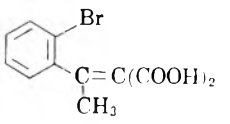

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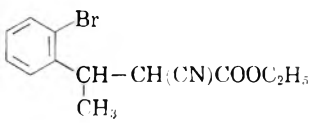
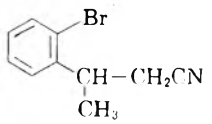
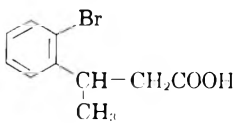


VI



VII



VIII

Better results were achieved after the hydrogenation of the double bond in III which gave ethyl β-(*o*-bromophenyl)-α-cyanobutyrate (VI) in 85% yield. It has not been established whether this oily product is sterically homogeneous or not. Its treatment with hydrobromic acid in glacial acetic acid gave mixtures of the nitrile VII and the acid VIII; the nitrile, which is formed first, hydrolyzes only with difficulty. Another method for the preparation of the key substance of the synthesis, the acid VIII, consists in the transformation of VI into the diethyl ester of the dicarboxylic acid by means of alcoholic hydrogen chloride, hydrolysis of the ester with methanolic potassium hydroxide,

(1) L. F. Fieser and A. Seligman, *J. Am. Chem. Soc.*, **61**, 136 (1939).

(2) Vesely, F. Stursa, H. Olejnicek, and E. Rein, *Collection Czechoslov. Chem. Commun.*, **2**, 145 (1930) [*Chem. Abstr.*, **24**, 3008 (1930)].

(3) J. Meisenheimer, *et al.*, *Ann.*, **446**, 219 (1926).

(4) L. A. Elson, C. A. Gibson, and J. D. A. Johnson, *J. Chem. Soc.*, 1128 (1930).

(5) W. Borsche and W. Scriba, *Ann.*, **541**, 283 (1939).

(6) R. E. Lutz, *et al.*, *J. Org. Chem.*, **12**, 617 (1947).

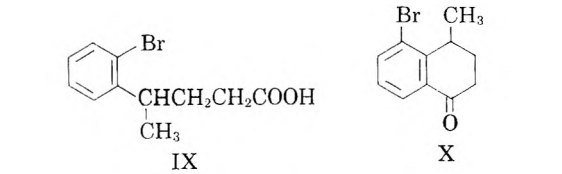
(7) V. Venkateswarlu, *Current Sci. (India)*, **24**, 155 (1955) [*Chem. Abstr.*, **50**, 4832 (1956)].

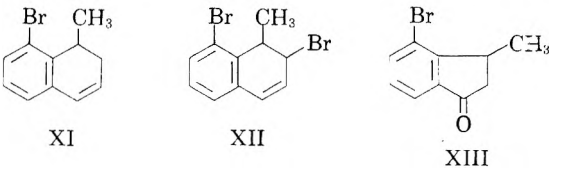
(8) H. G. Walker and Ch. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946). Similarly *o*-ethylacetophenone has recently been prepared from *o*-ethylbenzoyl chloride by T. Mitsui, M. Kitahara, and T. Nagase, *J. Sci. Research Inst. (Tokyo)*, **50**, 65 (1956).

(9) A. C. Cope, C. M. Hoffman, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

and decarboxylation of the dicarboxylic acid thus formed.

The chloride of the acid VIII was subjected to the Arndt-Eistert reaction, using silver benzoate in triethylamine[10] for the decomposition of the diazoketone. Thus γ-(*o*-bromophenyl)valeric acid (IX) was obtained in quantitative yield; it was characterized by its benzylisothiuronium salt. The acid chloride was cyclized to 4-methyl-5-bromo-1-tetralone (X) by means of aluminum chloride (yield, 75%) and X was reduced by means of aluminum isopropoxide to the corresponding alcohol in 83% yield. Dehydration of the alcohol by azeotropic distillation with toluene in the presence of *p*-toluenesulfonic acid gave a 78% yield of 8-bromo-1-methyl-1,2-dihydronaphthalene (XI).





Upon treatment of this compound with *N*-bromosuccinimide, a mixture of the desired 8-bromo-1-methylnaphthalene and of 2,8-dibromo-1-methyl-1,2-dihydronaphthalene (XII) was obtained; the latter is converted into the former by treating it with pyridine, a reaction which also establishes the structure of the compound.[11] The over-all yield of 8-bromo-1-methyl-naphthalene, calculated on II, was 7%. It had the correct melting point and its picrate showed the melting point reported in the literature.

In the course of this investigation the chloride of the acid VIII was also cyclized to 4-bromo-3-methyl-1-hydrindone (XIII) in 80% yield.

EXPERIMENTAL

o-Bromoacetophenone (II). (*a*) The mixture of 150 g. of *o*-bromobenzoic acid and 450 ml. of thionyl chloride was kept at room temperature for 12 hr. and refluxed for 1 hr. Distillation gave 136 g. (83%) of *o*-bromobenzoyl chloride, b.p. 130–132° (20 mm.).

(*b*) In a 3-l. flask, 15 ml. of anhydrous ethanol and 1.5 ml. of carbon tetrachloride was added to 23.7 g. of magnesium turnings. As soon as the reaction started, one added 150 ml. of chlorobenzene and, dropwise, a mixture of 156 g. of diethyl malonate and 60 ml. of ethanol. The temperature was not allowed to rise above 70° during this period. At its end, the mass was heated at 75° for 3 hr., cooled to room temperature and, at a temperature not exceeding 35°, a solution of 127 g. of *o*-bromobenzoyl chloride in 250 ml. of chlorobenzene was added drop by drop. After 12 hr. at room temperature, 200 ml. of 25% sulfuric acid was added, the mixture heated for 1 hr. on the water bath, cooled, and the organic layer separated. The latter was concentrated in the vacuum of the water pump at 100° and the residue refluxed for 7 hr. with a mixture of 200 ml. of glacial acetic acid and 200 ml. of 20% sulfuric acid. The work-up gave 107 g. (92%) of *o*-bromoacetophenone; b.p. 133–135° (20 mm.); semicarbazone, m.p. 177° (lit.: 177°).

Ethyl α-cyano-β-(o-bromophenyl)crotonate (III). The mixture of 124 g. of *o*-bromoacetophenone, 72 g. of ethyl cyanoacetate, 130 ml. of benzene, 60 ml. of glacial acetic acid, and 12 g. of ammonium acetate was subjected to azeotropic distillation for 11 hr. Then benzene was added and the product washed with water, sodium bicarbonate, and again water, and dried. The product was an oil, b.p. 175–180° (2.5 mm.); yield, 160 g. (86%).

Anal. Calcd. for $C_{13}H_{12}BrNO$: C, 53.1; H, 4.1; Br, 27.2; N, 4.8. Found: C, 53.6; H, 4.3; Br, 27.0; N, 5.2.

β-(o-Bromophenyl)crotononitrile (IV). When the solution of 25 g. of the preceding compound in 100 g. of ethylene glycol monomethyl ether was heated for 2.5 hr. with 10.5 g. of potassium hydroxide in 6 ml. of water, no ammonia was liberated. The reaction product was diluted with water and extracted with benzene. The product boiled at 140–145° (5 mm.), 114° (0.4 mm.), and weighed 14 g. (71%).

Anal. Calcd. for $C_{10}H_8BrN$: C, 54.1; H, 3.6. Found: C, 54.8; H, 3.8.

α-(o-Bromophenyl)ethylidene malonic acid (V). A mixture of 14.5 g. of (III), 30 ml. of glacial acetic acid, and 50 ml. of 48% hydrobromic acid was refluxed for 3 hr. The product was diluted with water, extracted with ether, and the extract treated with a 10% sodium carbonate solution. Acidification of the alkaline solution gave 9.5 g. (70%) of a grey solid which was recrystallized from toluene and melted then at 186°.

Anal. Calcd. for $C_{11}H_9O_4Br$: Br, 28.3. Found: Br, 29.0.

Ethyl β-(o-bromophenyl)-α-cyanobutyrate (VI). A solution of 10 g. of (III) in 50 ml. of ethanol was hydrogenated in the presence of 100 mg. of platinum oxide. The absorption of the theoretical amount of hydrogen required 16 hr. Distillation gave 8.5 g. (85%) of an oil, b.p. 170° (2.5 mm.).

Anal. Calcd. for $C_{12}H_{14}BrNO_2$: C, 52.7; H, 4.8; N, 4.8. Found: C, 53.4; H, 4.7; N, 4.8.

Acid hydrolysis. When 5.5 g. of the preceding substance (VI) was refluxed for 8 hr. with a mixture of 30 ml. of glacial acetic acid and 25 ml. of 48% hydrobromic acid, there were obtained, after elimination of the solvent and treatment with 10% sodium carbonate solution, two products: (*a*) an acidic one (3.4 g., 50%) of b.p. 148–150° (0.2 mm.), m.p. 61–62° (from petroleum ether), which was identified as β-(*o*-bromophenyl)-butyric acid (VIII) (see below).

Anal. Calcd. for $C_{10}H_{11}BrO_2$: C, 49.4; H, 4.5. Found: C, 49.8; H, 4.4.

(*b*) A neutral one (2.0 g., 31%) of b.p. 118–120° (2 mm.), which according to the analysis and spectrum was β-(*o*-bromophenyl)-butyronitrile (VII).

Anal. Calcd. for $C_{10}H_{10}BrN$: N, 6.2. Found: N, 6.2.

The infrared spectrum shows the C≡N band at 2250 cm.$^{-1}$, in accordance with the observations of Kitson and Griffith.[12]

Diethyl[α-(o-bromophenyl)ethyl]malonate. A solution of 35 g. of VI in 150 ml. of anhydrous alcohol was saturated with gaseous hydrogen chloride and, after 12 hr. at room temperature, refluxed for 3.5 hr. in a current of hydrogen chloride. The alcohol was evaporated, the residue was diluted with water and extracted with ether, and the ether solution

(10) M. S. Newman and P. F. Beal, *J. Am. Chem. Soc.*, 72, 5163 (1950).

(11) According to K. Ziegler, A. Spaeth, E. Scharf, W. Schumann, and E. Winkelmann [*Ann.*, 551, 80 (1942)], a tertiary hydrogen atom is generally not attacked by *N*-bromosuccinimide.

(12) R. E. Kitson and N. E. Griffith, *Anal. Chem.*, 24, 334 (1952).

was distilled to yield 28 g. (70%) of product b.p. 165° (1 mm.).

Anal. Calcd. for $C_{15}H_{19}BrO_4$: Br, 23.3. Found: Br, 24.0.

[α-(o-Bromophenyl)ethyl]malonic acid. A mixture of 10.3 g. of the foregoing ester, 5 g. of potassium hydroxide, 5 g. of methanol, and 5 g. of water was heated at 100° for 30 min. The methanol was distilled off and the remaining clear aqueous solution acidified. Trituration of the product with carbon tetrachloride and recrystallization from toluene gave 5 g. (63%) of the desired acid, m.p. 156–157°.

Anal. Calcd. for $C_{11}H_{11}BrO_4$: Br, 27.9. Found: Br, 27.5.

β-(o-Bromophenyl)butyric acid (VIII). When the malonic acid (4.55 g.) was heated at 180–185° for 30 min., it gave the acid (VIII) (yield 2.2 g., 57%). The acid crystallized only slowly and showed a m.p. of 61–62°. It was identified by a well-defined *benzylisothiuronium salt* of m.p. 136–137°.

Anal. Calcd. for $C_{18}H_{21}BrN_2O_2S$: C, 52.9; H, 5.1; N, 6.9. Found: C, 53.5; H, 5.9; N, 6.7. Infrared spectrum of the acid (KBr pellet): $\nu_{c=0}$ 1700 cm.$^{-1}$

The *chloride* (31.5 g., 91%) was obtained when the acid (32 g.) and thionyl chloride (100 ml.) were kept at room temperature for 12 hr. and refluxed for 1 hr.; b.p. 118–120° (0.9 mm.).

Anilide, from a mixture of benzene and ligroin, m.p. 97–98°.

Anal. Calcd. for $C_{16}H_{16}BrNO$: C, 60.4; H, 5.0; N, 4.4; Br, 24.1. Found: C, 60.7; H, 5.2; N, 4.4; Br, 24.6.

p-Toluidide, from a mixture of benzene and ligroin, m.p. 106°.

Anal. Calcd. for $C_{17}H_{18}BrNO$: N, 4.2; Br, 25.2. Found: N, 4.3; Br, 25.2.

γ-(o-Bromophenyl)valeric acid (IX). To an ethereal solution of 5.5 g. of diazomethane, 10.5 g. of the acid chloride of VIII was added, dropwise, and with stirring. After 12 hr. at room temperature, the ether was removed *in vacuo* and the oily residue taken up in 75 ml. of anhydrous methanol. To the solution was added gradually 1 g. of silver benzoate in 10 ml. of triethylamine and the mixture was refluxed, after 30 min., for 1 hr. The filtered solution was refluxed for 5 hr. with a solution of 10 g. of potassium hydroxide in 10 ml. of water, and the methanol was distilled off. The residue was then taken up with water and ether and the aqueous layer acidified. The acid (IX) was an oil which boils at 153° (0.2 mm.). Yield, 10.5 g. (quantitative).

Anal. Calcd. for $C_{11}H_{13}O_2Br$: C, 51.4; H, 5.1. Found: C, 50.8; H, 4.9. Infrared spectrum: $\nu_{c=0}$ 1700 cm.$^{-1}$

The acid gave a well-defined *benzylisothiuronium salt*, which crystallized from aqueous dioxane and melted at 135°. Its melting point is depressed by admixture of the analogous derivative of (VIII).

Anal. Calcd. for $C_{19}H_{23}BrN_2O_2S$: N, 6.6. Found: N, 6.9.

The *chloride* (8 g., 83%), was obtained from the acid (9 g.) as described above; b.p. 133–135°/0.3 mm.

Anilide, from benzene-ligroin, m.p. 85–86°.

Anal. Calcd. for $C_{17}H_{18}BrNO$: N, 4.2. Found: N, 4.0.

p-Toluidide, from benzene-ligroin, m.p. 89–90°.

Anal. Calcd. for $C_{18}H_{20}BrNO$: N, 4.1. Found: N, 4.1.

5-Bromo-4-methyl-1-tetralone (X). To an ice-cold solution of 6.5 g. of the chloride of X in 50 ml. of carbon disulfide, 3 g. of aluminum chloride was added with stirring, during 30 min. The stirring was continued for 4 hr. at 0°, and the mixture was kept at room temperature for 12 hr. and decomposed with ice and concentrated hydrochloric acid. B.p. 160–163° (5 mm.); yield, 4.3 g. (75%).

Anal. Calcd. for $C_{11}H_{11}BrO$: C, 55.2; H, 4.8. Found: C, 55.6; H, 4.8.

Ultraviolet spectrum (in ethanol): 253 mμ (4.03); 298 mμ (3.26); infrared spectrum $\nu_{c=0}$ 1695 cm.$^{-1}$ (α-tetralone: 1691 cm.$^{-1}$).[13]

2,4-Dinitrophenylhydrazone, from butanol, m.p. 225–226°.

Anal. Calcd. for $C_{17}H_{15}BrN_4O_4$: C, 48.7; H, 3.6; Br, 19.1. Found: C, 49.2; H, 3.8; Br, 19.2.

5-Bromo-4-methyl-1-tetralol. In the usual way, 14.5 g. of the ketone X was reduced with 12.5 g. of aluminum isopropoxide and 70 ml. of isopropyl alcohol. The reduction was complete in 5 hr. After removal of the solvent, the product was treated with dilute hydrochloric acid and extracted with benzene. B.p. 125–130°/2 mm.; yield, 12 g. (83%). Infrared spectrum: ν_{O-H} 3350 cm.$^{-1}$

Anal. Calcd. for $C_{11}H_{13}BrO$: C, 54.8; H, 5.4. Found: C, 54.3; H, 5.4.

8-Bromo-1-methyl-1,2-dihydronaphthalene (XI). The solution of 11 g. of 5-bromo-4-methyl-1-tetralol and 0.5 g. of *p*-toluenesulfonic acid in 50 ml. of toluene was subjected to azeotropic distillation. After 5 hr., the solution was washed with water and sodium bicarbonate solution and distilled. B.p. 100–104°/2 mm.; yield, 8 g. (80%).

Anal. Calcd. for $C_{11}H_{11}Br$: C, 59.2; H, 4.8. Found: C, 59.1; H, 5.0.

Ultraviolet spectrum (in ethanol); 259 mμ (3.98). This figure conforms with the spectrum of 1,2-dihydronaphthalene [260 mμ (3.96)], as reported by Mousseron and coworkers.[14]

8-Bromo-1-methylnaphthalene. The mixture of 2.5 g. of XI, 2 g. of *N*-bromosuccinimide, a few crystals of benzoyl peroxide, and 20 ml. of carbon tetrachloride was refluxed for 2 hr., filtered and subjected to distillation. Two fractions were obtained. (a) B.p. 115–130° (3.5 mm.); 1.5 g. This fraction solidified; recrystallization from methanol gave platelets of the correct m.p. 79–80°.

Anal. Calcd. for $C_{11}H_9Br$: C, 59.7; H, 4.1. Found: C, 59.7; H, 4.4. Picrate, m.p. 152–153°.

(b) B.p. 140–150° (3.5 mm.); 0.8 g. According to the analysis and the behavior, this product was 2,8-dibromo-1-methyl-1,2-dihydronaphthalene (XII); it has not been possible to obtain it in analytically pure form.

Anal. Calcd. for $C_{11}H_{10}Br_2$: C, 43.7; H, 3.3. Found: C, 42.5; H, 3.2.

When this product was heated for 1 hr. with 5 ml. of pyridine, it gave the above 8-bromo-1-methylnaphthalene, m.p. 79–80°.

4-Bromo-3-methyl-1-hydrindone (XIII). To a solution of 6 g. of *β-(o-bromophenyl)butyryl chloride* in 60 ml. of carbon disulfide, 3.5 g. of aluminum chloride was added with stirring. After 12 hr. at room temperature, the mass was decomposed with ice and concentrated hydrochloric acid and the oily product isolated by distillation. B.p. 140–145° (5 mm.); yield, 4.1 g. (82%).

Anal. Calcd. for $C_{10}H_9OBr$: C, 53.3; H, 4.0. Found: C, 53.2; H, 4.4.

2,4-Dinitrophenylhydrazone, from butyl acetate, m.p. 267°. Ultraviolet spectrum (in chloroform): 389 mμ (4.33).

Anal. Calcd. for $C_{16}H_{13}BrN_4O_4$: C, 47.4; H, 3.2. Found: C, 47.0; H, 2.9.

JERUSALEM, ISRAEL

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(13) E. D. Bergmann and S. Pinchas, *J. chim. phys.*, **49**, 537 (1952).

(14) M. Mousseron, R. Jacqnier, and H. Christol, *Compt. rend.*, **243**, 1532 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CANISIUS COLLEGE, AND THE RESEARCH LABORATORIES, INTERCHEMICAL CORPORATION]

Reactions of Carbinolamines. II.[1] Acylation of 1-Hydroxymethyl-1*H*-Benzotriazole[2]

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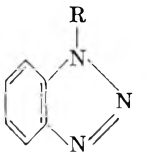
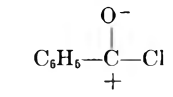
The benzoate of 1-hydroxymethyl-1*H*-benzotriazole (I) has been prepared by the reaction of I with benzoyl chloride in the presence of aqueous sodium hydroxide, with benzoic acid and *p*-toluenesulfonyl chloride in pyridine solution and with benzoic anhydride at 160°. 1-Benzoyl-1*H*-benzotriazole has been prepared from I and benzoyl chloride in the presence of pyridine or dilute hydrochloric acid. 1,1′-Methylenebisbenzotriazole was prepared by the reaction of I with benzoyl chloride at 160°. Treatment of I with acetyl chloride in the presence of pyridine yielded 1-acetyl-1*H*-benzotriazole and possibly the acetate of I.

The reaction of 1-hydroxymethyl-1*H*-benzotriazole (I) with benzoyl chloride and pyridine in dioxane solution has been shown to yield the amide 1-benzoyl-1*H*-benzotriazole (II) instead of the benzoate (III) of I.[1] The present investigation was concerned with the behavior of I under acylating conditions.



I, R = CH_2OH
II, R = COC_6H_5
III, R = CH_2OCOC_6H

The reaction of I with benzoyl chloride and pyridine in dioxane solution at 60° gave a 56% yield of the amide (II). The reaction of I with benzoyl chloride in pyridine solution at 20° gave 19% of II. No reaction was observed when I was heated in a pyridine solution at 60° for 2 hr. It has previously been postulated[1] that II may arise either by the elimination of formaldehyde to yield 1*H*-benzotriazole followed by amide formation or by the direct displacement of the methylol group by



The absence of a reaction when I was heated with pyridine at 60° precludes the elimination of formaldehyde from I prior to the reaction with benzoyl chloride at either 20° or 60°. The presence of pyridine may enhance the polarization of the carbonyl group in the acyl chloride or may even participate in the ionization of the compound in the form of the acyl pyridinium chloride.

1-Benzoyloxymethyl-1*H*-benzotriazole (III) was prepared by a Schotten-Baumann reaction of I with benzoyl chloride in the presence of a 10% sodium hydroxide solution, in 40% yield at 20° and in 26.5% yield at 45–65°. III was identified by elemental analysis, an infrared absorption band at 5.75 μ, characteristic of an ester group, and its behavior on reduction with lithium aluminum hydride and sodium borohydride.[4] Whereas I and II yield the picrate of benzotriazole,[1] attempts to prepare a picrate from III were unsuccessful.

The Schotten-Baumann reaction with I at 60° gave a 52% yield of benzotriazole without the formation of III. Treatment of I with a dilute sodium hydroxide solution gave 8% of benzotriazole at 20° and 91% at 60°, with the residual recovered material being unreacted I.

The loss of formaldehyde from I at 60° in the presence of base is responsible for the failure to obtain III in the Schotten-Baumann reaction. The isolation of benzotriazole instead of II under these conditions is probably due to the hydrolysis of the acyl chloride. At 20° I is not as readily decomposed by the base, so that esterification occurs in the presence of benzoyl chloride. At 45° the yield of III is reduced as a result of the considerably greater decomposition of I and/or benzoyl chloride.

The reaction of I with benzoyl chloride in the presence of dilute hydrochloric acid in dioxane at 20° gave 39% of II. At 60° the only product isolated besides I was benzoic acid. Dilute hydrochloric acid with I in dioxane at 60° gave no reaction. Apparently I is not attacked by dilute acid at 60° although the elimination of formaldehyde occurs in the presence of base. However, at 60° the acid hydrolyzes the benzoyl chloride so that reaction with I does not occur. At 20° neither hydrolysis of the acid chloride nor attack on I occurs to an extent to interfere with the formation of II by a reaction which may be analogous to that which occurs in the presence of pyridine.

Treatment of I with benzoyl chloride for 1 hr. at 160° gave a 36% yield of a condensation product, 1,1′-methylenebisbenzotriazole (IV), previously prepared from benzotriazole and 1-chloromethyl-

(1) Part I: N. G. Gaylord, *J. Am. Chem. Soc.*, **76**, 285 (1954).

(2) Abstracted in part from the M.S. thesis of J. M. Naughton, Canisius College, June 1955.

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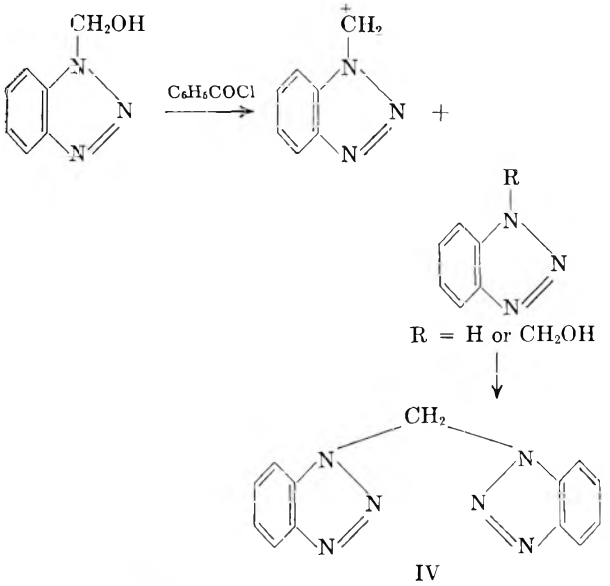
(4) N. G. Gaylord and D. J. Kay, unpublished work.

1*H*-benzotriazole with sodamide in toluene.[5] No isomeric 1,2-methylenebisbenzotriazole, obtained in 4% yield in the latter reaction, was identified in the present case. No picrate could be obtained from IV.

The formation of the condensation product (IV) may be analogous to the curing mechanism of urea-formaldehyde and melamine-formaldehyde resins. Thus, the elimination of formaldehyde and water between two molecules of the *N*-methylol compound would yield the methylene derivative. Alternatively, the elimination of water between molecules of I and benzotriazole would yield IV. The benzotriazole may arise through the thermal decomposition of I. A carbonium ion, arising by the action of benzoyl chloride on I, may be an intermediate in the reaction as shown.



The reaction of I with benzoic anhydride at 160° gave III in 24% yield. Treatment of I with benzoic acid and *p*-toluenesulfonyl chloride in pyridine solution[6] gave a 27% yield of III.

An alcoholysis reaction between I and ethyl benzoate with acid catalysis in dioxane solution was unsuccessful.

Treatment of I with acetyl chloride and pyridine in dioxane solution at 60° yielded 30% of the amide, 1-acetyl-1*H*-benzotriazole. An impure liquid fraction, isolated in 8% yield, had an elemental analysis which indicated the probable presence of the ester. The amide gave the picrate of benzotriazole.

EXPERIMENTAL

1-Hydroxymethyl-1H-benzotriazole (I), m.p. 148–149°, was prepared in 84% yield from benzotriazole, formalin, and acetic acid, according to the procedure of Burckhalter, Stephens, and Hall.[5]

Reaction of I with benzoyl chloride in pyridine at 60°, according to the procedure of Gaylord,[1] gave 1-benzoyl-1*H*-benzotriazole (II), m.p. 110–112°, in 56% yield.

Reaction of I with benzoyl chloride in pyridine at 20°. I (14.6 g., 0.098 mole) was dissolved in 75 ml. of pyridine and the solution was cooled to 12°. Benzoyl chloride (21.1 g., 0.15 mole) was added dropwise over a period of 1 hr. and the temperature was raised to 20°. A white precipitate formed during the addition. The reaction mixture was diluted with 350 ml. of ether and stirred for 30 min. while the flask was immersed in an ice bath. The ethereal solution was decanted from the precipitate and washed successively with aqueous solutions of sodium carbonate, hydrochloric acid, sodium bicarbonate, and water. The volatile solvents were removed under vacuum and the residual solid, 14.6 g., was recrystallized from ethyl acetate to yield 4.0 g. (18.5% yield) of II, m.p. 110–112° (reported[1] m.p. 110–113°). A mixed melting point with authentic material showed no depression while a mixed melting point with benzotriazole, m.p. 98°, was m.p. 70–85°.

The attempted *reaction of I with pyridine at 60°* for 2 hr. resulted in the quantitative recovery of I.

Reaction of I with benzoyl chloride in sodium hydroxide solution. A. At 60°. A slurry of 29.1 g. (0.19 mole) of I in 50 ml. of water was heated with stirring to 60°. While the temperature was held at 60°, 200 g. of a 10% sodium hydroxide solution and 42.2 g. of benzoyl chloride were simultaneously added over 1 hr. at such a rate that three drops of the basic solution were added for each drop of acyl chloride. A white precipitate formed during the addition. The mixture was stirred for an additional 20 min. until the temperature dropped to 40°. After standing overnight the mixture was filtered to yield 40 g. of crude, air-dried product. The crude material was recrystallized once from ethyl acetate and twice from a benzene-hexane mixture to yield 12 g. (52%) of benzotriazole, m.p. 95°, no depression on admixture with authentic material.

B. At 20° The slurry of I in water was cooled to 5°. During the first 0.5 hr. of the addition of sodium hydroxide and benzoyl chloride the temperature rose to 20° and was held at 20° for the remaining 0.5 hr. The crude, air-dried product, 40 g., was recrystallized from 75 g. of ethyl acetate to yield 19.5 g. (39.5%) of III, m.p. 93–94°, unchanged after recrystallization from hexane. Admixture with benzotriazole gave m.p. 70–84° and admixture with II gave m.p. 78–100°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.35; N, 16.61. Found: C, 66.19; H, 4.20; N, 16.69.

The infrared absorption spectrum of III showed a strong band at 5.75 μ, characteristic of an ester grouping.

C. At 45–65°. I (29.1 g., 0.19 mole) was dissolved in 200 g. of 10% sodium hydroxide (0.5 mole) solution at 25° and cooled at 20°. Benzoyl chloride (42.2 g., 0.3 mole) was added dropwise over 45 min. during which time the temperature rose to 45°. The reaction mixture was maintained at 45° for an additional 45 min. after the addition was complete, and then the temperature was raised to 65° over a 15 min. period. The mixture was cooled to 25°, filtered, and the precipitate was washed with ice cold water and air dried to yield 35 g. of crude product. Recrystallization from 125 ml. of ethanol gave 22.0 g. of material which was dissolved in 70 g. of ethyl acetate and precipitated with 65 g. hexane, cooled to 10° and filtered to yield 13.0 g. (26.4%) of white needles, m.p. 93–94°, no depression on admixture with III obtained in 20° reaction.

Reaction of I with sodium hydroxide. A. At 60°. I (14.6 g.) was dissolved in 100 g. of a 10% sodium hydroxide solution and heated in a water bath at 60° for 2 hr. The solution was cooled to 25° and treated with 75 ml. of 10% hydrochloric acid to adjust the *p*H to 6.0. The mixture was cooled to 5° and filtered to yield 11.0 g. (91%) of benzotriazole, m.p. 98°.

B. At 20°. The solution obtained after holding I in aqueous sodium hydroxide for 2 hr. at 20° was treated with 85 ml.

(5) J. H. Burckhalter, V. C. Stephens, and L. A. R. Hall, *J. Am. Chem. Soc.*, **74**, 3868 (1952).

(6) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

of 10% hydrochloric acid to adjust the *p*H to 3.0. The mixture was cooled to 10° and filtered to yield 11.5 g., m.p. 142–145°. Recrystallization from water gave a 62% recovery of I. The filtrate from the recrystallization yielded 2.0 g. (8%) of benzotriazole.

Reaction of I with benzoyl chloride in hydrochloric acid. A. At 20°. I (20.1 g., 0.19 mole) was mixed with 100 ml. of dioxane and the slurry was cooled to 12°. A 10% hydrochloric acid solution, 200 ml., and 42.2 g. of benzoyl chloride were added dropwise over a period of 45 min. at a 3:1 drop ratio, respectively, while the temperature was maintained at 20°. The mixture was stirred for an additional .5 min., filtered, and air dried to yield 34 g. of crude product. Recrystallization from ethyl acetate gave 17 g. (39%) of II, m.p. 112–113°, no depression on admixture with authentic material.

B. At 60°. I (14.6 g.) was dissolved in 150 ml. of dioxane by heating at 53°. The temperature was raised to 60° and 100 ml. of a 10% hydrochloric acid solution and 21.1 g. of benzoyl chloride were added over 1 hr. while maintaining this temperature. The solution was cooled to 30° while stirring for 1 hr. and partially concentrated by blowing air over the solution at 25°. The mixture was cooled to 5°, filtered, and the precipitate was air dried to yield 12 g. of crude material. Recrystallization from benzene gave 3.5 g. (19%) of benzoic acid, m.p. 121–123°. The filtrate from the reaction mixture was evaporated with air to yield crude I which was recrystallized from ethyl acetate.

Reaction of I with hydrochloric acid at 60°. A solution of 14.6 g. of I in 100 ml. of dioxane and 25 ml. of a 10% hydrochloric acid solution was heated for 2 hr. at 60°. The solution was cooled to 25° and air evaporated to yield 15 g. of crude I, recrystallized from ethyl acetate to yield 12 g. (82%) of I, m.p. 146–147°.

Reaction of I with benzoyl chloride. A mixture of 24.8 g. (0.17 mole) of I and 25.0 g. (0.17 mole) of benzoyl chloride was heated in an oil bath at 160° for 1 hr. The clear melt partially crystallized on cooling to room temperature. After the addition of 750 ml. of ether the mixture was stirred for 1 hr. in an ice bath. The ethereal solution was decanted and washed successively with aqueous solutions of sodium carbonate, hydrochloric acid, sodium bicarbonate, and water. After removal of the ether under vacuum the residue was recrystallized several times from an aqueous ethanol solution to yield 2.0 g. of IV, m.p. 191–192°. The residue, 15.0 g., from the original reaction mixture was washed as above to yield 10 g. of crude material which was recrystallized from ethyl acetate. A total of 5.5 g. (36% yield) of IV was obtained. On recrystallization from dilute ethanol the product had m.p. 191–193° (reported[5] m.p. 192–193°).

Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.48. Found: C, 62.45; H, 3.91; N, 33.43.

Reaction of I with benzoic anhydride. A mixture of 24.8 g. (0.17 mole) of I and 38 g. (0.17 mole) of purified benzoic anhydride was heated in an oil bath at 160° for 1 hr. The crude product was crystallized from dilute ethanol to yield 5.5 g. of product, m.p. 88–92°. Recrystallization from dilute ethanol gave 5.0 g. (24%) of III, m.p. 92–94°, no depression on admixture with the product from the Schotten-Baumann reaction at 20°, and benzoic acid.

Reaction of I with benzoic acid and p-toluenesulfonyl chloride. A solution of 10 g. (0.067 mole) of I in 50 ml. of pyridine was added slowly with stirring to a mixture of 23.6 g. (0.124 mole) of *p*-toluenesulfonyl chloride and 7.6 g. (0.062 mole) of benzoic acid in 100 ml. of pyridine. The temperature was maintained at 5–10° during the addition and for an additional 1.5 hr. The reaction mixture was poured into 3 volumes of ice water and the precipitated solid was filtered and air dried to yield 2.6 g. of III. The filtrate was concentrated by blowing air over the surface of the solution to yield an additional 1.0 g. of III, total 3.6 g. (21.4% yield). Acidification of the filtrate to pH 2 resulted in the precipitation of 3.15 g. (31.5%) of I.

When the reaction was carried out with 25.4 g. (0.134 mole) of *p*-toluenesulfonyl chloride and 8.1 g. (0.067 mole) of benzoic acid in 50 ml. of pyridine, a total of 4.7 g. (27.4% yield) of III was obtained.

Reaction of I with acetyl chloride in pyridine. A solution of 23.5 g. (0.3 mole) of acetyl chloride in 25 ml. of dioxane was added dropwise over 0.5 hr. to a solution of 29.1 g. of I in 100 ml. of dioxane and 31.6 g. (0.4 mole) of pyridine. The temperature was maintained at 20° during the addition and then the mixture was heated at 55° for 1 hr. The mixture was diluted with 750 ml. of ether and stirred for 0.5 hr. at 5° in an ice bath. The ethereal solution was decanted and washed successively with aqueous solutions of sodium carbonate, hydrochloric acid, sodium bicarbonate, and water. After drying over calcium chloride the ether was evaporated to yield 16.4 g. of crude product which was distilled and collected at 95–115° (0.5 mm.). A white solid (7.5 g., 24%) distilled first, followed by 6.5 g. of a clear liquid. The solid had m.p. 49–51° and on recrystallization had m.p. 50–51°.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.63; H, 4.35; N, 26.09. Found: C, 59.42; H, 4.41; N, 25.87.

Redistillation of the liquid gave an additional 2.0 g. (total yield 30%) of *1-acetyl-1H-benzotriazole* and 3.0 g. (8%) of liquid, b.p. 112–120° (0.3 mm.). Analysis of the liquid fraction indicated the probable presence of the ester *1-acetoxymethyl-1H-benzotriazole.*

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.99. Found: C, 57.60; H, 4.50; N, 23.10.

Acknowledgment. The assistance of Daniel J. Kay and Karl Schmidt in portions of the experimental work is gratefully acknowledged.

NEW YORK, N. Y.

[CONTRIBUTION FROM E. I. DU PONT DE NEMOURS & CO., INC., EASTERN LABORATORY]

Reduction of Nitroparaffins by Alkylation. I. Aklylation with Trialkyl Oxonium Salts[1]

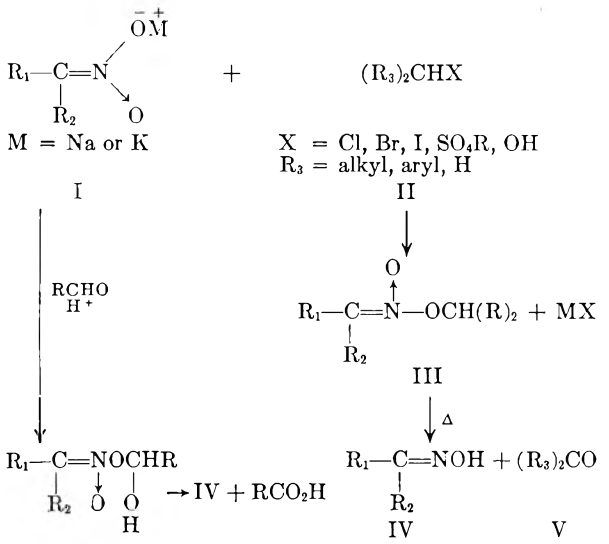
L. GUY DONARUMA[2]

Received February 22, 1957

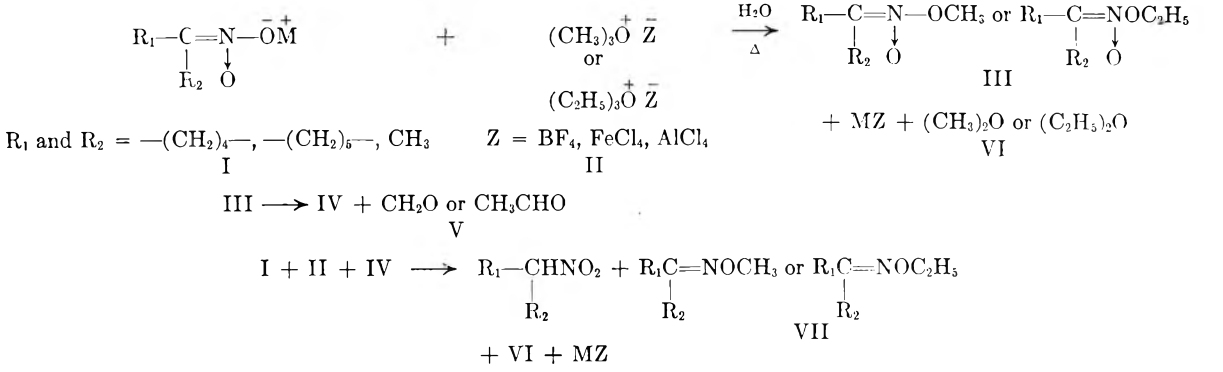
The reduction of the sodium *aci* salts of nitrocyclohexane, nitrocyclopentane, and 2-nitropropane by alkylation is described. The preparation of trialkyl oxonium salts is discussed. The preparation and certain reactions of some cyclohexanone oxime-*O*-alkyl ethers is described.

The oxygen alkylation of nitroparaffin *aci* salts (I) has been studied by various investigators.[3–6] The usual products of the reaction are an oxime (IV) and a carbonyl compound (V). The nature of the

carbonyl compound (V) is determined by the constitution of the alkylating agent (II).[3-6]

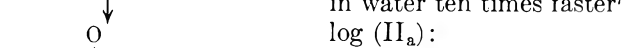


We have studied the alkylation of nitroparaffin *aci* salts (I) with various types of alkylating agents. This initial report describes the reaction of nitronate salts with trialkyl oxonium salts (II)[7,8] to yield the oxime (IV) and oxime-*O*-alkyl ether (VII)



corresponding to the nitroparaffin *aci* salt (I) employed, the ether (VI) from which the oxonium salt (II) was prepared,[7,8] and products characteristic of the oxonium salt anion. Listed in Table I are the data obtained by reacting three alkyl nitronate sodium salts (I) with various trialkyl oxonium salts (II).

The table shows data which indicate that certain nitronate salts (I) can be reduced to oximes (IV) in good yield by alkylation with trialkyl oxonium fluoborates (II). Oxime-*O*-alkyl ethers (VII) are formed as by-products. The yield of oxime ether (VII) can be increased by using an excess of the oxonium fluoborate (II) and excess base. The table also shows that triethyl oxonium fluoborate (II_a) is slightly superior to trimethyl oxonium fluoborate (II_d). The trimethyl oxonium salt (II_d) decomposes in water ten times faster[7,8] than the triethyl homolog (II_a):



$$(CH_3)_3\overset{+}{O}\ \bar{B}F_4 + H_2O \rightarrow (CH_3)_2O + HBF_4 + CH_3OH$$

Therefore, in order to obtain high yields of oxime (IV) by alkylation with II_d it was necessary to decrease the amount of water in the reaction mixture by 50%.

The trialkyl oxonium tetrachloroferrates (II_b) and tetrachloroaluminates (II_c) were not good alkylating agents. The yields of cyclohexanone oxime and cyclohexanone oxime-*O*-ethyl ether from alkylation of sodium *aci* nitrocyclohexane with these oxonium salts were low. This may have been because of the regeneration of the nitroparaffin or the formation of iron and aluminum *aci* salts from the nitronate salt by ferric chloride or aluminum chloride generated from the oxonium salt (II_b or II_c) by alkylation or hydrolytic decomposition.

This explanation seems reasonable because the yield of products (IV and VII) increased as the amount of excess sodium hydroxide in the reaction mixture was increased. This might be expected because the excess alkali would prevent loss of I by regeneration to the nitroparaffin, would presumably precipitate more metal ions as hydroxides than as heavy metal *aci* salts, and leave more of the *aci* salt (I) available for alkylation.

The alkylation of the sodium *aci* salt of nitrocyclopentane with trimethyl oxonium fluoborate (II_d) did not proceed well. The yield of cyclopentanone oxime was only 42%. However, when the triethyl homolog (II_a) was used the yield increased to 86%. An explanation for this observation may be the surmise that in order for the intermediate nitronate ester (III) to decompose and form an aldehyde or ketone (V) and an oxime (IV), the nitrogen-

(1) Portions of this material were disclosed in the specification of U. S. Patent **2,763,685**.

(2) Present address: Explosives Department Laboratory, Bldg. 336, Du Pont Experimental Station, Wilmington, Del.

(3) F. Arndt and J. D. Rose, *J. Chem. Soc.*, 1 (1935).

(4) K. Harman and K. Bauer (to Farbenfabriken Baeyer), German Patent **825,547** (Dec. 20, 1951).

(5) H. Welz and J. Weise (to Farbenfabriken Baeyer), German Appln. **F 1,054** (May 23, 1950).

(6) H. Welz (to Farbenfabriken Baeyer), German Appln. **F 1,053** (May 23, 1950).

(7) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang, *J. prakt. Chem.*, **154**, 83 (1940).

(8) H. Meerwein, G. Hing, P. Hofmann, E. Kroning. and E. Pfeil, *J. prakt. Chem.*, **147**, 257 (1937).

TABLE I

REACTION OF *aci* SALTS OF NITROCYCLOHEXANE, NITROCYCLOPENTANE, AND 2-NITROPROPANE WITH VARIOUS OXONIUM SALTS

Legend

Na(NCH) = Sodium *aci* nitrocyclohexane
K(NCH) = Potassium *aci* nitrocyclohexane
Na(NCP) = Sodium *aci* nitrocyclopentane
Na(2NP) = Sodium *aci* 2-nitropropane
CHO = Cyclohexanone oxime
CPO = Cyclopentanone oxime
(CHO)Me = Cyclohexanone oxime-*O*-methyl ether
(CHO)Et = Cyclohexanone oxime-*O*-ethyl ether
(CPO)Me = Cyclopentanone oxime-*O*-methyl ether
(CPO)Et = Cyclopentanone oxime-*O*-ethyl ether
II_a = Triethyl oxonium fluoborate; $(C_2H_5)_3O^+BF_4^-$
II_b = Triethyl oxonium tetrachloroferrate; $(C_2H_5)_3O^+FeCl_4^-$
II_c = Triethyl oxonium tetrachloroaluminate; $(C_2H_5)_3O^+AlCl_4^-$
II_d = Trimethyl oxonium fluoborate; $(CH_3)_3O^+BF_4^-$

aci Salt (I)	Oxonium Salt (II)	Temp., °C.	% Yield, Oxime (IV)	% Yield, Oxime Ether (VII)	Remarks
Na(NCH)	II_a	50–60	74, CHO	19, (CHO)Et	
Na(NCH)	II_a	50–60	79, CHO	12, (CHO)Et	
Na(NCH)	II_a	80–100	51, CHO	18, (CHO)Et	
Na(NCH)	II_a	25–30	52, CHO	7, (CHO)Et	
Na(NCH)	II_a	50–60	41, CHO	8, (CHO)Et	Absolute alcohol used as solvent
Na(NCH)	II_a	50–60	32, CHO	35, (CHO)Et	1 molar excess NaOH used with 0.5 molar excess II
Na(NCH)	II_b	50–60	5, CHO	9, (CHO)Et	
Na(NCH)	II_b	50–60	10, CHO	5, (CHO)Et	0.5 molar excess NaOH used
Na(NCH)	II_b	50–60	7, CHO	10, (CHO)Et	1.5 molar excess NaOH used
Na(NCH)	II_b	50–60	17, CHO	10, (CHO)Et	5 molar excess NaOH used
Na(NCH)	II_c	50–60	7, CHO	10, (CHO)Et	
Na(NCH)	II_c	50–60	5, CHO	8, (CHO)Et	
Na(NCH)	II_d	50–60	35, CHO	8, (CHO)Me	
K(NCH)	II_d	50–60	31, CHO	21, (CHO)Me	
Na(NCH)	II_d	50–60	66, CHO	13, (CHO)Me	*aci* salt concentration doubled over preceding reactions
Na(NCP)	II_a	60–70	86, CPO	5, (CPO)Et	
Na(NCP)	II_d	60–70	42, CPO	trace, (CPO)Me	*aci* salt concentration doubled over preceding reaction
Na(2-NP)	II_a	60–70	20, acetoxime		

$$I + II_b \text{ or } II_c \xrightarrow{H_2O} III + [MAlCl_4] \text{ or } [MFeCl_4] + VI$$

$$III \longrightarrow IV + V$$

$$I + IV + II_b \text{ or } II_c \longrightarrow VII + [MAlCl_4] \text{ or } [MFeCl_4] + VI + R_1{-}\underset{\displaystyle R_2}{\underset{|}{C}}HNO_2$$

$$II_b \text{ or } II_c \xrightarrow[H_2O]{M^+} VI + [MAlCl_4] \text{ or } [MFeCl_4] + C_2H_5OH$$

$$[MAlCl_4] \longrightarrow MCl + AlCl_3$$
$$[MFeCl_4] \longrightarrow MCl + FeCl_3$$

$$3I + \underset{\text{or } AlCl_3}{FeCl_3} + 3H_2O \longrightarrow 3R_1{-}\underset{\displaystyle R_2}{\underset{|}{C}}HNO_2 + 3MCl + Fe(OH)_3 \text{ or } Al(OH)_3$$

$$\underset{\text{or } AlCl_3}{FeCl_3} + 3I \longrightarrow \left[\begin{array}{c} R_1C{=}NO_2 \\ | \\ R_2 \end{array}\right]_3 Fe \text{ or } \left[\begin{array}{c} R_1C{=}NO_2 \\ | \\ R_2 \end{array}\right]_3 Al + 3MCl$$

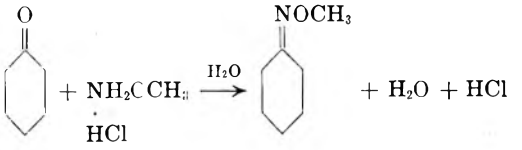
oxygen bond should weaken to allow for the formation of specie(s) which might give rise to the products (IV and V). Examination of molecular models indicates that a cyclopentyl nitronate ester (III) derived from triethyl oxonium fluoborate (II_a)

$$\underset{III}{\begin{array}{c} R_2 \quad O \\ | \quad \uparrow \\ R_1C{=}N{-}OCH(R)_2 \end{array}} \longrightarrow \underset{IV}{\begin{array}{c} R_2 \\ | \\ R_1C{=}NOH \end{array}} + \underset{V}{O{=}C(R)_2}$$

might be more unstable than a methyl nitronate ester due to more crowding of the ester portion of

the molecule by the α-carbon atoms and their hydrogen substituents. This might tend to weaken the bond and facilitate the decomposition of the nitronate ester (III). Since the model of the ethyl ester exhibited more crowding than the model of the methyl ester, this rationalization might explain the difference in product yields obtained by the alkylation of sodium *aci* nitrocyclopentane with the two oxonium salts. Difficulties of this nature were not present in models of the cyclohexyl homologs. Construction of models of cyclohexyl nitronate methyl and ethyl esters indicates that spatial relationships between the nitronate ester group and the rest of the molecule are present which might aid in weakening the bonds necessary to form the products of the reaction.

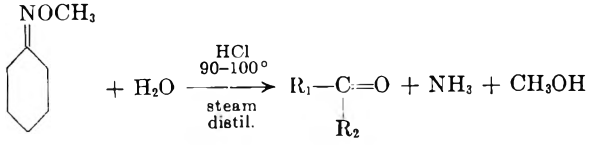
As stated earlier, oxime ethers (VII) are formed as by-products of the reaction. Some cyclohexanone oxime-*O*-alkyl ethers have been prepared previously by Hudlicky and Hokr[9] by alkylation of cyclohexanone oxime with dialkyl sulfates or alkyl halides. The properties of the cyclohexanone oxime-*O*-methyl and *O*-ethyl ethers (VII) obtained from the alkylation of nitronate salts of nitrocyclohexane were comparable with those formed by alkylation of cyclohexanone oxime. As a further means of proving the structure of the oxime ethers, cyclohexanone oxime-*O*-methyl ether was prepared by condensing cyclohexanone with methoxyamine hydrochloride.

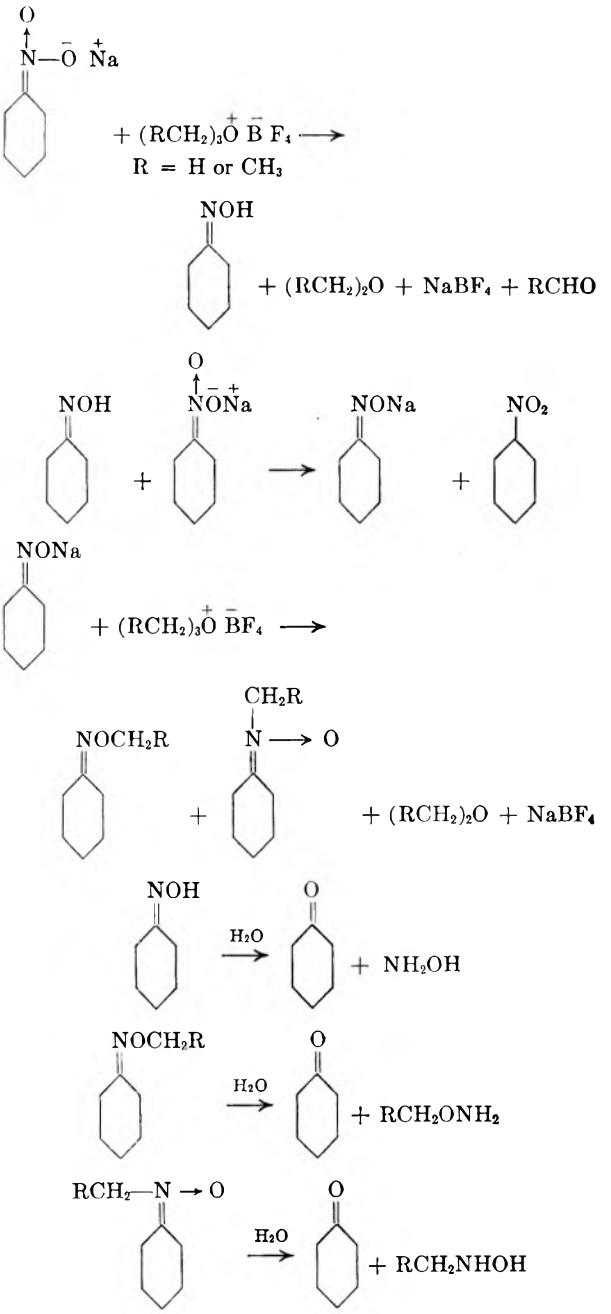


The infrared spectra of the *O*-methyl ethers prepared by the three methods were identical. The hydrobromide salts of the cyclohexanone oxime-*O*-methyl ether obtained from the nitronate salt (I) could be decomposed in water and titrated to give values of the neutral equivalent close to the theoretical value (211 observed; 208 calculated).

Cyclohexanone oxime-*O*-ethyl ether was characterized in a similar manner. Cyclopentanone oxime-*O*-alkyl ethers were present in reaction mixtures only in very small amounts. They were not characterized. However, the characteristic terpene-like odor of cycloalkanone oxime-*O*-alkyl ethers was always present.

The oxime-*O*-alkyl ethers (VII) appear to be very easily hydrolyzed by both acids and bases. It was possible to isolate cyclohexanone and ammonium chloride by hydrolysis of cyclohexanone oxime-*O*-methyl ether with hydrochloric acid. Samples of cyclohexanone oxime-*O*-methyl ether which were presumed to be pure showed an increase of carbonyl content (by infrared spectroscopy) upon standing. The removal of cyclohexanone from the crude cyclohexanone oxime-*O*-alkyl ethers (VII) obtained by distillation of the reaction mixtures was difficult. The ketone may have been present as a result of the hydrolytic decomposition of cyclohexanone oxime and/or one of its *O*-alkyl ethers or a cyclohexyl-*N*-alkyl nitrone.[10] Nitrones are known to be one of the products formed by the alkylation of oximes.[10]



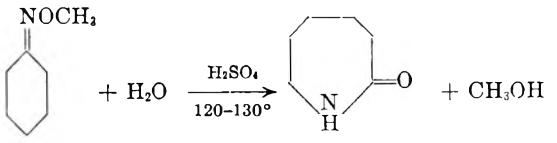


(9) M. Hudlicky and J. Hokr, *Collection Czechoslov. Chem Communs.*, **14**, 561 (1943).

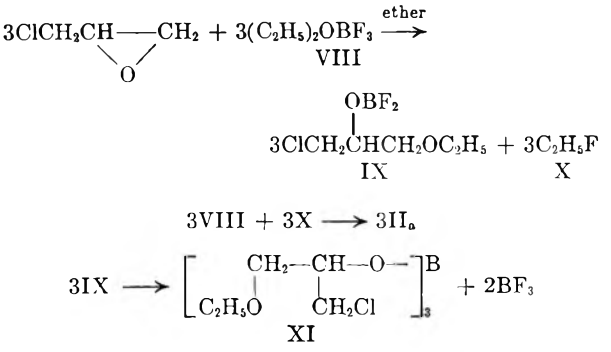
(10) L. I. Smith, *Chem. Revs.*, **23**, 194 (1938).

To purify a cyclohexanone oxime-*O*-alkyl ether it was necessary to wash the crude ether with a large excess of water prior to distillation.

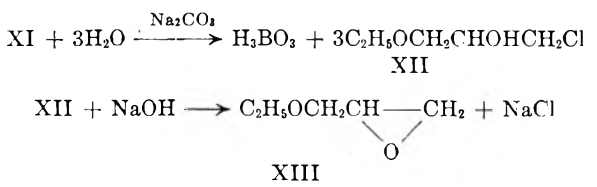
Cyclohexanone oxime-*O*-methyl ether was converted to ϵ-caprolactam by treatment with hot concentrated sulfuric acid.[9]



Meerwein[7,8] has described the preparation of oxonium salts (II) in some detail and formulated the reactions involved in the synthesis of triethyl oxonium fluoborate using epichlorohydrin as follows:



We were able to duplicate Meerweins[7,8] results. In addition, we were able to utilize the borate ester (XI) to prepare oxonium salts.



Epiethylin (XIII) could then be utilized in place of epichlorohydrin to prepare trialkyl oxonium salts.

EXPERIMENTAL

Oxonium salts (II). The oxonium salts used were prepared according to the directions of Meerwein.[7,8] The salts appeared to be stable for several months when stored under ether. The epoxide used to prepare the oxonium salts was epichlorohydrin except in the case where epiethylin (XIII) was prepared from by-products formed by using epichlorohydrin to prepare triethyl oxonium fluoborate.

Preparation of epiethylin (XIII). The preparation of 1.5 moles of triethyloxonium fluoborate from 140 g. (1.5 moles) of epichlorohydrin was carried out.[7,8] After removal of the oxonium salt by filtration, the ether was removed from the filtrate by distillation and the residue agitated with 100 ml. of saturated sodium carbonate solution and 100 ml. of water for 1 hr. At the end of this time, the mixture was extracted with ether and the extract washed with water and dried. The solvent was removed by distillation and the residue distilled under vacuum to yield 122 g. of 1-chloro-2-hydroxy-3-ethoxypropane (XII) (b.p.$_{14}$ 73°) and 22 g. of mixed borate esters (b.p.$_{10}$ 155°) derived from epichlorohydrin. Epiethylin was prepared from XII by the method of Flores-Gallardo and Pollard.[11] When epiethylin was employed to prepare triethyloxonium fluoborate (II$_a$) instead of epichlorohydrin, the yield of oxonium salt (II$_a$) was 80%.

Reaction of trialkyl oxonium salts (II) *with nitroparaffin aci salts* (I). The method can be best illustrated by describing the preparation of cyclohexanone oxime from sodium *aci* nitrocyclohexane. The departures from this procedure were by the addition of excess reagents (Table I) or where trimethyl oxonium fluoborate (II$_d$) was used as the alkylating agent and the quantity of water employed was reduced 50%.

Preparation of cyclohexanone oxime (IV). Twenty-five and eight-tenths grams (0.2 mole) of nitrocyclohexane was dissolved in 100 ml. of water containing 8.0 g. (0.2 mole) of sodium hydroxide by warming on a steam bath with good agitation. To this solution at 50–60° was added, in small portions, 38 g. (0.2 mole) of solid triethyl oxonium fluoborate (II$_a$). During the reaction, diethyl ether was liberated and refluxed very vigorously. When the addition was complete, the mixture was stirred 30 min. at 50°. The reaction mixture was cooled to room temperature and, if necessary, the *p*H was adjusted to 5. Enough sodium chloride was added to the reaction mixture to saturate the water and the mixture extracted with ether. The solvent was removed from the dry extract by distillation and the residue distilled under vacuum to yield 16.7 g. (74%) of cyclohexanone oxime (b.p.$_{10}$ 162°) and 5.4 g. (19%) of cyclohexanone oxime-*O*-ethyl ether (b.p.$_{10}$ 60°). The oxime ether was contaminated with small amounts of cyclohexanone. Cyclohexanone was also found in the cold trap. Fluoborate ion, which was present in the water, was isolated by precipitation as potassium fluoborate with potassium acetate.

The reaction products were characterized by comparison of their infrared spectra with the spectra of authentic specimens of the products.

Oxime-O-alkyl ethers (VII). For characterization purposes, cyclohexanone oxime-*O*-methyl ether and cyclohexanone oxime-*O*-ethyl ether were prepared by the method of Hudlicky and Hokr.[9]

In order to take the infrared spectra of the methyl and ethyl ethers, cyclohexanone had to be removed. This was accomplished by washing the ethers with water and drying the washed ethers with magnesium sulfate. The spectra of the *O*-methyl and *O*-ethyl cyclohexanone oxime ethers were then taken on a Perkin-Elmer Model 21 Spectrometer.

Condensation of cyclohexanone with methoxyamine. Twenty grams (0.24 mole) of methoxyamine hydrochloride was dissolved in 60 ml. of water. Twenty-grams (0.20 mole) of cyclohexanone was added to this solution dropwise with strong agitation. A water-insoluble liquid soon began forming in the reaction mixture. When the addition of cyclohexanone was complete, 80 ml. of 10% sodium hydroxide was added dropwise to the reaction mixture at 25°. The mixture was allowed to stir 30 min. at room temperature and extracted with ether. The extract was washed with water and dried. The solvent was removed from the extract by distillation to leave a residue of 24.2 g. (95%) of crude cyclohexanone oxime-*O*-methyl ether. The product was distilled under vacuum (b.p.$_{12}$ 50°). The product had an infrared spectrum identical with that of the cyclohexanone oxime-*O*-methyl ether prepared by the method of Hudlicky and Hokr[9] and to the material obtained by the reaction of sodium *aci* nitrocyclohexane with trimethyl oxonium fluoborate (II$_d$).

Preparation of ϵ-caprolactam from cyclohexanone oxime-O-methyl ether. Twenty-seven and six-tenths grams (0.22 mole) of cyclohexanone oxime-*O*-methyl ether was added slowly with stirring to 60 g. of 105% sulfuric acid. The temperature of the acid during the addition was held at 25° or below by external cooling. When the addition was com-

(11) H. Flores-Gallardo and C. B. Pollard, *J. Org. Chem.*, 12, 831 (1947).

plete, the acid mixture was added with stirring to 30 g. of 105% sulfuric acid at 120–130°. The hot acid solution was then allowed to stir at 120° for 10 min. The mixture was cooled in an ice bath and neutralized with concentrated ammonia at a temperature of 25° or below. One hundred milliliters of chloroform was added to the neutral mixture. After agitation for 10 min., the mixture was filtered and the filter cake washed with chloroform. The organic layer was separated, the aqueous phase extracted with chloroform, and the combined chloroform solution dried. The solvent was removed from the extract by distillation to leave 18.5 g. of crude semi-solid ϵ-caprolactam. The crude lactam was distilled under vacuum to yield 17 g. (68%) of ϵ-caprolactam (b.p.$_{10}$ 138°). The infrared spectrum of the product was identical with the spectrum of an authentic sample of ϵ-caprolactam.

WILMINGTON, DEL.

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

Some Reactions of 3,3-Bis(chloromethyl)oxetane

TOD W. CAMPBELL

Received January 2, 1957

The neopentyl type halides in bis(halomethyl)oxetanes are readily displaced by nucleophilic reagents. A number of such reactions have been studied, and the products characterized.

In comparison to the tremendous amount of research which has been devoted to a study of the chemistry of ethylene oxides, the chemistry of trimethylene oxides (oxetanes) has been overlooked under quite recently. Reviews of certain phases of earlier work have appeared[1] and in the past few years, a number of workers, notably Searles[2–8] have contributed to the field. In this paper some work carried out in these laboratories will be presented.

In general, the preparation of trimethylene oxides is carried out by removing the elements of HX from a 1,3-halohydrin, or better, a halohydrin acetate by treatment with alkali at elevated temperatures.[2,9–11] The yields may be poor because of competing elimination reactions, resulting in the formation of open chain, unsaturated derivatives.[2] If the central carbon atom is substituted with negative groups, for example with two chloromethyl groups,[12] the ring closure by alkali can be carried out at low temperatures, thus minimizing side reactions. A convenient source of an appropriately substituted trimethylene oxide which has been recognized[12] and exploited[13–15] recently is pentaerythritol. This inexpensive raw material reacts readily in glacial acetic acid with hydrogen chloride at elevated temperatures (ca. 160°) to give tris(chloromethyl) ethyl acetate in high yield:

$$C(CH_2OH)_4 + 3HCl + HOAc \xrightarrow[\text{solvent}]{HOAc} (ClCH_2)_3CCH_2OAc$$

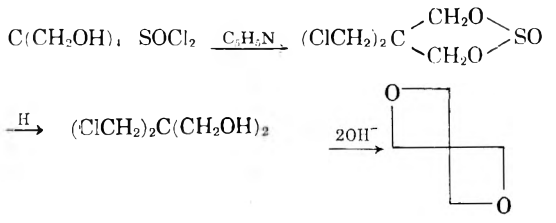
The corresponding bromo derivative may be made in the same fashion.

Ring closure in refluxing methanol with two equivalents of alkali yields the trimethylene oxide easily, despite the fact that the halogen displaced during ring closure is of the neopentyl type.[16]

The product, 3,3-bis(chloromethyl)oxetane, is quite stable under normal conditions, although it is quite sensitive to acidic reagents, and under proper conditions can be converted to a high molecular weight polyether, as reported by several workers.[13,14,17,18] We find the halogen atoms are surprisingly reactive[19] considering that they are still nominally neopentyl halides. They can be displaced by a variety of nucleophilic reagents under mild conditions. This enhanced reactivity undoubtedly arises from the altered geometry of the

(1) S. F. Marrian, *Chem. Revs.* **43**, 149 (1948).
(2) S. Searles and M. J. Gortakowski, *J. Am. Chem. Soc.*, **75**, 3030 (1953).
(3) S. Searles and V. F. Butler, *J. Am. Chem. Soc.*, **76**, 56 (1954).
(4) S. Searles, M. Tamres, and E. R. Lippincott, *J. Am. Chem. Soc.*, **75**, 2775 (1953).
(5) S. Searles and V. P. Gregory, *J. Am. Chem. Soc.*, **76**, 2789 (1954).
(6) S. Searles, *J. Am. Chem. Soc.*, **76**, 2313 (1954).
(7) H. S. Gutowsky, R. L. Rutledge, M. Tamres, and S. Searles, *J. Am. Chem. Soc.*, **76**, 4242 (1954).
(8) S. Searles and M. Tamres, *J. Am. Chem. Soc.*, **73**, 3704 (1951).
(9) C. Derick and D. D. Bissell, *J. Am. Chem. Soc.*, **38**, 2485 (1916).
(10) G. Bennett and W. Philip, *J. Chem. Soc.*, 1938 (1928).
(11) J. Rose, *J. Chem. Soc.*, 542, 546 (1956).
(12) F. Govaert and M. Beyaert, *Natuurw. Tijdschr Belg.*, **22**, 73 (1940).
(13) A. C. Farthing and W. J. Reynolds, *J. Polymer Sci.*, 12, 503 (1954).
(14) A. C. Farthing, *J. Chem. Soc.*, 3648 (1955).
(15) H. K. Boardman, paper presented before Delaware section of the AMERICAN CHEMICAL SOCIETY, Symposium Feb. 18, 1956.
(16) S. Winstein and R. B. Henderson, *Heterocyclic Compounds*, Vol. 1, R. Elderfield, ed., J. Wiley and Sons, Inc., New York, 1950, p. 60.
(17) U.S. Patents **2722340, 2722492, 2722493, 2722520**, issued Nov. 1, 1955 and assigned to Hercules Powder Co.
(18) British Patent **723,777** assigned to Imperial Chemical Industries.
(19) Compare Ref. 14.

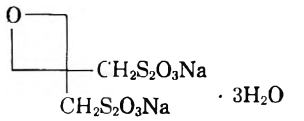
quaternary carbon atom, imposed by the four membered ring, which should force the halogen atoms into a more available position in space, where they may be displaced more easily.[20] Despite this reactivity, it becomes more difficult to close a second ring onto the first; thus pentaerythritol dichloride[21] prepared by the acid hydrolysis of its cyclic sulfite,[21c] yields only small amounts of dioxaspiroheptane[22] under similar conditions.



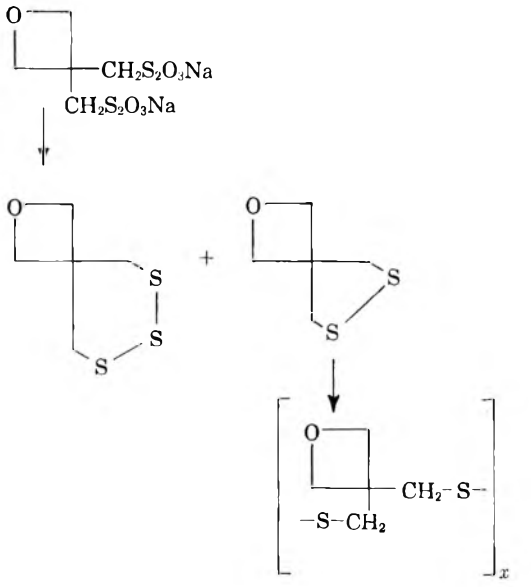
In the present study, a number of displacements have been carried out on bischloromethyloxetane without disrupting the oxetane ring. Thus with iodide ion, cyanide ion, and liquid ammonia the previously reported 3,3-bis(iodomethyl)oxetane,[12] 3,3-bis(cyanomethyl)oxetane,[23] and 3,3-bis(aminomethyl)oxetane[24] were prepared. The physical constants reported in *Chemical Abstracts* for 3,3-bis(aminomethyl)oxetane do not agree with the values we have observed, hence, the preparations are described in the Experimental Section. The diamine was further characterized by the preparation of derivatives with benzoyl chloride and phenyl isocyanate, and a study of the infrared spectra of the compounds.

With thiocyanate ion, it was found possible to isolate from the reaction mixture (preferably in acetone) both the mono and the dithiocyano derivatives. The former was a liquid, the latter a well-defined crystalline solid. The reaction mixture tended to polymerize spontaneously to dark, undefined solid tars during preparation.

Sodium thiosulfate reacted rapidly with 3,3-bis(chloromethyl)oxetane in aqueous ethanol to give a good yield of a crystalline, water soluble di-Bunte salt (I) which crystallized from 85% ethanol with 3 molecules of water of crystallization.

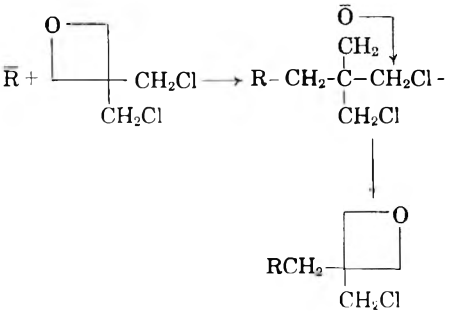


The di-Bunte salt (I) was hydrolyzed under different conditions and the products isolated. Two substances were obtained: The first, a colorless, crystalline material, was probably 2,3,4-trithia-8-oxaspiro[5,5]nonane, produced by reaction of the intermediate dithio compound with sulfur produced in the acid hydrolysis of excess sodium thiosulfate.[25] The other product, a yellow oil, stable in benzene solution, polymerized on distillation to a rubbery polymer, probably a linear polymeric disulfide such as that obtained from trimethylene disulfide.[26,27]



Reaction of 3,3-bis(chloromethyl)oxetane with sodium sulfide or thiourea under a variety of conditions gave 2-oxa-6-thiaspiroheptane, which was

(20) An alternative mode of displacement would involve a cyclic mechanism, in which the *ring* is attacked by the entering group, displacing —Ō, which then eliminates the halogen:



The net result would be the same.

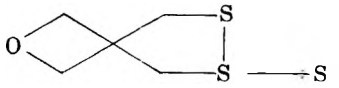
(21) (*a*) A. Mooradian and J. B. Cloke, *J. Am. Chem. Soc.*, **67**, 942 (1945). (*b*) H. Rapoport, *J. Am. Chem. Soc.*, **68**, 341 (1946). (*c*) H. Pietsch and H. Nagel, German Patent 875,804.

(22) H. J. Backer and K. J. Kenning, *Rec. trav. chim.*, **53**, 812 (1934).

(23) R. Fonteyn, P. Cornand, and M. Ticket, *Natuurw. Tijdschr.* **25**, 67 (1943).

(24) M. Beyaert and F. Govaert, *Proc. Acad. Sci. Amsterdam*, **42**, 776 (1939) [*Chem. Abstr.*, **34**, 5414 (1940)].

(25) A stucture such as

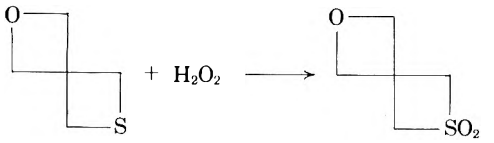


cannot be ruled out.

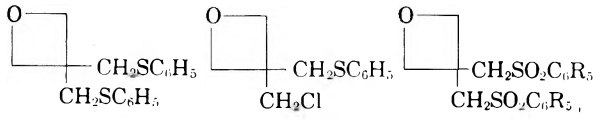
(26) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Am. Chem. Soc.*, **76**, 4348 (1954).

(27) J. A. Affleck and A. Dougherty, *J. Org. Chem.*, **15**, 865 (1950).

oxidized with hydrogen peroxide to an unusual cyclic sulfone.

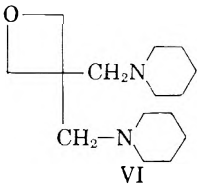


Sodium thiophenolate reacted rapidly with 3,3-bis(chloromethyl)oxetane to give both 3,3-bis-(phenylthiomethyl)oxetane (II), and 3-chloromethyl-3-phenylthiomethyloxetane (III). The former was oxidized with hydrogen peroxide in acetic acid to the crystalline disulfone (IV).



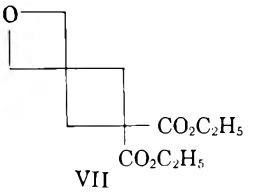
II III IV

Similarly, piperidine gave bispiperidinomethyloxetane VI, which yielded a crystalline dipicrate.



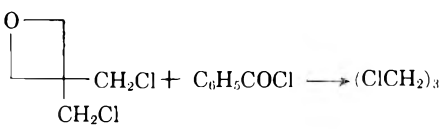
VI

Sodiomalonic ester was allowed to react with bischloromethyloxetane under a variety of conditions. It is interesting to note that even under conditions specifically designed to favor monoalkylation, the internal displacement is so favored[28] that the only product isolated was 2,2-biscarboxyethyl-5-oxaspiroheptane (VII).



VII

It was observed earlier[9] that trimethylene oxide itself reacts explosively with acetyl chloride to give *gamma*-chloropropyl acetate. Similarly, bischloromethyloxetane and bisbromomethyloxetane react readily with benzoyl chloride or benzoyl bromide to give respectively *β,β,β*-trischloromethylethylbenzoate and *β,β,β*-trisbromomethylethylbenzoate.

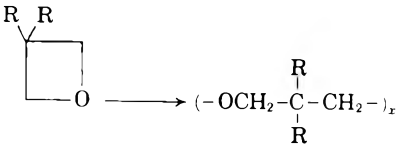


(28) This is to be expected from the work of Cason and Allen, *J. Org. Chem.*, **14**, 1036 (1949), on the reaction of trimethylene dibromide and sodiodiethylmalonate.

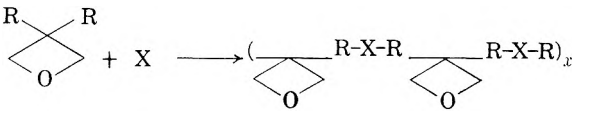
This reaction probably proceeds by a nucleophilic attack of the oxide ring on the acid chloride. The similarity of this reaction to the reaction of acid halides with aldehydes[29,30] and epoxides[31] to give haloesters is noteworthy.

POLYMERS FROM OXETANES

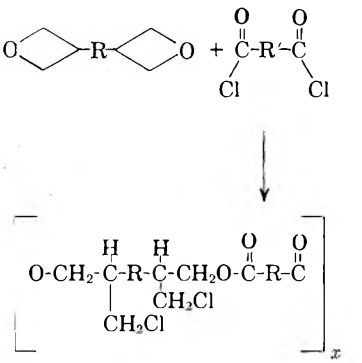
Three ways can be visualized for the conversion of oxetanes to polymers. In the first, a Lewis acid catalyst opens the trimethylene oxide ring to give a linear polyether.[13-15]



In the second, a reactive group R on the oxetane nucleus is caused to condense with a second difunctional molecule X.



In the third, a diacid chloride is added to a bisoxetane to give a polyester.



In the first category, the most interesting example is the polymer from 3,3-bis(chloromethyl)oxetane, described in detail in the recent literature by Farthing and Reynolds[13,14] and by Boardman.[15] Polymers of this type which have not been described in the literature previously have been prepared, in the hope of finding some other useful and unique polymers. Thus 3,3-bis(bromomethyl)oxetane gave a polymer with a melting point in the range of 220°, while 3,3-bis(iodomethyl)oxetane gave a polymer *stable up to its melting point* (290°) which was unusual in that it was 75.2% by weight iodine. In addition, 2-oxa-5-thiaspiro-(3,3)heptane-5,5-dioxide and 3,3-bis(phenylthiomethyl)oxetane di-

(29) R. Adams and E. H. Volweiler, *J. Am. Chem. Soc.*, **40**, 1732 (1918).

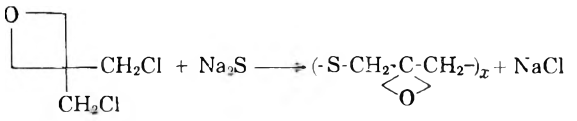
(30) H. E. French and R. Adams, *J. Am. Chem. Soc.*, **43**, 657 (1921).

(31) E. L. Gustus and P. G. Stevens, *J. Am. Chem. Soc.*, **55**, 374 (1933).

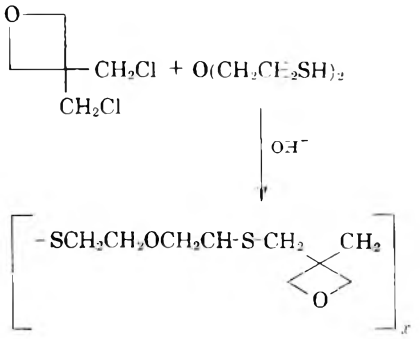
sulfone gave polymers by ring-opening polymerization and 2,5-dioxaspiroheptane gave an infusible, cross-linked polymeric powder.

Copolymers of 3,3-bis(chloromethyl)oxetane and 3,3-bis(iodomethyl)oxetane were prepared. These showed a minimum melting point at a composition corresponding to about 85 mole % of 3,3-bis(chloromethyl)oxetane.

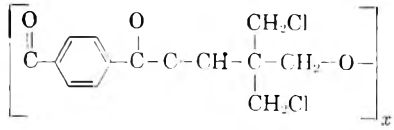
Polymers which were presumably of the second type were obtained as by-products of the reaction of 3,3-bis(chloromethyl)oxetane and sodium sulfide:



They were viscous oils which cross-linked when treated with boron fluoride etherate. A similar, low-molecular weight oil was obtained from 3,3-bis(chloromethyl)oxetane and bis(mercaptoethyl)ether:



Polymers of the third type were investigated only briefly. Thus terephthaloyl chloride and 3,3-bis(chloromethyl)oxetane gave a polymer presumed to be



It was, however, cross-linked, and contained less than the calculated amount of chlorine.

INFRARED SPECTRA OF OXETANES

All of the compounds described in this article as being oxetane derivatives have been examined in the infrared. The position of the characteristic bands are shown in Table 1. Previous workers[32] have observed bands characteristic of oxetanes at about 8.1 and 10.2 μ. The intense 10.2 μ band showed up consistently as might be expected from its assignment as an antisymmetric stretching vibration. A splitting of this band may be observed with KBr pellet spectra. There was also usually a weaker, less definite band at 10.5–10.6 μ. The 8.1 μ band, which has been assigned to a methylene wagging motion[32] seems rather variable, and was at times obscured. It is therefore not considered to be a reliable criterion of structure.

(32) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

EXPERIMENTAL

Preparation of 3,3-bis(chloromethyl)oxetane.[12-15] This compound was made by the action of alkali in refluxing methanol on pentaerythritol trichlorohydrin acetate, which was obtained by the action of gaseous hydrogen chloride on pentaerythritol in acetic acid at 100°. Bis(chloromethyl)-oxetane boiled at 101°/27 mm., 65°/5 mm.

Preparation of 3,3'-bis(bromomethyl)oxetane.[12] This substance was made in the same way as the bischloro compound. It boiled at 125°/23 mm.

Anal. Calcd. for $C_5H_8OBr_2$: C, 24.62; H, 3.30. Found: C, 24.67, 24.85; H, 3.28, 3.58.

Bis(bromomethyl)oxetane was polymerized in a manner similar to that described in the literature for the bischloro compound.[13-17] The product was a solid melting at about 220°.

Anal. Calcd. for $(C_5H_8OBr_2)_n$: C, 24.62; H, 3.30. Found: C, 24.98, 25.04; H, 3.28, 3.58.

Preparation of 3,3-bis(iodomethyl)oxetane.[12] A mixture of 15.5 g. of 3,3-bis(chloromethyl)oxetane, 150 cc. of methyl ethyl ketone and 35 g. of dry sodium iodide was refluxed for 24 hr. The solution was cooled, filtered, and the solvent partially removed by distillation. The residue solidified on standing and was recrystallized from cyclohexane. The yield was 30 g. (89%) of coarse, colorless, very dense crystals with a melting point of 50°.

Anal. Calcd. for $C_5H_8OI_2$: C, 17.75; H, 2.37. Found: C, 17.97, 18.09; H, 2.41, 2.40.

The polyether, prepared as described under the bisbromo derivative, melted at 290° with decomposition. However, it was stable up to this temperature.

Anal. Calcd. for $(C_5H_8OI_2)_n$: C, 17.75; H, 2.37. Found: C, 17.87, 17.84; H, 2.24, 2.28.

Copolymers of 3,3-bis(iodomethyl)oxetane and 3,3-bis(chloromethyl)oxetane. A series of copolymers of these two monomers, prepared in quantitative yields by polymerizing various mixtures of the monomers as in preceding experiments, is described in Table II.

TABLE II

COPOLYMERS OF BIS(IODOMETHYL)OXETANE AND BIS(CHLOROMETHYL)OXETANE

Molar Ratio Cl_2 monomer / I_2 monomer	M.P.	Observed Analysis C	Observed Analysis H	Analysis Calcd. on Basis of Monomer Ratio C	Analysis Calcd. on Basis of Monomer Ratio H
3.05 / 1.00	163°	29.94 30.39	4.12 4.05	30.0	4.0
1.02 / 2.00	240°	21.81 21.90	2.92 2.90	21.7	2.9
2.00 / 1.00	185°	28.11 28.18	3.88 3.98	27.8	3.7
1.08 / 1.00	210°	24.88 25.00	3.57 3.66	24.8	3.3

Preparation of 3,3-bis(cyanomethyl)oxetane. A mixture of 10 g. of 3,3-bis(chloromethyl)oxetane, 7 g. of sodium cyanide, and 25 ml. of 95% ethanol was refluxed for 24 hr. The dark brown mixture was filtered hot and the filtrate was then

cooled in ice. The crystalline product was filtered, dried, and recrystallized from benzene. The pure 3,3-bis(cyanomethyl)oxetane melted at 76.5° and was obtained in about 40% yield. 3,3-Bis(cyanomethyl)oxetane is soluble in water, insoluble in ether and petroleum ether, soluble in hot benzene and cold methylene chloride.

Anal. Calcd. for $C_7H_8ON_2$: C, 61.76; H, 5.92; N, 20.51. Found: C, 62.01, 62.33; H, 6.08, 5.99; N, 20.31, 20.19.

It was polymerized to low molecular weight oils by ionic catalysts.

Reaction of sodiomalonic ester with 3,3-bis(chloromethyl)-oxetane. Sodiomalonic ester was prepared from 53 g. of malonic ester, 7.6 g. of sodium, and 200 ml. of ethyl alcohol. This mixture was added dropwise with stirring and refluxing to 50 g. of 3,3-bis(chloromethyl)oxetane mixed with 100 g. of excess malonic ester and 100 ml. of ethyl alcohol. The reaction mixture was worked up as above and distilled from a simple Claisen Flask rapidly to minimize thermal decomposition. The desired product was obtained at about 120° at 3 mm. This temperature is probably not reliable, however, because the distillation was carried out quite rapidly. The distillate weighed 63 g. and consisted of the tailings of malonic ester as well as the spiro condensation product. This material was fractionated through a spinning band column to give 31 g. of product, boiling point 105–107°/1.1 mm.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.47; H, 7.49; Cl, 0.0. Found: C, 58.9, 58.9; H, 7.16, 7.03; Cl, 0.0, 0.0.

Reaction of 3,3-bis(chloromethyl)oxetane with liquid ammonia.[12] Fifty grams of 3,3-bis(chloromethyl)oxetane was mixed with 250 ml. of liquid ammonia in a stainless steel bomb and heated at 80° for 8 hr. The bomb was cooled to room temperature, the excess ammonia was carefully vented, and the solid product was removed from the reaction vessel. The white crystalline solid consisted of a mixture of ammonium chloride and the mono-hydrochloride of 3,3-bis(aminomethyl)oxetane. The mixture was dissolved in 50% aqueous methanol and sufficient hydrogen chloride was added to convert the diamine monohydrochloride to the dihydrochloride. The solution was cooled and the solid crystalline product was filtered. It was then recrystallized twice from aqueous methanol. The product, 3,3-bis(aminomethyl)-oxetane dihydrochloride, was obtained in large, coarse, non-hygroscopic crystals, stable up to the melting point of 249°. The yields ran from 55 to 75%.

Anal. Calcd. for $C_5H_{12}ON_2{\cdot}2HCl$: C, 31.75; H, 7.46; N, 14.71. Found: C, 31.77, 31.47; H, 7.10, 7.45; N, 14.73, 14.87.

Liberation of free 3,3-bis(aminomethyl)oxetane from its dihydrochloride. The free diamine was prepared by treating the dihydrochloride with saturated potassium carbonate solution. The mixture was then separated and distilled rapidly. The diamine was obtained as a thick liquid, b.p. 97–99°/2 mm.; 71°/0.5 mm., 90°/1.5 mm. Redistillation through a spinning band column gave constant boiling material, b.p. 75.5/0.5 mm.

Anal. Calcd. for $C_5H_{12}ON_2$: C, 51.64; H, 10.41. Found: C, 51.46, 51.49; H, 10.20, 10.31.

3,3-Bis(benzamidomethyl)oxetane. The diamine was dibenzoylated by the usual Schotten-Bauman procedure. The solid product was filtered, washed, and dried. The solid was nearly pure as shown by its analysis. The dibenzamide was difficult to recrystallize, since it came out of most solvents as a gum. It was finally dissolved in ethyl acetate, treated with Norite, and filtered. The filtrate was placed in the refrigerator at −20° for one week. The crystals were filtered and dried, m.p. 168–169°.

Anal. Calcd. for $C_{19}H_{20}O_3N_2$: C, 70.34; H, 6.21. Found: C, 70.03, 70.05; H, 6.47, 6.40.

Reaction of 3,3-bis(aminomethyl)oxetane with phenylisothiocyanate. One gram of the diamine in dimethyl formamide (15 ml.) was mixed with 2 g. of phenylisothiocyanate in 15 ml. of the same solvent. The mixture became warm. After one hour it was poured into water and the solid was filtered. The solid was recrystallized from ethanol, m.p. 164–165°.

Anal. Calcd. for $C_{19}H_{22}OS_2N_4$: C, 59.07; H, 5.73. Found: C, 59.25, 59.09; H, 6.11, 6.36.

2,6-Dioxaspiro[3,3]heptane.[21] Dichloropentaerythritol[21] was made in over-all yields of above 80% by the conversion of pentaerythritol to the dichlorocyclic sulfite[22] followed by acid hydrolysis in aqueous methanol. A mixture of 50 g. of pentaerythritol dichloride, 48 g. of potassium hydroxide, and 200 ml. of 95% ethanol was refluxed 6 hr. and then allowed to stand at room temperature overnight. The mixture was brought to pH 7 with dilute hydrochloric acid and filtered. The filtrate was distilled through a spinning band column at atmospheric pressure. In this manner 10 g. of 2,6-dioxaspiro[3,3]heptane was obtained as a crystalline solid boiling at 170–172°. It was recrystallized twice from hexane to give a white crystalline solid melting sharply at 90°.

Anal. Calcd. for $C_5H_8O_2$: C, 60.06; H, 8.06. Found: C, 60.02, 59.85; H, 8.22, 8.26.

Polymerization with boron fluoride etherate gave a white, infusible, insoluble cross-linked polyether.

Reaction of 3,3-bis(chloromethyl)oxetane with sodium thiosulfate. A mixture of 99 g. (0.4 mole) of sodium thiosulfate pentahydrate in 100 ml. of water and 31 g. (0.2 mole) of bis(chloromethyl)oxetane in 150 ml. of ethanol was refluxed with stirring overnight. Two liquid phases of about equal volume were present initially, but merged to one after about 1–2 hr. refluxing, indicating that the reaction was probably complete. The reaction mixture was diluted with an equal volume of alcohol, and allowed to stand overnight again. The fine needle-like crystals were filtered and dried. The solid was boiled with 85% ethanol, which dissolved most of the product. The hot solution was filtered, and allowed to cool. After several hours, the needle-like crystals were filtered, recrystallized once more from the minimum amount of 85% ethanol and dried at room temperature. The yield was 57 g.

Anal. Calcd. for $C_5H_8O_6S_4Na_2{\cdot}3H_2O$: C, 15.32; H, 3.5; S, 32.5. Found: C, 15.61, 15.58; H, 3.1, 3.0; S, 31.1, 31.1.

In another experiment 15.5 g. of 3,3-bis(chloromethyl)-oxetane was dissolved in 150 ml. of ethanol and 49.6 g. of sodium thiosulfate pentahydrate in 30 ml. of hot water was added. This two-phase mixture was heated gently until the two layers became one. The mixture was then refluxed for an additional 48 hr. in the presence of a trace of dilute acid. Water was added and the oily precipitate was extracted into chloroform. Distillation of the chloroform gave about equal amounts of 3,3-bis(chloromethyl)oxetane, b.p., 6.52° at 2.5 mm. and a yellowish crystalline compound, b.p. 115–120° at 2.5 mm. This latter material was recrystallized twice from methylene chloride-hexane mixture. The product was a colorless crystalline compound melting at 90–91°.

Anal. Calcd. for $C_5H_8OS_3$: C, 33.30; H, 4.47; S, 53.36. Found: C, 33.52, 33.62; H, 4.55, 4.79; S, 53.9, 54.0.

The recrystallized di-Bunte salt was hydrolyzed by refluxing with dilute hydrochloric acid. The bright yellow product was extracted into dichloromethane and distilled. The distillate was a bright yellow liquid, b.p. 100–110°/2.5 mm. However, it could not be isolated since it polymerized rapidly in the receiving vessel to a rubbery polymer.

Reaction of 3,3-bis(chloromethyl)oxetane with sodium thiocyanate. A mixture of 20 g. of sodium thiocyanate and 250 ml. of acetone was heated to boiling to give a homogeneous solution. To this solution was added 31 g. of bis(chloromethyl)oxetane in an additional 100 ml. of acetone. The mixture rapidly assumed a yellow color which did not change with time. The mixture was refluxed over the weekend after which the precipitated sodium chloride was filtered. The filtrate was distilled to yield two compounds, after removal of the residual solvent and unreacted bis(chloromethyl)oxetane. The first (5.9 g.) b.p. 115°/1.5 mm., n_D^{25} 1.5298 was 3-chloromethyl-3-thiocyanomethyloxetane.

Anal. Calcd. for C_6H_8OSNCl: N, 7.88. Found: N, 7.60, 7.65.

The second, a solid (2.5 g.) pot residue, was recrystallized twice from absolute ethanol, using decolorizing carbon.

The product was obtained readily in the form of fine needles, m.p. 81.8–82.1.°

Anal. Calcd. for $C_7H_8OS_2N_2$: C, 42.0; H, 4.0; N, 14.0. Found: C, 42.0, 42.0; H, 4.0, 3.9; N, 13.8, 13.9.

Using a higher ratio of thiocyanate to oxetane, 6.3 g. of pure dithiocyano compound was obtained from 15.5 g. of 3,3-bis(chloromethyl)oxetane. Attempts to distil the dithiocyanate caused it to polymerize spontaneously to a dark tar. This tar also formed occasionally during the initial reaction with sodium thiocyanate in acetone, for no apparent reason, usually with such vigor as to eject the contents of the flask through the condenser.

Reaction of 3,3-bis(chloromethyl)oxetane with sodium thiophenoxide. A mixture of 31 g. of 3,3-bis(chloromethyl)oxetane, 200 ml. of absolute ethanol, and 11 g. of thiophenol was treated with a solution of 2.3 g. of sodium in 50 ml. of ethyl alcohol. The mixture was refluxed and stirred for 3 hr. at which time the solution was neutral. The precipitated sodium chloride was filtered and the filtrate was distilled. After a forerun of about 11 g. consisting of unreacted bis(chloromethyl)oxetane, the main product, 3-chloromethyl-3-phenylthiomethyloxetane was obtained, b.p. 144°/1.3 mm. The yield was 23 g.

Anal. Calcd. for $C_{11}H_{13}OSCl$: C, 57.6; H, 5.68. Found: C, 58.0, 57.8; H, 5.6, 5.7.

The undistillable pot residue appeared to be 3,3-bis(phenylthiomethyl)oxetane.

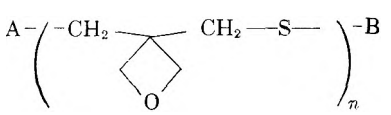
Anal. Calcd. for $C_{17}H_{18}OS_2$: S, 21.2.

Found: S, 21.08, 21.56, 21.30.

In another experiment employing a different ratio of reactants, 15.5 g. of bis(chloromethyl)oxetane was allowed to react with 22 g. of thiophenol in the presence of 4.6 g. of sodium in a manner described above. After 3 hr. the mixture was filtered and volatile materials removed. The pot residue which was a light straw-colored, viscous liquid was taken into 100 ml. of acetic acid and the mixture was filtered. Fifty ml. of 30% hydrogen peroxide was added to the acetic acid solution and the exothermic reaction was controlled by external cooling. After 3 hr. at room temperature the mixture was heated for an additional 2 hr. on a steam bath, then poured into water. The heavy oil which precipitated soon crystallized. The solid was filtered and dried. It was recrystallized from boiling ethyl alcohol to give 19.5 g. of product melting at 154–157°. An additional 8.5 g. of product melting at 140–147° was obtained from the filtrate by concentration. This product had a mixed melting point with the first fraction of 144–150°. Recrystallization of the first fraction from absolute ethanol gave a product melting at 159–159.5°.

Anal. Calcd. for $C_{17}H_{18}O_5S_2$: C, 55.8; H, 4.91; S, 17.46. Found: C, 56.2, 56.5; H, 4.9, 5.0; S, 17.47, 17.41.

2-Oxa-6-thiaspiro[3.3]heptane. A mixture of 38 g. of 3,3-bis(bromomethyl)oxetane, 38 g. of $Na_2S \cdot 9H_2O$, and 100 ml. of 95% ethanol was refluxed for 24 hr. and then cooled. Several grams of white solid which was incompletely soluble in water was filtered. This product was insoluble in alcohol, acetone, and ether but was soluble in chloroform. It was considered to be mainly



of unknown chain length and end groups.

Anal. Found: C, 45.33, 45.37; H, 6.23, 6.23; S, 21.3, 21.4, 21.2.

None of the desired spiro[3,3]heptane could be obtained from the nonpolymeric fraction.

Metallic sodium (11.5 g.) was added under nitrogen to 500 cc. of absolute ethanol. Hydrogen sulfide was passed into this solution until no more was absorbed. At this point another 11.5 g. of sodium was added. To the resulting solution of sodium sulfide was added 77.5 g. of bis(chloromethyl)oxetane and the mixture was refluxed for 24 hr. The reaction was stopped and the precipitate was filtered. The precipitate was washed repeatedly with ether and the combined filtrates were distilled, giving 10.3 g. (20%) of 2-oxa-6-thiaspiro[3.3]heptane, b.p. 60°/3 mm.

Anal. Calcd. for C_5H_8OS: S, 27.5. Found: S, 26.9, 26.3.

The filter cake, which was similar to that obtained above, was leached with water and dried at 90° at 1 mm. The solid polymer was broken up and extracted in a Soxhlet extractor with methylene chloride. The undissolved portions, consisting of approximately half of the total, was organic since it burned completely. However, it was infusible at 350°. The methylene chloride extract was evaporated to remove the solvent and was dried at 1 mm. The product was a very viscous oil which on standing became a wax. Solutions in methylene chloride on treatment with boron trifluoride etherate immediately gave insoluble, infusible polymer.

Anal. Found: C, 45.15, 45.27; H, 6.69, 6.81; S, 25.9, 25.9, 26.2.

2-Oxa-6-thiaspiro[3.3]heptane-6,6-dioxide. A sample of oxathiaspiroheptane, weighing 7.5 g., was treated with a mixture of 12.5 g. of 30% hydrogen peroxide and 12 ml. of glacial acetic acid. An exothermic reaction occurred which was moderated with ice water. When the reaction was complete, the residue was evaporated to dryness, recrystallized twice from methanol, and once from toluene. The product was obtained in a yield of 4.7 g. with a melting point of 161–162°.

Anal. Calcd. for $C_5H_8O_2S$: C, 40.54; H, 5.44. Found: C, 40.32, 46.62; H, 5.37, 5.46.

Polymerization of 2-Oxa-6-thiaspiro[3.3]heptane-6,6-dioxide. A sample of monomer weighing 1.90 g. was dissolved in about 5 ml. liquid sulfur dioxide at −50°. The solution was treated with a trace of BF_3 catalyst and allowed to stand overnight without external cooling. Next day the solid polymer was ground with alcohol and dried. The polymer melted at about 220°.

Anal. Calcd. for $(C_5H_8O_3S)_x$: C, 40.54; H, 5.40; S, 21.6. Found: C, 39.56, 39.60; H, 5.42, 5.40; S, 20.9, 20.8, 21.1.

The rather poor analyses reported above were probably the result of unknown end groups. The polymer was not of very high molecular weight.

Condensation of 3,3-bis(chloromethyl)oxetane and β,β'-dimercaptodiethyl ether. Ten grams of the dithiol and 11.2 grams of 3,3-bis(chloromethyl)oxetane were mixed with 25 ml. of 80% ethyl alcohol, treated with excess alkali, and refluxed under N_2. After 3 hr., the mixture was diluted with cold water and extracted with methylene chloride. This was in turn extracted with water, then dried and evaporated. The gummy residue was rubbed with methanol and the methanol extract was discarded. This procedure was repeated twice and the methanol-insoluble residue was dried in a high vacuum over P_2O_5.

Anal. Found: S, 28.0, 28.0, 27.9; Mol. wt. 1200 (ebullioscopic in benzene).

Reaction of piperidine with 3,3-bis(chloromethyl)oxetane. A mixture of 15.5 g. of 3,3-bis(chloromethyl)oxetane and 34 g. of piperidine was heated on a steam bath without solvent for 20 hr. The crystalline mush so obtained was treated with alkali and the liberated amines were taken into benzene. The benzene layer was washed with water, dried, and distilled. After considerable forerun the desired product, 3,3-bis(piperidinomethyl)oxetane was obtained in a yield of 8 g. with a b.p. 145°/3 mm.

Anal. Calcd. for $C_{15}H_{28}ON_2$: C, 71.39; H, 11.18; N, 11.09. Found: C, 71.49, 71.72; H, 10.81, 11.42; N, 10.59, 10.81.

A dipicrate, m.p. 180–185°, was prepared by mixing alcoholic solutions of picric acid and the diamine.

Anal. Calcd. for $C_{27}H_{34}O_{15}N_8$: N, 15.6. Found: N, 15.45, 15.90.

Reaction of 3,3-bis(chloromethyl)oxetane with benzoyl chloride. A mixture of 0.5 g. of 3,3-bis(chloromethyl)oxetane and 0.45 g. of benzoyl chloride was warmed at 110° for 16 hr. in a stoppered tube. The product, which solidified on

cooling, was recrystallized from aqueous methanol, then from hexane. The yield was 0.86 g. of fine needles, melting point 77°.

Anal. Calcd. for $C_{12}H_{13}O_2Cl_3$: C, 48.76; H, 4.43. Found: C, 49.08, 48.83; H, 4.34, 4.45.

An authentic specimen of β,β,β-tris(chloromethyl)ethyl benzoate was prepared by benzoylating pentaerythritol trichloride with benzoyl chloride and pyridine. The product was recrystallized from hexane and had a melting point of 77° which was not depressed by a mixture of the reaction product of benzoyl chloride with 3,3-bis(chloromethyl)oxetane.

Reaction of bis(bromomethyl)oxetane with benzoyl bromide. Benzoyl bromide (3.70 g.) was added to 4.88 g. of 3,3-bis(bromomethyl)oxetane. Reaction was rapid and exothermic in contrast to the slow reaction of benzoyl chloride reported above. β,β,β-Tris(bromomethyl)ethyl benzoate was obtained in a yield of 77% after recrystallization from hexane, m.p. 99.5–100°.

Anal. Calcd. for $C_{12}H_{13}O_2Br_3$: C, 33.58; H, 3.05. Found: C, 33.77, 33.73; H, 3.10, 3.12.

Condensation of terephthaloyl chloride with 2,5-dioxaspiro heptane. Equivalent amounts of terephthaloyl chloride (0.2 g.) and dioxaspiroheptane (0.1 g.) were mixed and the mixture was heated at about 150° for several hours. The reaction mixture gradually thickened and finaly solidified. The final product appeared to be cross-linked since it was not soluble in any solvents tested. Residual monomer was removed by swelling the polymer with dimethyl formamide. The swollen polymer was then triturated with ethanol and the resulting powder was washed repeatedly with more ethanol.

Anal. Calcd. for $(C_{13}H_{12}O_4Cl_2)_n$: Cl, 23.4. Found: Cl, 17.9, 18.2.

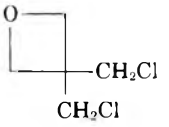
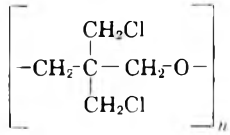
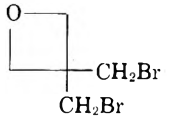
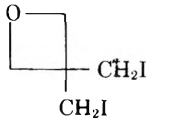
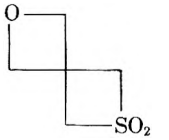
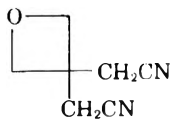
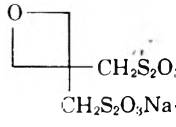
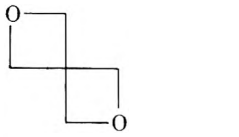
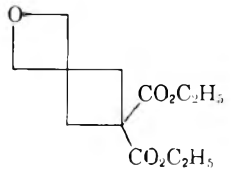
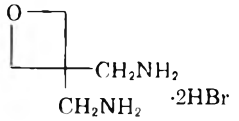
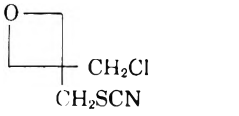
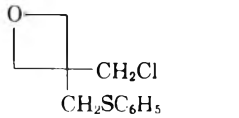
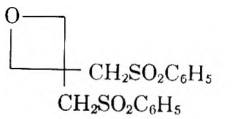
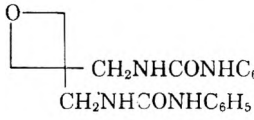
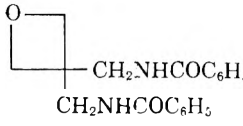
The same reaction was carried out in nitrobenzene solution at 150°. The solution rapidly became thick and finally set to a stiff gel in approximately 0.5 hr. The polymer was washed free of solvent and unreacted monomer as in the preceding experiment.

Anal. Calcd. for $(C_{13}H_{12}O_4Cl_2)_n$: C, 51.5; H, 3.96. Found: C, 52.60, 52.52; H, 4.12, 4.25.

WILMINGTON, DEL.

TABLE I

INFRARED BAND CHARACTERISTIC OF OXETANE RING

Structure Assigned to Compound	Position of Characteristic Band, μ	Remarks
	10.15 10.48	Band at 8.1 μ.
	9.0 (broad)	Measured as thin film. Bands at 10.15 and 10.48 completely absent.
	10.20 10.57	
	10.20 10.60 10.20 10.42 10.60	In chloroform solution. As a KBr pellet.
	10.05 10.30 10.65	Strong bands in —SO_2— stretching vibration region. (7.6–8.5 μ)
	10.22 10.42	Shows also characteristic —CN band at 4.48 μ.
	10.35 10.52 (10.85)	Sharp bands at 2.85–6.17 μ. Indicate water of crystallization.
	10.31 10.88	
	10.28 10.57	Ester band at 5.8 + 8.0 μ.
	10.45 10.68	Nothing in 8 μ region.
	10.18 10.50	Intense split band at 4.65–4.75 (—SCN). Band at 8.16.
	10.2 10.53	Bands assigned to mono substituted benzene rings present. These overlap and make uncertain presence of C—Cl band.
	10.13 10.52	—SO_2— vibrations at 7.7 and 8.8 μ. Nothing at *ca.* 8.0 μ. 10.13 band did not split in solid state.
	10.28	KBr pellet.
	10.55 10.15 10.35	In chloroform solution In KBr pellet.

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

Studies on the Synthesis of Ethyleneimines from Interaction of Ketoximes and Grignard Reagents[1]

HENRY R. HENZE AND W. D. COMPTON[2]

Received March 8, 1957

The formation of ethyleneimines from interaction of ketoximes and Grignard reagents has been extended to include aliphatic ketoximes. Whereas interaction of acetophenone oxime with ethylmagnesium bromide might be expected to yield the same product as that from propiophenone oxime and methylmagnesium bromide, actually different ethyleneimines result from these reactions.

The formation of ethyleneimines from ketoximes and Grignard reagents was first reported by Hoch.[3] Subsequently, Campbell *et al.*[4–7] established that alkyl aryl ketoximes react with Grignard reagents in toluene solution at 90–110° to yield ethyleneimines. Vigorous hydrolysis of the reaction mixtures gave α-amino alcohols. Campbell's group prepared 10 ethyleneimine derivatives by this procedure and suggested a sequence of intermediates to account for the products obtained. The present investigation was undertaken with the idea of extending the reaction to purely aliphatic ketoximes and confirming, if possible, the reaction sequence suggested by Campbell.

EXPERIMENTAL[8]

The experimental procedure described by Campbell[6] was employed, modified only by the substitution of an electric heating mantle for the oil bath. Hydrolysis of the ethyleneimines to obtain amino alcohols was also accomplished by Campbell's method.[7]

3-Ethyl-2-phenyl-2-propylethyleneimine. This compound was prepared from interaction of one mole of propylmagnesium bromide and 0.2 mole(32.8 g.) of butyrophenone oxime; b.p. 100–117° (7 mm.); n_D^{20} 1.5150; d_4^{20} 0.9382; mol. refr. calcd.[9] 60.75; summation 60.03; yield 16.3 g. (43%).

Anal. Calcd. for $C_{13}H_{19}N$: N, 7.41. Found: N, 7.44.

This imine formed a hydrochloride, m.p. 140–141° (from ethanol–absolute ether), and a phenylthiourea, m.p. 93–95° (from benzene–Skellysolve B).

Anal. Calcd. for $C_{13}H_{19}N \cdot HCl$: N, 6.06. Found: N, 6.01.

2,2-Diethyl-3-methylethyleneimine. Prepared from interaction of 1 mole of ethylmagnesium bromide and 0.2 mole (20 g.) of diethylketoxime; b.p. 136–142°. n_D^{20} 1.4337; d_4^{20} 0.862; M.R. summation 35.93; M.R. calcd. 36.07; 7.5 g. (14% yield). The product formed a hydrochloride, m.p. 94–95° (from ethanol–absolute ether) and a phenylthiourea, m.p. 97–100° (from benzene–Skellysolve B).

Anal. Calcd. for $C_7H_{15}N \cdot HCl$: N, 9.35. Found: N, 9.73. Calcd. for $C_{14}H_{20}N_2S$: N, 11.28. Found: N, 11.31.

Hydrolysis of this ethyleneimine yielded 2-amino-3-ethyl-3-pentanol, isolated as the hydrochloride, m.p. 143.0–144.5° (from ethanol–absolute ether).

Anal. Calcd. for $C_7H_{17}NO \cdot HCl$: N, 8.36. Found: N, 8.31.

3-Ethyl-2,2-dipropylethyleneimine. Prepared from 0.75 mole of propylmagnesium bromide and 0.25 mole (37 g.) of dipropyl ketoxime; b.p. 70–95° (15 mm.); n_D^{20} 1.4428; d_4^{20} 0.8182; M.R. summation 49.78; M.R. calcd. 50.21; yield 6 g. When the reaction time was increased from 2 hr. to 6 hr., the yield was increased to 11.1 g. (37%).

Anal. Calcd. for $C_{10}H_{21}N$: N, 9.02. Found: N, 9.17.

The compound formed a hydrochloride, m.p. 152–155°.

Anal. Calcd. for $C_{10}H_{23}N$ HCl: N, 7.31. Found: N, 7.66.

Hydrolysis of this imine yielded 3-amino-4-propyl-7-heptanol, isolated as the hydrochloride, m.p. 201.0–201.5° (from ethanol–absolute ether).

Anal. Calcd. for $C_{10}H_{23}NO \cdot HCl$: N, 6.68. Found: N, 6.74.

2-Butyl-2-methylethyleneimine. Prepared from 0.75 mole of butylmagnesium bromide and 0.25 mole (18 g.) of acetoxime; b.p. 81–84°; n_D^{20} 1.4360; d_4^{20} 0.8314; M.R. summation 40.54. M.R. calcd. 40.52, 6 g. (16% yield).

Anal. Calcd. for $C_8H_{17}N$: N, 11.02. Found: N, 10.33.

Hydrolysis of this imine gave 1-amino-2-methyl-2-hexanol, isolated as the phenylthiourea, m.p. 114–116° (from benzene–Skellysolve B).

Anal. Calcd. for $C_{15}H_{24}N_2OS$: N, 10.00. Found: N,10.06.

2-Methyl-3-phenyl-3-propylethyleneimine. Interaction of 3 moles of propylmagnesium bromide with 0.52 mole (81 g.) of propiophenone yielded 53.3 g. of basic material boiling at 80–110° (3 mm.); n_D^{20} 1.5299; d_4^{20} 0.9445; M.R. summation 55.41; M.R. calcd. 56.33. Fractionation of this material through a 15 cm. Widmer column gave 14 ml. with principal fraction boiling at 107–108° (9 mm.); n_D^{20} 1.5155; d_4^{20} 0.9448; M.R. calcd. 55.91.

Anal. Calcd. for $C_{13}H_{17}N$: N, 8.00. Found: N, 8.25.

The lower boiling fractions of the reaction contained 6.64–7.54% N. The principal fraction formed a phenylthiourea derivative, m.p. 112–113° (from benzene–Skellysolve B); the lower boiling fractions yielded the same material (m.p. 112–113°, mixture melting point with derivative from main fraction, 112–113°), thus the fractionation is indicated as being incomplete.

Anal. Calcd. for $C_{19}H_{22}N_2S$: N, 9.02. Found: N, 9.17.

Hydrolysis of the principal fraction yielded 2-amino-3-phenyl-3-hexanol, n_D^{20} 1.5267.

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(1) Taken in part from the dissertation submitted by W. D. Compton in partial fulfillment of the requirements for the Ph.D. degree at The University of Texas, January 1956.

(2) Humble Oil and Refining Co. Fellow in Chemistry, 1954–55. Present address: Department of Chemistry, West Texas State College, Canyon, Tex.

(3) J. Hoch, *Compt. rend.*, **198**, 1865 (1934).

(4) K. N. Campbell and J. F. McKenna, *J. Org. Chem.*, 4, 198 (1939).

(5) K. N. Campbell, B. K. Campbell, and E. P. Chaput, *J. Org. Chem.*, **8**, 99 (1943).

(6) K. N. Campbell, B. K. Campbell, J. F. McKenna and E. P. Chaput, *J. Org. Chem.*, **8**, 102 (1943).

(7) K. N. Campbell, B. K. Campbell, L. G. Hess and I. J. Schaffner, *J. Org. Chem.*, **9**, 184 (1944).

(8) Melting points are corrected unless otherwise noted; boiling points are uncorrected.

(9) Molar refraction (M.R.) "calculated" is obtained by substitution of experimental data into the Lorentz-Lorenz equation; molar refraction "summation" is obtained by appropriate summing of the atomic refractivities and of those for linkages in the molecule.

Anal. Calcd. for $C_{12}H_{19}NO$: N, 7.25. Found: N, 7.15.

On reaction with phenyl isothiocyanate, the hydrolysis product formed a phenylthiourea derivative, m.p. 148–151° (from benzene–Skellysolve B).

Anal. Calcd. for $C_{19}H_{24}N_2OS$: N, 8.53. Found: N, 8.60.

2-Amino-3-phenyl-3-hexanol was synthesized from α-aminopropiophenone hydrochloride and propylmagnesium bromide; b.p. 145–150° (17 mm.); n_D^{20} 1.5212; d_4^{20} 1.002; this product reacted with phenyl isothiocyanate to form a derivative of m.p. 153–154° (from benzene–Skellysolve B) which did not alter the melting point of the derivative of the hydrolysis product described above. This sample of the amino alcohol yielded a hydrochloride, m.p. 231° (dec.) (from ethanol–absolute ether).

Anal. Calcd. for $C_{19}H_{24}N_2OS$: N, 6.10. Found: N, 5.96.

Anal. Calcd. for $C_{12}H_{19}NO \cdot HCl$: N, 8.53. Found: N, 8.37.

Reaction of propiophenone oxime with methylmagnesium bromide. From 0.75 mole of methylmagnesium bromide and 0.25 mole (35 g.) of propiophenone oxime there was obtained about 10 g. of a basic product; b.p. 85–95° (10 mm.); n_D^{20} 1.5288; d_4^{20} 0.9885; M.R. summation (for 2-ethyl-2-phenylethyleneimine or an isomer) 46.18; M.R. calcd. 45.82.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.59; H, 8.89; N, 9.25. Found: C, 81.12; H, 9.02; N, 9.34.

The imine formed a phenylthiourea derivative, m.p. 122–123° (from benzene-Skellysolve B).

Anal. Calcd. for $C_{17}H_{18}N_2S$: N, 9.92. Found: N, 10.17.

Hydrolysis of this imine yielded a basic product which was isolated as the hydrochloride, m.p. 234° (dec.) (from ethanol–absolute ether).

Anal. Calcd. for $C_{10}H_{15}NO \cdot HCl$: N, 6.95. Found: N, 6.88.

The physical properties of this imine and the melting points of its derivatives and of those of its hydrolysis product differ significantly from those reported[7] for the expected imine, namely, 2-ethyl-2-phenylethyleneimine. An authentic sample of the latter showed significant differences from the product of this reaction outlined above. The phenylthiourea derivative of authentic 2-ethyl-2-phenylethyleneimine melts at 100–102°; a mixture of it with the phenylthiourea of the new product (m.p. 122–123°) melted at 88–115°. Hydrolysis of authentic 2-ethyl-2-phenylethyleneimine gave a product the hydrochloride of which melted at 180–182°. The latter melting point is to be contrasted with that of 234° (dec.) for the hydrochloride of the hydrolysis product of the isomeric imine; the melting point of a mixture of the two hydrochlorides was 161–186°.

Since 3-amino-2-phenyl-2-butanol could not be obtained directly from hydrolysis of 2-ethyl-2-phenylethyleneimine, but could be from 2,3-dimethyl-2-phenylethyleneimine, it was concluded that interaction of propiophenone oxime and methylmagnesium bromide yields 2,3-dimethyl-2-phenylethyleneimine rather than the 2-ethyl isomer.

Reaction of acetoxime with butylmagnesium bromide. After interaction of 0.1 mole (18 g.) of acetoxime and 0.75 mole of butylmagnesium bromide, treatment of the reaction mixture with diluted acid, drying, and removal of the organic solvent left 13.5 g. of a red-brown liquid. Fractionation of the latter gave 5.5 g. (17% yield) of product, b.p. 60–70° (30 mm.), n_D^{20} 1.4341; d_4^{20} 0.8294; M.R. summation (for 2-butyl-2-methylethyleneimine) 35.93; M.R. calcd. 35.49; the product did not yield a derivative either with hydrogen chloride or with phenyl isothiocyanate.

Anal. Calcd. for $C_7H_{15}N$: N, 12.38. Found: N, 11.60.

A portion of the product was subjected to hydrolysis with dilute sulfuric acid, but attempts to isolate the hydrolysis product as the phenylthiourea yielded a liquid which could not be caused to crystallize.

Reaction of acetoxime with amylmagnesium bromide. One-fourth mole (18 g.) of acetoxime and 0.75 mole of amylmagnesium bromide were allowed to react; after the usual procedure, 11 g. of red-brown liquid was subjected to fractionation. Fraction 1: b.p. 81–84° (30 mm.); n_D^{20} 1.4360; d_4^{20} 0.8134; M.R. calcd. 40.52. Fraction 2: b.p. 84–90° (30 mm.); n_D^{20} 1.4375; d_4^{20} 0.8173; M.R. calcd. 40.75; M.R. summation (for 2-amyl-2-methylethyleneimine) 40.54.

Neither fraction yielded a solid derivative with either hydrogen chloride or phenyl isothiocyanate. The two fractions were recombined and refractionated to obtain a sample for analysis.

Anal. Calcd. for $C_8H_{17}N$: N, 11.02. Found: N, 10.33.

The basic reaction product was hydrolyzed in sulfuric acid solution to give a liquid; the latter reacted with phenyl isocyanate to yield a difficultly crystallizable solid; m.p. 114–116°.

Anal. Calcd. for $C_{15}H_{21}N_2OS$: N, 10.00. Found: N, 10.06.

Reaction of diethyl ketoxime with phenylmagnesium bromide. From interaction of 0.25 mole (25 g.) of diethylketoxime and one mole of phenylmagnesium bromide, and subsequent hydrolysis, there remained about 25 g. of a dark yellow liquid. Vacuum distillation of the product gave considerable volatile material (collected in the Dry Ice–acetone cold trap) and only a small amount of distillate of b.p. 90–92° (5 mm.); n_D^{20} 1.5173. Attempts to prepare solid derivatives of this material were unsuccessful.

The experiment was repeated and 9 g. of distilled product was obtained: it, too, failed to form the usual ethyleneimine derivatives. It was fractionated; b.p. 70–78° (3 mm.); n_D^{20} 1.5160; d_4^{20} 0.9679; M.R. calcd. 50.2; [the expected product, 2-ethyl-3-methyl-2-phenylethyleneimine, had previously been found to possess quite different physical properties, namely; b.p. 88–90° (5 mm.); n_D^{20} 1.5202; d_4^{20} 0.9572; M.R. summation 50.8; M.R. calcd. 51.2]. The preparation was repeated again and yielded a liquid of b.p. 80–90° (4 mm.); n_D^{21} 1.5160. These products, too, failed to yield a solid hydrochloride of phenylthiourea derivative.

Anal.[10] Calcd. for $C_{11}H_{15}N$: C, 81.95; H, 9.37; N, 8.70. Found: C, 79.35; H, 9.69; N,[11] 7.14.

The product could be shown to contain an "active hydrogen," but was completely destroyed by boiling with dilute hydrochloric acid solution. The infrared absorption spectrum of this reaction product was determined and compared with that of an authentic sample of 2-ethyl-3-methyl-2-phenylethyleneimine. The high degree of similarity of the two spectra suggested that the reaction product represented a slightly impure sample of the anticipated imine.

DISCUSSION

The formation of ethyleneimines from ketoximes and Grignard reagents has been extended in this investigation to include dialkyl ketoximes. The latter appear to give poorer yields than do alkyl aryl ketoximes; this fact is attributed to the production of an insoluble intermediate, probably of the type $R_2C{=}NOMgBr$, which is formed in considerable amounts from the dialkyl ketoximes. This insoluble material is infusible, contains magnesium and bromine, and in one case was hydrolyzed by ice and water to regenerate the dialkyl ketoxime. An analogous material could be obtained from interaction of equimolecular quantities of propiophenone oxime and ethylmagnesium bromide, and, also, when the Grignard reagent was added to the oxime ("inverse addition"). In this latter case, further addition of the Grignard reagent caused the insoluble material to redissolve.

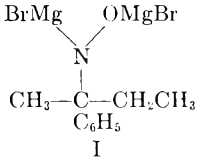
The facts observed tend to support, in general,

(10) Analyses made by Huffman Analytical Laboratories, Wheatridge, Colo.

(11) Two analyses on freshly prepared and fractionated material yielded N, 8.47 and 8.88.

the reaction sequence proposed by Campbell *et al.*,[6] which involves (1) replacement of the active hydrogen of the oxime by MgBr, (2) addition of RMgBr to the C=N linkage, (3) elimination of Mg(OH)Br by closure of the ethyleneimine ring at an α-carbon, and (4) formation of the free imine by hydrolysis. The only modification of this sequence seemingly necessitated by the present work is some accounting for the unidirectional ring closure.

According to Campbell, the same intermediate, I, should be obtained from either of two pairs of



I

reactants, acetophenone oxime and ethylmagnesium bromide or propiophenone oxime and methylmagnesium bromide. But actually, these two pairs of reactants, after mixing and hydrolysis, yield different products; in each instance the alkyl side chain of the oxime becomes incorporated into the ethyleneimine nucleus. Quite probably this directional influence is a result of steric hindrance in the intermediate product of reaction—inspection of molecular models suggests such hindrance. The results seem to be explainable on the basis that the OMgBr grouping is in close proximity to the side chain of the oxime, and are thus dependent upon the configuration of the oxime. Ring closure, therefore, is favored in a unidirectional manner; at least it appears to take place exclusively in that sense.

During the course of this investigation, hydrolysis of 2-ethyl-3-methyl-2-phenylethyleneimine was carried out and yielded 2-amino-3-phenyl-3-pentanol. The latter was described by Campbell[7] as being a liquid, but, in our experience, the once-distilled liquid crystallized slowly on standing. The solid, after repeated recrystallization from ether, melted at 98–99°. Its hydrochloride melted at 225–226°, in agreement with the melting point of 228° recorded by Campbell.

AUSTIN, TEX.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

Syntheses of *N*-Substituted Isoindolines. I. Derivatives of Phthalimide

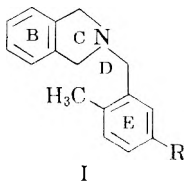
RODERICK A. BARNES AND JOHN C. GODFREY[1]

Received March 14, 1957

A series of four *N*-benzyl isoindolines has been prepared *via* alkylation of potassium phthalimide and reduction of the resulting *N*-benzylphthalimides with lithium aluminum hydride. Basic hydrolysis of the intermediate phthalimides has been shown to yield *N*-benzylphthalamic acids. A new infrared band characteristic of *N*-benzylphthalimides is reported.

Recent advances in the chemistry and pharmacology of reserpine and its derivatives have spurred interest in the synthesis of heterocycles bearing some of the structural features present in these natural products, in the hope that useful ataractics might result. The isoindolines discussed herein contain a basic tertiary amine bound to an aromatic system and to a benzyl group carrying a labile *meta*-substituent. This grouping may be considered to be roughly analogous to that found in the B, C, D, and E rings of reserpine, as shown in structure I.

It was necessary to develop an improved synthesis for the 2-methyl-5-nitrobenzyl chloride (II),[2] which was required for the Gabriel reaction. It was condensed with potassium phthalimide in refluxing ethanol-acetone. Reduction of the product, *N*-(2-methyl-5-nitrobenzyl)phthalimide, III, over Adams' catalyst afforded a high yield of *N*-(2-methyl-5-aminobenzyl)phthalimide, VI. Curiously, compound VI was bright yellow as obtained from the reaction mixture, but the crystals became colorless when suspended in dilute hydrochloric acid, presumably because of formation of a colorless, insoluble hydrochloride at the crystal surface. Basification regenerated the original yellow color. These observations suggested the possibility that the product was not VI, but was instead 3-(2′-methyl-5′-aminophenyl)-1,2,3,4-tetrahydroisoquinoline-1,4-dione. Gabriel[3] demonstrated conclusively that certain *N*-substituted-phthalimides may be rearranged to 3-substituted-1,2,3,4-tetrahydroisoquinoline 1,4-



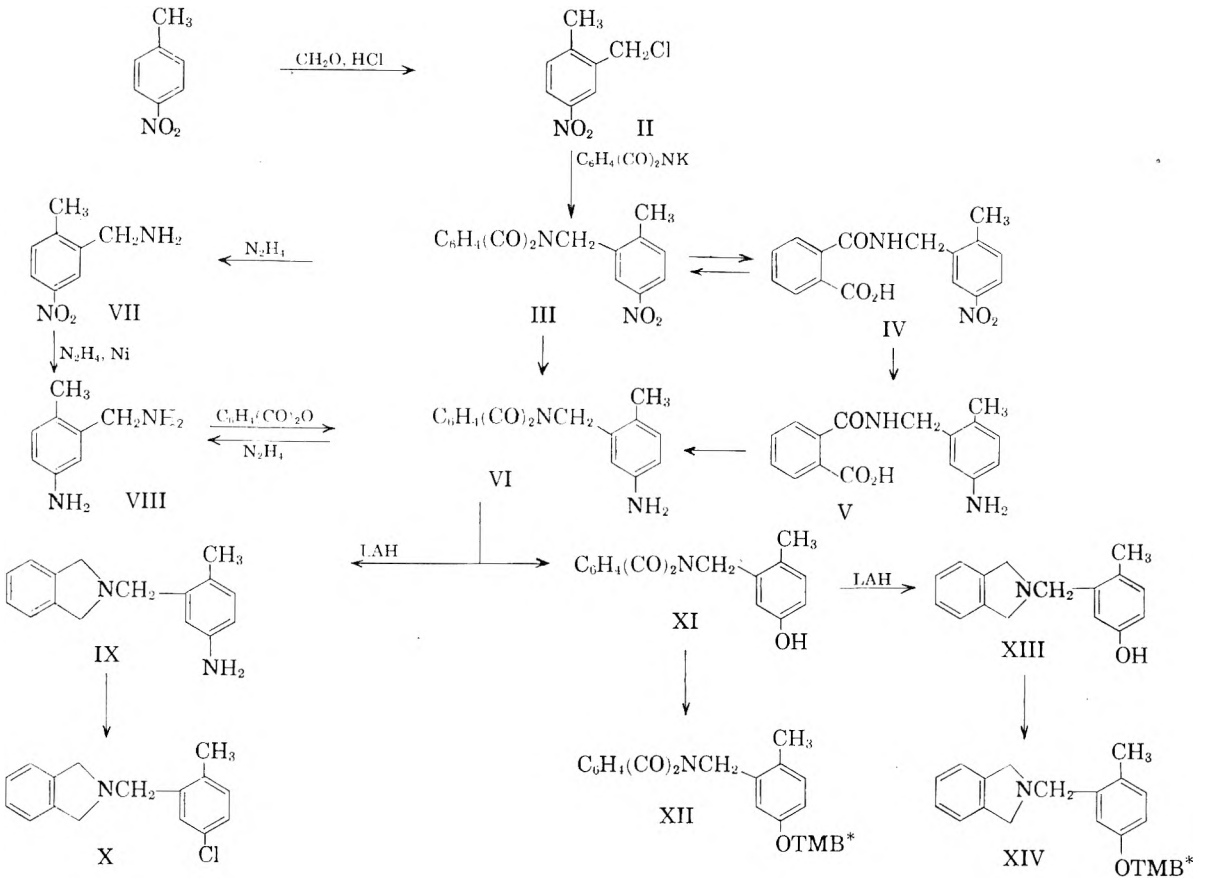
I

(1) Smith, Kline & French, postdoctoral fellow, 1955–1957.

(2) H. Stephen, W. F. Short, and G. Gladding, *J. Chem. Soc.*, 510 (1920).

(3) S. Gabriel and J. Coleman, *Ber.*, **33**, 980 (1900).

CHART I



* TMB = 3,4,5-trimethoxybenzoyl.

diones, which are yellow in basic solution. However, the infrared spectrum, with typical phthalimide bands at 5.66 and 5.87 μ,[4] as well as a strong band at 10.51 μ, which was found to be associated with all of the N-benzylphthalimides encountered in this study, supported structure VI. Further, the ultraviolet spectrum of VI, λ_{max} 222 mμ (log ϵ 4.63) and 298 (3.07) is very similar to that of *N*-phenylphthalimide,[5] λ_{max} 302 (3.35). Significantly, solutions of VI in benzene, ethanol, and chloroform are colorless, and their solutions do not absorb appreciably in the near-ultraviolet and visible regions. The yellow color of the crystalline solid must be a result of intermolecular resonance, or electron transfer from one molecule to another.[6]

Attempts to rearrange III to a tetrahydroisoquinoline under the conditions described by Gabriel[3] (sodium ethoxide in ethanol) or with dry sodium methoxide in refluxing benzene or xylene resulted only in decomposition.

None of the several variations in reaction conditions resulted in anything but poor recovery of starting material. Compound III dissolved readily in dilute, aqueous ethanolic potassium hydroxide. Acidification of the resulting solution with acetic acid precipitated IV, *N*-(2-methyl-5-nitrobenzyl)-phthalamic acid, in a nearly quantitative yield. Compound IV reverted to III on recrystallization or heating above its melting point. *N*-(4- and 2-Nitrobenzyl)phthalimides, compounds XV and XVI, behaved similarly, and no evidence for the expected rearrangement could be found.

Hydrogenation of IV over platinum gave a high yield of the unstable amino acid V. When heated slowly in vacuum to about 160°, V was dehydrated to VI, identical in all respects with the product obtained by direct hydrogenation of III.

Treatment of III with hydrazine in refluxing ethanol[7] produced 2-methyl-5-nitrobenzylamine, VII, which on reduction with hydrazine and Raney nickel[8] was converted to 2-methyl-5-aminobenzylamine, VIII. Diamine VIII was also obtained in good yield by treatment of VI with hydrazine.

(4) J. Chouteau, *Bull. soc. chim. France*, 20, 1148 (1953).

(5) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, Wiley and Sons, Inc., New York, 1951, serial no. 149.

(6) R. S. Mulliken, *J. Am. Chem. Soc.*, **72**, 600 (1950); R. S. Mulliken, *J. Am. Chem. Soc.*, **74**, 811 (1952); C. Reid and R. S. Mulliken, *J. Am. Chem. Soc.*, **76**, 3869 (1954).

(7) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2356 (1926).

(8) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

When equimolar amounts of VIII and phthalic anhydride were heated to 190°, the product consisted of VI accompanied by an equal weight of colorless material which is believed to be *N*-(2-methyl-5-phthalimidobenzyl)phthalimide.

Reduction of VI was accomplished by treatment with excess lithium aluminum hydride in ether. The spectrum, analyses, and molecular weight[9] of the product were as expected for structure IX, *N*-(2-methyl-5-aminobenzyl)isoindoline, and indicated that the reduction had proceeded normally. Diazotization of IX in concentrated hydrochloric acid produced approximately equal quantities of *N*-(2-methyl-5-chlorobenzyl)isoindoline, X, and impure *N*-(2-methyl-5-hydroxybenzyl)isoindoline, XIII.

In order to more closely approximate the structure of reserpine, it was considered desirable to substitute the 3,4,5-trimethoxybenzoyl group at the 5-benzyl position, as in structures XII and XIV. To this end, VI was diazotized in 69% sulfuric acid, affording a respectable yield of *N*-(2-methyl-5-hydroxybenzyl)phthalimide, XI. A 3 to 4 molar excess of the acid chloride was required for the conversion of XI to its 3′,4′,5′-trimethoxybenzoate, XII, in dry pyridine. An equimolar quantity of the acid chloride gave an unsatisfactory yield.

Compound XI was reduced to *N*-(2-methyl-5-hydroxybenzyl)isoindoline, XIII, with lithium aluminum hydride. The pyridine procedure was found not to be suitable for the conversion of XIII to its trimethoxybenzoate, XIV, because of the sensitivity of the isoindoline nucleus. The desired ester was obtained in excellent yield as its hydrochloride by refluxing the dry sodium salt of the phenol with three equivalents of 3,4,5-trimethoxybenzoyl chloride in benzene. The free base, which was quite sensitive to light and oxygen, was readily obtained by extracting a chloroform solution of the hydrochloride with dilute potassium hydroxide.

Condensations carried out under the same conditions employed in the preparation of III yielded XV, *N*-(4-nitrobenzyl)phthalimide;[10] XVI, *N*-(2-nitrobenzyl)phthalimide;[11] and XVII, *N*-(2-methyl-5-nitrobenzyl)succinimide (Chart II). Compound XV was reduced to *N*-(4-aminobenzyl) phthalimide, XVIII. This product was only slightly less yellow than VI, and exhibited the same behavior as VI in acid, base, and organic solvents.

N-(2-Nitrobenzyl)phthalimide, XVI, is very insoluble in most organic solvents, and was therefore reduced to 12-keto isoindolino(1,2-*b*)quinazoline, XIX, according to the procedure of Gabriel.[12] The characteristic absorptions of XIX in the 6 μ region occur at 5.78 (carbonyl) and 6.05 (C=N) μ, and are of approximately equal intensity.

All of the *N*-substituted phthalimides encountered in this study exhibited strong absorption bands between 10.45 and 10.75 μ (Table I). Changes in the *N*-substituent did not markedly affect this band, while any alteration of the 5-membered imide ring caused its disappearance.

CHART II

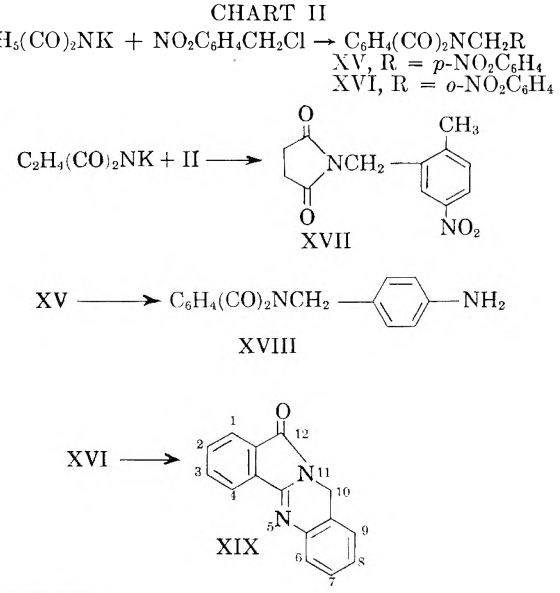


TABLE I

INFRARED BANDS OF *N*-SUBSTITUTED PHTHALIMIDES

Phthalimide	λ_{max}, Microns
N-(2-methyl-5-nitrobenzyl), III	10.58
N-(2-methyl-5-aminobenzyl), VI	10.51
N-(2-methyl-5-acetamidobenzyl)	10.49
N-(2-methyl-5-hydroxybenzyl), XI	10.51
N-[2-methyl-5-(3′,4′,5′-trimethoxybenzoyl) benzyl], XII	10.48
N-(4-nitrobenzyl), XV	10.60
N-(2-nitrobenzyl), XVI	10.55
N-(4-aminobenzyl), XVIII	10.72

EXPERIMENTAL[13]

2-Methyl-5-nitrobenzyl chloride (II). In a 5-l. 3-necked flask fitted with a stirrer and reflux condenser were placed 400 g. (2.92 mole) of *p*-nitrotoluene and 225 g. of trioxane dissolved in 885 ml. of concentrated sulfuric acid. (Cooling is sential when dissolving the trioxane.) The solution was stirred, 206 g. of anhydrous zinc chloride was added, and the mixture was cooled to about 0°. Dry hydrogen chloride was passed through the solution for 4.5 hr. while the ice bath was allowed to melt. The mixture stood overnight, 2 l. of ice and water were added, the solution was cooled to 20° and filtered, removing 130 g. of starting material. The filtrate was extracted with three 700 ml. portions of ether, the solution was dried, the solvent removed, and the dark oil which remained was distilled at 0.5 mm. *p*-Nitrotoluene (156 g.) distilled at 55–65°, and the product (117 g.) came over at 104–108°. Recrystallization from *ca.* one liter of isooctane yielded 104 g. (67.5%), m.p. 62.5–64.0°. A sample was recrystallized for analysis, m.p. 63.0–64.0°.

Anal. Calcd. for $C_8H_8O_2NCl$: C, 51.76; H, 4.34. Found: C, 51.86; H, 4.41.

(9) K. G. Cunningham, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 2305 (1951).

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

(11) S. Gabriel, *Ber.*, 20, 2227 (1897).

(12) S. Gabriel, *Ber.*, 45, 713 (1912).

(13) Microanalyses by W. Manser, Zurich, Switzerland. All melting points are corrected.

2-Methyl-5-nitrobenzyl alcohol. Prepared according to the method of Weinmayr,[14] 1.0 g. of II yielded 0.80 g. of the alcohol (89%), crystallized several times from ethanol-water, m.p. 78–79°. As this value was several degrees above previous reports, the sample was analyzed.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43. Found: C, 57.64; H, 5.49.

N-(2-Methyl-5-nitrobenzyl)phthalimide (III). In a 3-l. 3-necked flask fitted with a stirrer and 2 reflux condensers, 17.27 g. of 85% potassium hydroxide (0.262 mole) was dissolved in 985 ml. of absolute ethanol. To the hot solution was added 38.50 g. (0.262 mole) of phthalimide and 1060 ml. of dry acetone, and the mixture was stirred under reflux overnight. A solution of 48.50 g. (0.262 mole) of 2-methyl-5-nitrobenzyl chloride in 400 ml. of dry acetone was then added, and the mixture was refluxed for an additional 48 hr. It was filtered while hot, chilled, and the resulting precipitate, 44.2 g., colorless needles, m.p. 176–178°, was filtered off. A solid residue (28.5 g.) remained on removal of solvent from the filtrate. It was swirled with 100 ml. of cold chloroform, filtered, freed of solvents, and recrystallized from ethyl acetate and ligroin, yielding 16 g. of III, m.p. 176–178°. Total yield 77.7%. The analytical sample was recrystallized from ethyl acetate, m.p. 178.5–179.5°.[15]

Anal. Calcd. for $C_{16}H_{12}O_4N_2$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.84; H, 4.10; N, 9.44.

N-(2-Methyl-5-nitrobenzyl)phthalamic acid (IV). One gram of finely-ground *N*-(2-methyl-5-nitrobenzyl)phthalimide was suspended in 25 ml. of ethanol, a cooled solution of 2 g. of potassium hydroxide in 25 ml. of water was added, and the mixture was shaken for 30 min. It was filtered into a solution of 2 ml. of glacial acetic acid in 75 ml. of water and the flask was rinsed with 50 ml. of water. The precipitate which formed in the filtrate was filtered and washed with 100 ml. of water. The product was dried over phosphorus pentoxide at room temperature, 1.0 g. (94%), m.p. 190.1–190.9° dec.

Anal. Calcd. for $C_{16}H_{14}O_5N_2$: C, 61.14; H, 4.49; N, 8.92. Found: C, 61.49; H, 4.71; N, 8.87.

N-(2-Methyl-5-aminobenzyl)phthalamic acid (V). A mixture of 461 mg. (1.47 mmole) of IV, 40 mg. of Adams' catalyst, and 50 ml. of ethanol was hydrogenated in a Parr shaker, the theoretical amount of hydrogen being absorbed in 22 min. A yellow precipitate, which proved to be 43 mg. of VI, was filtered off. Removal of solvent from the filtrate left 351 mg. of the semi-crystalline amino acid V. Attempts to purify V were not successful, so the crude product was used for conversion to VI.

N-(2-Methyl-5-aminobenzyl)phthalimide VI. (*a*) *By reduction of III.* A mixture of 6.79 g. of *N*-(2-methyl-5-nitrobenzyl)phthalimide, 244 mg. of Adams' catalyst, and 300 ml. of glacial acetic acid was shaken at 25° and *ca.* 4 atmospheres of hydrogen pressure until a definite break in the hydrogen consumption curve occurred, which required 50 min. and *ca.* four molar equivalents of hydrogen. The catalyst was filtered off, solvent was immediately removed under vacuum at 100°, and the yellow residue boiled with 35 ml. of chloroform. Cooling produced VI, m.p. 241–242° dec., in 92% yield.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.16; H, 5.13; N, 10.47.

The same product was obtained on hydrogenation of III over Raney nickel or Adams' catalyst in benzene (83%), or by the treatment of III with ferrous ion in concentrated ammonium hydroxide (35%), according to the procedure of Eder and Widmer.[16]

Removal of solvent from the chloroform crystallization liquor yielded 4-xylidine, identified as its picrate m.p. 218–219° dec.[17] It must have arisen through hydrogenolysis of the benzyl C—N bond of *N*-(2-methyl-5-aminobenzyl) phthalimide.[18]

(*b*) *By dehydration of phthalic acid mono N-(2-methyl-5-aminobenzyl)amide* (V). One gram of V was heated under vacuum at 160° for 1 hr. Conversion to VI, m.p. 238–240°, was quantitative.

(c) *From 2-methyl-5-aminobenzylamine* (VIII). To 10 ml. of dry xylene were added 168 mg. (1.23 mmole) of 2-methyl-5-aminobenzylamine and 183 mg. (1.23 mmoles) of phthalic anhydride. The xylene was distilled off, the solid residue heated to 190°, dissolved in 50 ml. of chloroform, and the insoluble hydrochloride of VI was precipitated by the addition of 3*N* hydrochloric acid. Neutralization of the hydrochloride yielded 64 mg. of VI, m.p. 234–236°.

The chloroform solution was neutralized, washed with water, and dried. The 72 mg. of white needles obtained were recrystallized from ethanol-chloroform, m.p. 294°. This material is probably *N*-(2-methyl-5-phthalimidobenzyl)phthalimide as it exhibits rather broad carbonyl absorption at 5.66 and 5.80–5.85 μ, as well as *N*-benzylphthalimide absorption at 10.58 μ.

Anal. Calcd. for $C_{24}H_{16}O_4N_2$: N, 7.07. Found: N, 6.95.

The *picrate* of *N*-(2-methyl-5-aminobenzyl)phthalimide was prepared in chloroform, m.p. 218–219° dec.

Anal. Calcd. for $C_{16}H_{14}O_2N_2 + C_6H_3O_7N_3$: C, 53.34; H, 3.46; N, 14.14. Found: C, 53.41; H, 3.53; N, 14.21.

N-(2-Methyl-5-acetylaminobenzyl)phthalimide. A mixture of 162 mg. of *N*-(2-methyl-5-aminobenzyl)phthalimide, 20 ml. of acetic anhydride, and a trace of sodium acetate was heated at 136° for 48 hr. The solvent was removed, and the residue was refluxed for 24 hr. with 40 ml. of water containing enough ethanol to solubilize the organic material. The precipitate which formed on cooling was recrystallized from ethanol-water to constant m.p. 218.7–219.5°.

Anal. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09; $COCH_3$, 13.97. Found: C, 69.72; H, 5.14; N, 9.09; $COCH_3$, 13.45.

2-Methyl-5-nitrobenzylamine (VII). A mixture of 1.160 g. (3.92 mmoles) of N-(2-methyl-5-nitrobenzyl)phthalimide, 10 ml. of ethanol, and 23 drops of 85% hydrazine hydrate was refluxed for 20 min. The mixture, containing a voluminous precipitate, was cooled, acidified with 6*N* hydrochloric acid, warmed to decompose the salt completely, cooled, filtered, diluted to 50 ml. with water, and filtered again. The filtrate was made basic with 10% potassium hydroxide, extracted three times with 30 ml. of chloroform, and the combined extracts dried. Removal of the solvent left 543 mg. (83%) of oil which rapidly crystallized, m.p. 35–40°. It was crystallized several times from ligroin for analysis, m.p. 42.5–43.5°.

Anal. Calcd. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.85; H, 6.13; N, 16.66.

The *picrate* of 2-methyl-5-nitrobenzylamine formed readily in ethanol and was recrystallized from ethanol-chloroform, yellow rhombohedral prisms, m.p. 208° dec.

Anal. Calcd. for $C_8H_{10}O_2N_2 + C_6H_3O_7N_3$: C, 42.54; H, 3.31; N, 17.72. Found: C, 42.97; H, 3.32; H, 17.64.

2-Methyl-5-aminobenzylamine (VIII). (*a*) *From N-(2-methyl-5-aminobenzyl)phthalimide* (VI). When subjected to the same treatment employed in the preparation of 2-methyl-5-nitrobenzylamine, 336 mg. of VI yielded 110 mg. (71%) of 2-methyl-5-aminobenzylamine. The crude diamine melted at 99–100°, but absorbed carbon dioxide rapidly during

(14) V. Weinmayr, U. S. Patent **2,373,438**, April 10, 1945 [*Chem. Abstr.*, **39**, (3793)].

(15) J. Tscherniac, German Patent **134,979** [*Chem. Zentr.*, **76**, 1084 (1902)] obtained a product $C_{16}H_{12}O_4N_2$, m.p. 176°, from the condensation of *p*-nitrotoluene with *N*-hydroxymethylphthalimide, but was unable to distinguish between structure III and *N*-(2-nitro-5-methylbenzyl)-phthalimide. It seems probable that his product was III.

(16) R. Eder and C. Widmer, *Helv. Chim. Acta*, **5**, 1 (1922).

(17) Beilstein, 2nd Ed., **XII**, p. 602.

(18) For comparison, see H. Adkins and B. Wojcik, *J. Am. Chem. Soc.*, **56**, 2419 (1934).

crystallization from ethanol-ligroin. It was therefore converted to the dipicrate, which was shown by comparison of the infrared spectra to be identical with the product obtained by procedure *b*.

(*b*) *From 2-methyl-5-nitrobenzylamine* (VII). A solution of 716 mg. (4.31 mmoles) of VII and 16 drops of 85% hydrazine hydrate (*ca.* 13 mmoles) in 8 ml. of ethanol was warmed on a steam bath and Raney nickel was slowly added over a period of 50 min. When no more gas was evolved, the solution was boiled briefly, cooled, filtered, combined with 15 ml. of ethanol saturated with picric acid, and again brought to a boil. Cooling precipitated 2.01 g. (78.5%) of the dipicrate. It was crystallized several times from ethanol, m.p. 225–226° dec.

Anal. Calcd. for $C_8H_{12}N_2 + 2\ C_6H_3O_7N$: C, 40.45; H, 3.03; N, 18.89. Found: C, 41.20; H, 3.32; N, 18.84.

N-(2-Methyl-5-aminobenzyl)isoindoline (IX). To a solution of 0.56 g. (14 mmole) of lithium aluminum hydride in 100 ml. of ether contained in a 200 ml. 3-necked flask fitted with a gas inlet, stirrer, and reflux condenser was added 1.630 g. (6.14 mmole) of *N*-(2-methyl-5-aminobenzyl)-phthalimide (VI). The solution was stirred and refluxed for 30 hr., an additional 0.5 g. of lithium aluminum hydride added, and the reaction continued for another 42 hr. Then 8 ml. of ethanol in 8 ml. of ether was added, followed by 50 ml. of water. Separation of the ethereal layer and removal of solvent left 1.05 g. (72%) of pink crystals, m.p. 66–68°. The product was dissolved in 1*N* hydrochloric acid, heated with charcoal, filtered, and precipitated with sodium bicarbonate. Repetition of this procedure three times gave a colorless analytical sample, m.p. 73.5–74.5°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.60; H, 7.74; N, 11.66.

The *monopicrate* of *N*-(2-methyl-5-aminobenzyl)isoindoline formed readily in ethanol. Red plates recrystallized from ethanol, m.p. 171–172° dec.

Anal. Calcd. for $C_{16}H_{18}N_2 + C_6H_3O_7N_3$: C, 56.53; H, 4.53; N, 14.98; mol. wt., 467.4. Found: C, 57.15; H, 4.33; N, 14.05; mol. wt., 470.7.

N-(2-Methyl-5-chlorobenzyl)isoindoline (X). A solution of 5.062 g. (0.0171 mole) of *N*-(2-methyl-5-aminobenzyl)isoindoline in 100 ml. of concentrated hydrochloric acid was cooled to −20°, with stirring. To this solution was added 1.182 g. (0.0171 mole) of dry sodium nitrite, and after stirring for 5 min. at −20°, the mixture was rapidly heated to 100° and stirred for 10 min. Removal of solvent under vacuum left a red oil which was dissolved in 100 ml. of ether. Extraction of the ethereal solution with 3 × 15 ml. of 10% potassium hydroxide removed 600 mg. of crude *N*-(2-methyl-5-hydroxybenzyl)isoindoline (XIII). The ethereal solution was dried, the solvent was removed, and the remaining red oil was taken up in 20 ml. of dry benzene and passed over a 20 g. column of silica gel. Elution with 250 ml. of benzene removed nearly all of the *N*-(2-methyl-5-chlorobenzyl)isoindoline, contaminated with red dye. Successive elutions with 100 ml. of 10% ether in benzene, and 200 ml. of ether alone produced a mixed center fraction and a final fraction of 500 mg. of *N*-(2-methyl-5-hydroxybenzyl)isoindoline. The benzene eluate was freed of solvent and distilled in a molecular still at 190–195° and 2 mm., yielding 1.8 g. (33%) of a straw-yellow oil. It was converted to the hydrochloride in anhydrous ether and purified by treating with several portions of charcoal in dry chloroform at 25°. Precipitation from the latter solution by the addition of ether yielded colorless platelets, m.p. 211–213° dec. The infrared spectrum of this substance exhibited a strong tertiary amine hydrochloride doublet at 4.12 and 4.27 μ.

Anal. Calcd. for $C_{16}H_{18}NCl{\cdot}HCl$: C, 65.31; H, 5.83; N, 4.76. Found: C, 65.42; H, 5.79; N, 4.79.

N-(2-Methyl-5-hydroxybenzyl)phthalimide (XI). *N*-(2-Methyl-5-aminobenzyl)phthalimide, 17.796 g. (0.0669 mole), was dissolved in 125 ml. concentrated sulfuric acid, and 97 g. of ice was added, forming a thick slurry of the bisulfate salt. The slurry was cooled to −10°, and 4.62 g. (0.0671 mole) of sodium nitrite was added rapidly with good agitation. Stirring and cooling were continued for 10 min. The flask was then immersed in a steam bath for 10 min. with rapid stirring. Nitrogen was evolved, and the product precipitated. Cooling to 25° and dilution to 1100 ml. with water gave a 91% yield of yellow crystals, m.p. 164–168°. Treatment with charcoal and recrystallization from benzene gave 14.32 g. (79.5%) of XI, m.p. 180–181°.

Anal. Calcd. for $C_{16}H_{13}O_3N_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.78; H, 4.74; N, 5.07.

N-(2-Methyl-5-hydroxybenzyl)phthalimide 3′,4′,5′-trimethoxybenzoate (XII). To the dried acid chloride prepared from 14.6 g. (0.069 mole) of 3,4,5-trimethoxybenzoic acid was added 4.90 g. (0.0183 mole) of *N*-(2-methyl-5-hydroxybenzyl)phthalimide and 200 ml. of dry pyridine. The solution was heated at 100° for 10 hr. and poured into 1500 ml. of water. The precipitate was filtered off after 15 min., boiled with 200 ml. of ethanol, cooled, and filtered, yielding 6.85 g. (80.8%) of colorless needles, m.p. 179–180° (shrinkage at 165°). The analytical sample was recrystallized three times from ethyl acetate, m.p. 181.7–182.2°.

Anal. Calcd. for $C_{26}H_{23}O_7N$: C, 67.67; H, 5.02; N, 3.04. Found: C, 67.46; H, 5.08; N, 2.88.

N-(2-Methyl-5-hydroxybenzyl)isoindoline (XIII). In a 1-l. flask fitted with a Soxhlet extractor was placed 10.0 g. (0.26 mole) of lithium aluminum hydride and 500 ml. of dry ether. *N*-(2-Methyl-5-hydroxybenzyl)phthalimide, (14.32 g., 0.0536 mole), was placed in the thimble and extracted for 11 hrs. The excess reagent was decomposed with 58 ml. of ethanol in 58 ml. of ether and enough saturated sodium sulfate solution was added to clear the ether lyer, followed by 40 g. of dry sodium sulfate. The ether layer was filtered off and the remaining solids washed thoroughly with ether. Removal of solvent from the filtrate left a white solid which was washed with 100 ml. of water, dried, and recrystallized from benzene to give 4.373 g. (34%) of XIII, m.p. 136.5–137.5° dec.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.25; H, 7.13; N, 5.77.

N-(2-Methyl-5-hydroxybenzyl)isoindoline 3′,4′,5′-trimethoxybenzoate (XIV). To 1.948 g. (0.0371 mole) of sodium methoxide dissolved in 100 ml. of absolute ethanol was added 4.038 g. (0.0169 mole) of *N*-(2-methyl-5-hydroxybenzyl) isoindoline. As soon as all of the solid dissolved, the solvent was removed under vacuum at 60°, and dry benzene was added and removed twice under oil pump vacuum at 75° for 0.5 hr. To the resulting off-white solid was added 3,4,5-trimethoxybenzoyl chloride, freshly prepared from 14.0 g. (0.066 mole) of trimethoxybenzoic acid, in 100 ml. of dry benzene. An exothermic reaction occurred, and the solution was refluxed under nitrogen for 40 min. Removal of solvent under vacuum at 80° and addition of 100 ml. of 0.8*N* hydrochloric acid produced a gum which rapidly crystallized. The aqueous solution was decanted and the remaining solid was extracted *in situ* with 3 × 100 ml. of boiling ether, which removed the excess trimethoxybenzoic acid and most of the colored impurities. The solid crystal cake was washed with dilute hydrochloric acid and dried, yielding 7.80 g. (98.4%) of the hydrochloride of XIV. A sample was crystallized several times from ethyl acetate for analysis, m.p. 214.5–215.5° dec.

Anal. Calcd. for $C_{26}H_{27}O_5N{\cdot}HCl$: C, 66.45; H, 6.01; N, 2.98. Found: C, 66.42; H, 6.15; N, 2.97.

The *free base* was obtained by dissolving a sample of the hydrochloride in chloroform and extracting several times with dilute potassium hydroxide. The base remaining in the chloroform was crystallized 5 times from hexane, with charcoal treatment each time, to a constant melting point of 96.2–97.2°.

Anal. Calcd. for $C_{26}H_{27}O_5N$: C, 72.04; H, 6.28; N, 3.23. Found: C, 71.94; H, 6.36; N, 3.26.

N-(4-Nitrobenzyl)phthalimide[10] (XV) was prepared by the same method used for III, in 50% yield of flat, colorless needles, m.p. 74.5–75.5°.

N-(2-Nitrobenzyl)phthalimide[11] (XVI) was prepared in 62% yield by the procedure developed for III, m.p. 224–225°. (Reported,[11] 219–220°).

N-(2-Methyl-5-nitrobenzyl)succinimide (XVII) was prepared in 42% yield according to the procedure for III. It was recrystallized successively from ligroin, ethyl acetate-hexane, and twice from benzene-hexane, but a sharp melting point was never obtained, the compound softening at 116° and melting at 120.0–122.0°. Its infrared spectrum shows typical 5-membered ring imide absorption at 5.66 and 5.88 μ.

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.97; H, 4.83; N, 11.31.

N-(4-Nitrobenzyl)phthalamic acid. *N*-(4-Nitrobenzyl)-phthalimide, 580 mg., was stirred under nitrogen for 35 min. with 20 ml. of 5% potassium hydroxide in ethanol. Addition of 2 ml. of acetic acid and dilution to 100 ml. with water precipitated 103 mg. of starting material, which was filtered off. The filtrate slowly deposited 73 mg. (15%) of yellow crystals, m.p. 187–190° dec. Purification for analysis was effected by boiling with 7 ml. of acetone; solution in 2 ml. of dimethylformamide, filtration, and precipitation with water; and a final reflux with acetone. The product now melted at 214–215° dec.

Anal. Calcd. for $C_{15}H_{12}O_5N_2$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.96; H, 4.16; N, 9.35.

N-(2-Nitrobenzyl)phthalamic acid. To a solution of 500 mg. of *N*-(2-nitrobenzyl)phthalimide in 20 ml. of acetone was added 15 ml. of 2% potassium hydroxide in ethanol, and the solution was stirred with a stream of nitrogen for 3.00 min., while the color changed to light orange. Addition of 9 drops of concentrated hydrochloric acid and dilution to 220 ml. with water precipitated 372 mg. (74%) of *N*-(2-nitrobenzyl)phthalamic acid. The product changed from long needles to prisms at 190–200°, and then melted at 221–223°. The infrared spectrum of the product, after heating to complete conversion to prisms, proved it to be identical with starting material. The infrared spectrum of the unheated product (needles) showed absorption at 3.00, 5.90, and 6.04 μ, in agreement with the phthalamic acid structure. No further analyses were obtained.

N-(4-Aminobenzyl)phthalimide (XVIII). Reduction of *N*-(4-nitrobenzyl)phthalimide over Adams' catalyst in benzene produced XVIII, yellow crystals m.p. 205–207° dec., in 88% yield. It was crystallized from chloroform and ligroin for analysis, m.p. 207–208° dec.

Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.47; H, 4.84; N, 11.20.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

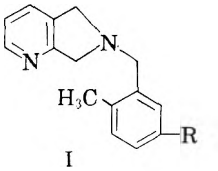
Syntheses of *N*-Substituted Isoindolines. II. Derivatives of Quinolinimide

RODERICK A. BARNES AND JOHN C. GODFREY[1]

Received March 14, 1957

A practical synthetic approach to 2-substituted 4-azaisoindolines has been developed. The nature of the basic hydrolysis products of *N*-benzhydrylquinolinimide has been investigated and their structures established.

The synthesis of 2-benzylhydryl-4-azaisoindoline, IX, was undertaken as a model for the synthesis of structure I.[2] It was anticipated that IX might have some interesting pharmacological action of its own.



I

The obvious methods for preparing *N*-benzhydrylquinolinimide, IV, (heating quinolinic acid and benzhydrylamine together in refluxing xylene, acetic anhydride, ethylene glycol, or without a solvent, or refluxing a mixture of diethyl quinolinate and benzhydrylamine at atmospheric pressure) led only to nicotinic acid benzhydrylamide, VII, because of the ease of decarboxylation of picolinic acids. However the mixed anhydride procedure of Vaughan[3] gave an acceptable yield of 3-carbethoxypicolinic acid *N*-benzhydrylamide, II, accompanied by the isomeric amide III. When heated to 200° in vacuum, the mixture of II and III was converted to *N*-benzhydrylquinolinimide, IV, which was readily separable from unchanged III on the basis of the solubility of III in ethanol, in which IV is only slightly soluble.

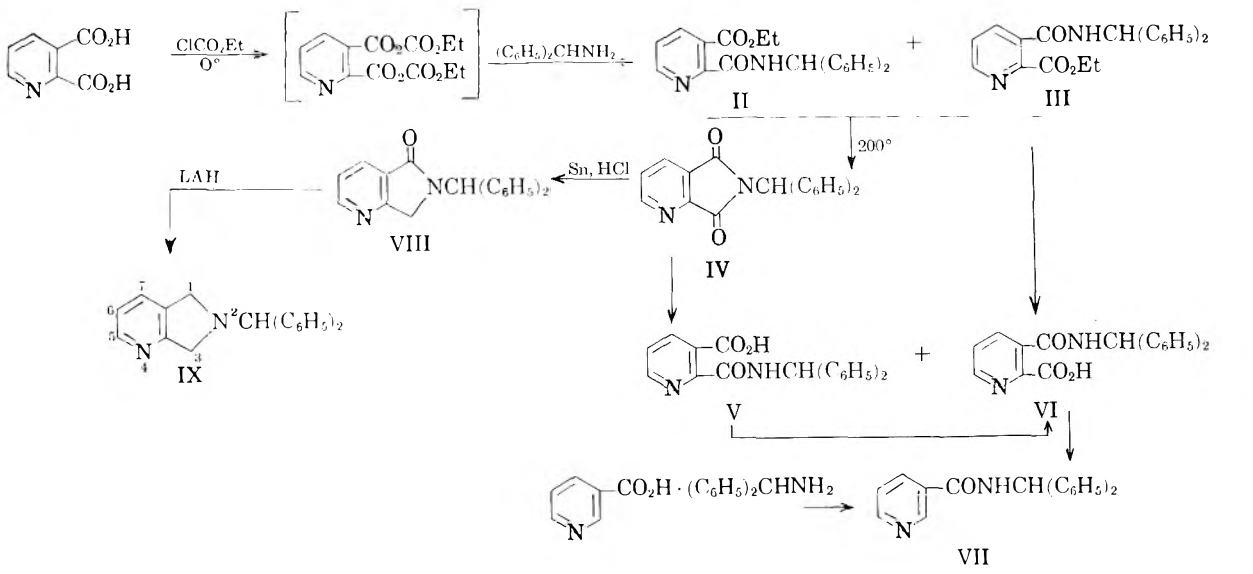
Dilute potassium hydroxide in aqueous ethanol rapidly hydrolyzed IV to a mixture of V and VI. The ratio of VI/V was found to increase rapidly with time. After 1 hr. the ratio was very nearly one, while VI was produced quantitatively in 24 hr. In addition, 3-carboxy-*N*-benzhydrylpicolinamide, V, rearranged to 2-carboxy-*N*-benzhydrylnicotinamide, VI, on attempted recrystallization from ethanol-water, or on heating its hydrochloride above 100°. The decarboxylation product of VI, nicotinic acid *N*-benzhydrylamide, VII, was synthesized independently by refluxing a mixture of nicotinic acid and benzhydrylamine briefly at atmospheric pressure.

The direct reduction of IV to 2-benzhydryl-4-

(1) Smith, Kline & French, postdoctoral fellow, 1955–1957.

(2) See paper I, R. A. Barnes and J. C. Godfrey, *J. Org. Chem.*, **22**, 1038 (1957).

(3) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **74**, 676 (1952).



azaisoindoline, IX, with lithium aluminum hydride gave only a trace of IX, accompanied by a complex mixture of by-products. Reduction of IV with tin and hydrochloric acid in glacial acetic acid[4] led to an intermediate which is thought to be 1-keto-2-benzhydryl-4-azaisoindoline, VIII. This product was completely resistant to basic hydrolysis, and on treatment with hydrogen iodide and red phosphorous at 180°[5] yielded a colorless amino acid which gave no color with ferrous sulfate solution,[6] indicating that it was not a picolinic acid. It did not decarboxylate below 200°, but neither did it yield a picoline on fusion with potassium hydroxide. The product of the latter reaction exhibited only basic properties but could not be obtained pure with the quantity of material available. The alternative 3-keto structure for VIII could hardly be accomodated by the above observations. In addition, coordination of tin at the pyridine nitrogen atom might be expected to favor reduction at the α- rather than the β-carbonyl of *N*-benzhydrylquinolinimide.

Reduction of VIII to 2-benzhydryl-4-azaisoindoline (IX) proceded smoothly with lithium aluminum hydride in ether only when the reaction was carried out at 0°. At higher temperatures further reactions of IX in the presence of the reducing agent produced colored products which were too unstable to be characterized.

EXPERIMENTAL[7]

3-Carbethoxypicolinic acid benzhydrylamide (II). Quinolinic acid 1.00 g. (6.00 mmole) was suspended in a mixture of 20 ml. dry chloroform and 15 ml. dry benzene, and treated with 1.20 g. (12.0 mmole) of triethylamine, resulting in the formation of two liquid phases. The mixture was cooled to 0° and 1.30 g. (12.0 mmole) of ethyl chlorocarbonate dissolved in 5 ml. of chloroform was added. After standing 20 min. at 0°, a solution containing 1 32 g. (6.00 mmoles) of benzhydrylamine hydrochloride and 0.60 g. (6.0 mmoles) of triethylamine in 16 ml. of dry chloroform was added, accompanied by evolution of gas. The mixture stood at 25° overnight. Removal of solvent left a crystalline mass which was washed with 100 ml. of water and 2 × 60 ml. of 10:1 ammonium hydroxide, leaving 1.620 g. (75%) of white crystals, m.p. 150–170°. It was treated with charcoal and crystallized 5 times from ethanol-hexane, m.p. 172.0–173.0°. The infrared spectrum shows absorption at 3.09 (N—H), 5.75 (ester carbonyl), and 6.08 (amide carbonyl) μ.

Anal. Calcd. for $C_{22}H_{20}O_3N_2$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.16; H, 5.49; N, 7.77.

2-Carbethoxynicotinic acid benzhydrylamide (II). Exhaustive dilution with water of the first recrystallization liquor from the preparation of II precipitated tan needles which, after 20 recrystallizations from ethanol-water, yielded colorless needles, m.p. 110.0–111.0°. It was air-dried for analysis, since vacuum drying over phosphorus pentoxide was found to depress the melting point and the carbon value obtained. Even with these precautions, the sample gave a consistently low carbon value, probably because of the ready loss of ethanol to form IV.

Anal. Calcd. for $C_{22}H_{20}O_3N_2$: C, 73.31; H, 5.59; N, 7.77. Found: C, 72.18; H, 5.52; N, 7.93.

When 2-carbethoxynicotinic acid benzhydrylamide was heated at 100° for 0.5 hr. with 10% aqueous potassium hydroxide, a mixture of 2-carboxynicotinic acid benzhydrylamide (VI) and *N*-benzhydrylnicotinamide (VII) was produced.

N-Benzylhydrylquinolinimide (IV). The crude mixture of II + III, 33.0 g., was heated under aspirator vacuum at 180–195° for 1 hr. The glass obtained on cooling was boiled with 200 ml. of absolute ethanol. Cooling gave 27.2 g. (93%) of IV, m.p. 159.7–161.0°. It was dissolved in 200 ml. of chloroform, treated with charcoal at room temperature, and the solvent replaced with ethanol by distilling off the chloroform through a short column while adding ethanol. The purified product melted at 160.3–161.8°.

Anal. Calcd. for $C_{20}H_{14}O_2N_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.49; H, 4.41; N, 8.98.

3-Carboxypicolinic acid benzhydrylamide (V). A solution of 1.40 g. (4.46 mmole) of *N*-benzhydrylquinolinimide (IV), 184 ml. of 95% ethanol, 176 ml. of water, and 3.50 g. (6.25 mmole) of potassium hydroxide was shaken at 25° for 50 min. The solution was acidified with 3 ml. of 6*N*

(4) A. Hafner, *Ber.*, **23**, 337 (1890).

(5) S. Gabriel and J. Coleman, *Ber.* **35**, 2831 (1902).

(6) H. S. Mosher and R. C. Elderfield, *Heterocyclic Compounds*, J. Wiley and Sons, Inc., New York, 1950, Vol. I, p. 569.

(7) Microanalyses by W. Manser, Zurich, Switzerland. All melting points are corrected.

hydrochloric acid, concentrated to 120 ml., and diluted with 60 g. of ice, which precipitated white crystals, m.p. 160–175° with evolution of gas. It was recrystalized from 25 ml. of ethanol-water, needles, m.p. 195–200°, and finally purified for analysis by solution in 5% ammonium hydroxide, treatment with charcoal, and precipitation with 5% acetic acid, m.p. 205–206°. The sample gave no color when dissolved in ethanol containing ferrous sulfate. Its infrared spectrum (Nujol mull) exhibited strong absorptions at 3.05, 5.92, and 6.03 μ.

Anal. Calcd. for $C_{20}H_{16}O_3N_2$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.54; H, 4.91; N, 8.67.

2-Carboxynicotinic acid benzhydrylamide (VI). Dilution of the original 180 ml. aqueous filtrate from V to one liter with water slowly precipitated VI, which was filtered off after 5 days and purified in the same manner as V. The product decarboxylated above *ca.* 152°, to form *N*-benzhydrylnicotinamide, m.p. 184°. It gave a bright orange color with ferrous sulfate in ethanol, and exhibited strong absorptions (Nujol mull) at 3.02, 5.85, and 6.12 μ.

Anal. Calcd. for $C_{20}H_{16}O_3N_2$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.36; H, 4.91; N, 8.51.

The relative amounts of V and VI obtained were found to depend upon duration of reaction, long reaction times favoring production of VI. In no experiment did the yield of V exceed 50%, while nearly quantitative yields of VI were obtained if the reaction was allowed to proceed for a day or more.

N-Benzhydrylnicotinamide (VII). (*a*) *From quinolinic acid and benzhydrylamine.* A mixture of 424 mg. (2.33 mmoles) of benzhydrylamine, 393 mg. (2.35 mmoles) of quinolinic acid, and 7.5 ml. of ethylene glycol was refluxed for 1 hr. Dilution with 45 ml. of water yielded a product which was crystallized from ethanol-water and ethanol-ligroin for analysis, m.p. 178.0–178.5°.

Anal. Calcd. for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.08; H, 5.58; N, 9.76.

(*b*) *From 3-carboxypicolinic acid benzhydrylamide* (V). The hydrochloride of V was quantitatively converted to VII by heating to 200° in vacuum. It was recrystallized several times from ethanol-water, m.p. 183.2–184.2°.

Anal. Found: C, 79.04; H, 5.54; N, 9.84.

(*c*) *From 2-carboxynicotinic acid benzhydrylamide* (VI). When heated to 190° under vacuum, 14 mg. of VI yielded 13 mg. of VII, m.p. 182–184°.

(*d*) *From nicotinic acid and benzhydrylamine.* Nicotinic acid, 1.14 g. (0.0062 mole), and 919 mg. (0.0075 mole) of benzhydrylamine was heated to 230° in a wax bath, and then at reflux over a small flame for 2.5 min. The cooled mass was boiled with 15 ml. of water, filtered, and the precipitate which separated on cooling was crystallized twice from ethanol and 4 times from ethyl acetate to a final m.p. 182–184°. Purified yield, 320 mg. (18%).

The samples of *N*-benzhydrylnicotinamide from all sources were shown to be identical by comparison of their infrared spectra.

1-Keto-2-benzhydryl-4-azaisoindoline (VIII). Twenty grams (0.064 mole) of *N*-benzhydrylquinolinimide (IV), 400 ml. of glacial acetic acid, and 15.3 g. (0.129 mole) of mossy tin were placed in a 1 liter flask fitted with a stirrer, reflux condenser, and dropping funnel, and heated to 100°. To this stirred mixture was added 26 ml. of concentrated hydrochloric acid, which caused rapid development of a yellow color. After 10 *min.* an additional 24 ml. of concentrated acid was added and the mixture was stirred at 100° for 50 min., then at reflux for 10 min. Removal of solvent under vacuum left a gummy solid which was washed *in situ* with 4 × 50 ml. of water. The product was dissolved in 750 ml. of ethanol, made basic with concentrated ammonium hydroxide to precipitate the oxides of tin, and filtered with the aid of "Filtercel". The resulting deep blue filtrate was diluted to 5 liters with water and allowed to stand for 36 hr. The resulting precipitate was filtered off, dissolved in 200 ml. of benzene, dried over magnesium sulfate, and treated with charcoal in the cold. The yellow solution thus obtained was freed of solvent under vacuum, and the remaining gum taken up in 120 ml. ethanol, acidified with dilute hydrochloric acid, and treated twice with charcoal. Removal of most of the solvent and neutralization with 500 ml. of 10:1 ammonium hydroxide yielded 10.5 g. (55%) of prisms, m.p. 121–123°. The product was recrystallized from 500 ml. of hexane containing a little ethyl acetate, 9.7 g. (50%), m.p. 124.5–125.8°.

Anal. Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.97; H, 5.44; N, 9.30.

The *picrate* was prepared in and recrystallized from ethanol, m.p. 161.0–162.0°.

Anal. Calcd. for $C_{20}H_{16}ON_2 + C_6H_3O_7N_3$: C, 58.98; H, 3.62; N, 13.23. Found: C, 58.36; H, 3.64; N, 12.90.

2-Benzhydryl-4-azaisoindoline (IX). To a solution of 11.9 g. (0.031 mole) of lithium aluminum hydride dissolved in 1 liter of dry ether and cooled to 0° was added 14.0 g. (0.047 mole) of finely ground 1-keto-2-benzhydryl-4-azaisoindoline, and the mixture was stirred at 0° for 30 hr. It was then allowed to warm to 20° during 8 hr., and the excess reagent was decomposed by the successive addition of 120 ml. of 1:1 ethanol-ether and 60 ml. of saturated sodium sulfate in water. The yellow-green solvent layer which separated was evaporated to 400 ml. and extracted with 3 × 75 ml. of 1*N* hydrochloric acid. An orange solid separated at this point and was removed by filtration. Basification of the aqueous extract with sodium carbonate precipitated an off-white solid, m.p. 160–163°. The product was dissolved in 200 ml. of benzene, thoroughly dried over magnesium sulfate, and passed over a 0.5 × 8.5 in. column of 80/200 mesh activated alumina. The column was eluted with 500 ml. of benzene. Removal of solvent from the eluate under vacuum left off-white crystals, from which the color was removed by boiling with 50 ml. of freshly-distilled dry ether. Cooling to 0° and filtration yielded 5.40 g. (40.5%) of prisms, m.p. 161–162° sl. dec. This material was shown by comparison of the infrared spectra to be identical with a sample previously obtained in trace amount by direct reduction of *N*-benzhydryquinolinimide. It was crystallized from hexane for analysis, m.p. 162.0–162.2° dec.

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.72; H, 6.36; N, 9.86.

The *dipicrate* formed in ethanol and was crystallized from the same solvent, m.p. 197.0–197.5° dec.

Anal. Calcd. for $C_{20}H_{18}N_2 + 2C_6H_3O_7N_3$: C, 51.62; H, 3.25; N, 15.05; mol. wt., 744.6. Found: C, 52.11; H, 3.26; N, 14.67; mol. wt., 745.8.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF QUEENS COLLEGE]

Replacement of Halogen by Hydrogen in Nitro Aryl Halides[1]

A. H. BLATT AND NORMA GROSS

Received March 14, 1957

The preparation of picryl iodide is described. HI and H_3PO_2, either together or separately, will reduce picryl iodide to trinitrobenzene. The reduction with HI is kinetically complex.

Some time ago we reported that picryl chloride was converted to trinitrobenzene on treatment with dilute hydriodic acid in an organic solvent at room temperature, *i.e.*, under the conditions that bring about the reduction of an α-halo ketone to a ketone.[2]

$$2,4,6\text{-}(O_2N)_3C_6H_2Cl + 2HI \longrightarrow 1,3,5\text{-}(O_2N)_3C_6H_3 + HCl + I_2$$

We have since undertaken a study of the mechanism of the reaction and of its usefulness. Our experiments designed to establish the mechanism have not led to clear cut results, but they have resulted in a number of findings of considerable interest. These by-product findings constitute the subject matter of this article.

In order to reduce the number of problems involved in the study of mechanism, we decided to examine first the reaction between picryl iodide and hydriodic acid as that would eliminate complications resulting from the reaction between picryl chloride and iodide ion to furnish picryl iodide and would also simplify the stoichiometry:

$$2,4,6\text{-}(O_2N)_3C_6H_2Cl + I^- \longrightarrow 2,4,6\text{-}(O_2N)_3C_6H_2I + Cl^-$$

$$2,4,6\text{-}(O_2N)_3C_6H_2I + HI \longrightarrow 1,3,5\text{-}(O_2N)_3C_6H_3 + I_2$$

For this purpose it was necessary to prepare picryl iodide and in the course of this preparation we were able to develop what promises to be a useful qualitative test for aromatic nitro compounds and the number of nitro groups they contain.

The only practical method for preparing picryl iodide is the reaction between picryl chloride and an alkali iodide, but the only description of this reaction lacks essential details and did not give satisfactory results when we tried to follow it.[3] In part at least the difficulty is probably a consequence of the reaction between picryl chloride and the solvent, ethanol, to yield picryl ethyl ether and hydrogen chloride, for the hydrogen chloride with potassium iodide would furnish hydriodic acid and this would lead to reduction to trinitrobenzene and oxidation to iodine.[4] By changing to acetone as the solvent and sodium iodide as the inorganic reagent it was possible to repress the side reactions and increase the concentration of reactants sufficiently to prepare the picryl iodide we needed.

In our first trial of the reaction between picryl chloride and sodium iodide in acetone we noticed, on mixing the solutions of the reactants, the development of an intense color comparable with that of liquid bromine. A series of test-tube experiments showed that the color was not specific for the reactants and products present or for the reaction taking place, and that similar or related colors developed whenever an aromatic nitro compound and iodide ion were together in acetone. When equal volumes of approximately 0.2*M* acetone solutions of sodium iodide and an aromatic nitro compound are mixed, the resulting solution will be very pale yellow if the aromatic compound contains one nitro group; deeper yellow, comparable with the color of 0.3*M* aqueous ferric chloride if the aromatic compound contains two nitro groups; and red brown, comparable with the color of 3.0*M* aqueous ferric chloride, if the aromatic nitro compound contains three nitro groups. Exact concentrations of reagents are not necessary, for on diluting with acetone a solution containing a trinitro aromatic compound and iodide ion the red-brown color becomes less intense but is still readily distinguished from the yellow color that characterizes a dinitro aromatic compound. An alkyl, hydroxyl, amino, carboxyl, or carbalkoxyl group or a halogen atom as a substituent modifies the color (*e.g.*, the color developed by picric acid is more brown and less red than that developed by trinitrobenzene), but these groups do not interfere with the use of the test to show the number of nitro groups present. The nitroso groups in *o*-dinitrosobenzene and in 3,5-dinitro-1,2-dinitrosobenzene likewise do not interfere; the first-named compound does not develop a color while the last-named compound behaves like other dinitro aromatics.[5] The aliphatic nitro compounds, nitromethane and 2-nitro-2-methylpropane, do not develop

(1) This work has been supported by the Office of Ordnance Research under Contract No. DA-30-069-ORD-1289.

(2) A. H. Blatt and E. W. Tristram, *J. Am. Chem. Soc.*, **74**, 6273 (1952).

(3) P. Hepp, *Ann.*, 215, 361 (1882).

(4) The reaction between picryl chloride and ethanol is reported to be very fast: C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, p. 804, Cornell University Press, Ithaca, N. Y., 1953. Apparently no detailed information on the reaction has been published.

(5) We are indebted to Dr. J. H. Boyer for this information.

colors.[6] Cyclotrimethylenetrinitramine (RDX) and pentaerythritol tetranitrate (PETN), examined as representative of nitramines and nitrate esters, also fail to develop colors with iodide ion.[7]

A much wider range of aromatic nitro compounds will, of course, have to be examined before the usefulness and limitations of this color test can be closely defined. We are trying additional compounds as they come to hand. So far we have found that 1,5- and 1,8-dinitronaphthalene, representative of fused ring aromatics, behave like typical dinitrobenzene derivatives; that 2,2′-dinitrobiphenyl at 0.2*M* behaves like a mononitrobenzene derivative at roughly 0.4*M*, and that 2,4,5-trinitro- and 2,4,5,7-tetranitrofluorenone develop deep purple colors like that of moderately concentrated aqueous potassium permanganate.

The colored complexes from aromatic nitro compounds and iodide ion are destroyed by the addition of water. From the one complex whose acetone solution we examined in a little more detail, that from *m*-dinitrobenzene, it was possible to recover the aromatic nitro compound essentially quantitatively after 24 hours by pouring the solution into water. We have found only one report of these colored complexes. In that report three trinitro- and two dinitrobenzene derivatives were examined, the solvent and inorganic halide were varied widely, and it was concluded that the complexes were probably composed of one molecule of aromatic nitro compound, one molecule of alkali iodide, and three molecules of solvents.[8] We do not propose to study the complexes themselves; they form the subject matter of a recent note in this Journal.[8a]

With picryl iodide available, we undertook to secure kinetic data on the reaction between it and hydriodic acid. Preliminary experiments showed that 0.56*M* picryl iodide and 0.113*M* hydriodic acid in acetone containing 9.6% water gave convenient rates and gross reproducibility for the early stages of the reaction when it was run in a nitrogen atmosphere in flasks covered with aluminum foil to exclude light. The careful follow-up of these preliminary experiments did not, however, increase their reproducibility sufficiently to permit their use for the calculation of reaction rate and order. The principal source of trouble was the decomposition of the hydriodic acid. Along with each pair of runs we ran a blank to which no picryl iodide had been added. After correcting for the iodine liberated in the blank, the two runs would usually agree to within a per cent or two on the amount of reduction that had taken place during forty minutes. However, the amount of iodine formed in the blanks was so large and so variable–amounting to from 12 to 22% of the total iodine formed in the reaction proper–that it was not safe to assume that the blanks were a reliable measure of the decomposition of the hydriodic acid in the reaction mixtures.

We next tried a number of variations in the experimental procedure in the hope of obtaining a more closely reproducible reaction. None of the variations was successful for the purpose for which it was intended, but several yielded interesting and significant information. The addition of sodium or potassium acetate in amount equivalent to the hydriodic acid present repressed in striking fashion the decomposition of the hydriodic acid but did not increase the reproducibility of runs sufficiently for our purpose, indicating that there were other variables in the system. Details of the inhibiting effect of sodium acetate on the decomposition of hydriodic acid are given in the experimental section for the information of any one who may want to make use of or to study it.

The results just described suggested the use of equivalent amounts of sodium iodide and acetic acid in the hope that this reagent combination would have the stability of the hydriodic acid-sodium acetate system and would eliminate any interfering species present in hydriodic acid. When the experiment was made we found that, under conditions such that hydriodic acid and sodium acetate gave 5% reduction in 40 minutes, sodium iodide and acetic acid gave only 1% reduction in the same time. The discrepancy was finally traced to the small amount of hypophosphorous acid (~1%) present as a stabilizer in commercial hydriodic acid and, with this lead, it could be shown that hypophosphorous acid alone is the most effective and convenient reagent for the reduction of picryl iodide to trinitrobenzene. With this reagent the reduction is quantitative and rapid at room temperature. The use of hypophosphorous acid for this type of reduction is, as far as we can find, new. We write the reaction in the following way which takes into account our observations that the other *ous* acids, phosphorous and sulfurous, also bring about the same reduction:

$$2,4,6\text{-}(O_2N)_3C_6H_2I + H_3PO_2 + H_2O \longrightarrow 1,3,5\text{-}(O_2N)_3C_6H_3 + H_3PO_3 + HI$$

$$2,4,6\text{-}(O_2N)_3C_6H_2I + H_3PO_3 + H_2O \longrightarrow 1,3,5\text{-}(O_2N)_3C_6H_3 + H_3PO_4 + HI$$

$$2,4,6\text{-}(O_2N)_3C_6H_2I + H_2SO_3 + H_2O \longrightarrow 1,3,5\text{-}(O_2N)_3C_6H_3 + H_2SO_4 + HI$$

We are studying the hypophosphorous acid reaction further and hope to be able to report on it in more detail later.

After hypophosphorous acid had been shown to be capable of reducing picryl iodide, we tried unstabilized hydriodic acid. Both the commercially available material as received and the freshly dis-

(6) We are indebted to Dr. Nathan Kornblum for the information about 2-nitro-2-methylpropane.

(7) We are indebted to the General Laboratory Section, Picatinny Arsenal, for this information.

(8) B. Tronow, L. Djakanowa-Schulz, and E. Sonowa, *J. Russ. Phys. Chem. Soc.*, 59, 333 (1927) [*Chem. Abstr.*, 22, 2555 (1928)].

(8a) Richard W. Shellman, *J. Org. Chem.*, 22, 818 (1957).

tilled material gave reasonably consistent results for a given sample. However, the results varied widely from sample to sample and were therefore of no value to us.

The conclusion from the experiments so far described is that the reaction between picryl iodide and hydriodic acid is in our hands not amenable to kinetic study; hydriodic acid stabilized with hypophosphorous acid contains at least two reducing species; sodium iodide and acetic acid reduce picryl iodide too slowly; and unstabilized hydriodic acid, judging from the variations between different samples, also contains more than one reducing species. However, the rough quantitative measurements of the amount of picryl iodide reduced under a number of different experimental conditions and of the amounts of other nitro aryl halides reduced under a standard set of conditions do give practical information about the best way to carry out the reduction and about the applicability of the reaction.

With picryl iodide as the substrate in acetone and with hydriodic acid stabilized with hypophosphorous acid as the reagent, reduction is strikingly inhibited by water. Reduction is faster in acetic acid than in acetone. (The solubility of picryl iodide in aqueous acetic acid is too small for us to determine whether water is also an inhibitor in this solvent.) Supporting data are in Table I. The obvious practical

TABLE I

REDUCTION OF PICRYL IODIDE TO TRINITROBENZENE IN 40 MINUTES AT 24.2°

Picryl iodide, 0.056*M*. Hydriodic acid (stabilized with ~1% H_3PO_2), 0.112*M*

Solvent	Per Cent Reduction
Acetone containing 9.6% water	5.5
Acetone containing 5.6% water	12–13
Acetone containing 1.66% water	76–77
Acetic acid containing 1.66% water	98–99

conclusions are confirmed by separate preparative experiments showing that 0.056*M* picryl iodide in acetone containing 1.66% water and four equivalents of hydriodic acid or in acetic acid containing 1.66% water and two equivalents of hydriodic acid is quantitatively reduced to trinitrobenzene in 40 minutes at room temperature.

Just as striking as the effect of water on the reduction of picryl iodide with stabilized hydriodic acid, is the effect of acidity on the reduction with hydriodic acid formed from sodium iodide and an added acid. Thus, under conditions such that sodium iodide and an equivalent amount of acetic acid in acetone brought about only 1% reduction of picryl iodide, sodium iodide and an equivalent amount of hydrochloric acid brought about essentially complete reduction to trinitrobenzene. The dependence of reduction on acidity enables one to control the course of the reaction between picryl chloride and hydriodic acid so as to yield either picryl iodide (in weakly acid solution) or trinitrobenzene (in strongly acid solution). Sodium iodide and an equivalent of acetic acid is the best reagent combination for the preparation of picryl iodide from picryl chloride. It remains to be seen whether the sodium iodide-acetic acid reagent is generally superior for the conversion of nitro aryl chlorides and bromides to the corresponding iodides and how this reagent compares with an alkali iodide alone in the formally analogous conversion of alkyl chlorides and bromides to iodides.

Considering now the behavior of other nitro aryl halides than picryl iodide toward stabilized hydriodic acid under a standard set of conditions (nitro aryl halide, 0.056*M*; hydriodic acid, 0.112 *M*; in acetone containing 1.66% water at 24.2°), we find that in the benzene series three nitro groups are necessary in order for reduction to take place. Picryl bromide and picryl chloride are reduced to trinitrobenzene, both more slowly than picryl iodide and the chloride more slowly than the bromide. The 2,4-dinitrophenyl halides (X = F, Cl, Br, I) are not reduced. Neither is 2,6-dinitroiodobenzene. A carbomethoxyl group will not effectively replace a nitro group in picryl chloride; the methyl esters of 2-chloro-4,6-dinitrobenzoic acid and 4-chloro-2,6-dinitrobenzoic acid are not reduced. Replacement of halogen by hydrogen is therefore of quite limited applicability in the benzene series. However, in the thiophene series two nitro groups are sufficient to permit reduction for 2-bromo-3,5-dinitrothiophene is reduced to 2,4-dinitrothiophene. This result suggests that the reduction may have wider application in suitable heterocyclic systems. We have begun a study of these applications and our results in the thiophene series are described in the accompanying article.[9]

EXPERIMENTAL

All acetone used was refluxed over potassium hydroxide and permanganate, distilled, and then redistilled over permanganate through a 24″ glass-packed column shortly before use. Other solvents were purified by standard procedure and distilled through the same column. Picryl chloride was crystallized from formic acid; picryl iodide was crystallized from benzene.

Preparation of picryl iodide. The bulk of the picryl iodide used was prepared in the following way. Fifty grams (0.2 mole) of picryl chloride was dissolved in 175 ml. of acetone, and 45 g. (0.3 mole) of Baker's Analyzed Reagent sodium iodide was dissolved in 125 ml. of acetone with cooling. The solutions were mixed and kept stoppered for 8 hr. protected from light. Immediately on mixing, the solution developed a deep red-brown color like that of liquid bromine and in a few minutes a precipitate, presumably sodium chloride, began to form. The reaction mixture was poured into 1.7 kg. of water containing a small amount of ice. The brown precipitate was allowed to coagulate for an hour and was then filtered from the red-brown solution. The crude prod-

(9) A. H. Blatt, Norma Gross, and E. W. Tristram, in press.

uct weighed 60 g. and melted at 138–152° after softening from 125° on. It was dissolved in 180 ml. of benzene, filtered, and concentrated to 60 ml. On cooling the solution, 39 g. (57%) of picryl iodide, melting at 161–163° with some preliminary softening, was obtained. A second crystallization from benzene was necessary to obtain a pure product. The filtrate from the first crystallization, on evaporation to dryness at room temperature, left 20 g. of solid melting over the range 30–90°. We were unable to separate this material into its constituents.

Occasional runs by the procedure just described, and by a variation of that procedure using shorter reaction times, gave products that did not coagulate satisfactorily. When this happened, the yield of picryl iodide was poor and there were indications of the intrusion of side reactions. One indication was the presence of a lachrymator (iodoacetone ?) in the reaction mixture; another was the formation of unidentified material that melted above 200°. We did not attempt to identify these side reactions or their products for we found that they could be avoided by operating in weakly acid solution in the following way.

A solution of 12 g. (0.08 mole) of sodium iodide in 50 ml. of acetone was added to a solution of 10 g. (0.04 mole) of picryl chloride in 25 ml. of acetone and 5 ml. of anhydrous acetic acid. The reaction mixture immediately developed a dark red color and in a few minutes a precipitate formed. After 30 min. the reaction mixture was poured into 340 ml. of water in which 0.1 g. of sodium bisulfite had been dissolved. The color disappeared and picryl iodide precipitated as a pale yellow solid. The crude product weighed 11.0–11.5 g. (80%) and melted over the range 130–148°. One crystallization from benzene furnished picryl iodide suitable for most purposes, but the material was crystallized a second time for use in quantitative experiments. The yield was comparable with that obtained in the absence of acid.

Reduction of picryl iodide to trinitrobenzene. A. Quantitative measurements. Little need be added to the description given in the discussion earlier. The course of the reaction was followed by titrating with thiosulfate the iodine formed. A check on the titrations could be made when reduction was very slight or was essentially complete by isolating the product and determining the melting point.

B. With hypophosphorous acid. To 1.0 g. (0.003 mole) of picryl iodide in 25 ml. of acetone, 2 ml. (0.019 mole) of 50% hypophosphorous acid was added. The reaction mixture rapidly developed a deep red color. After 2 hr. the solution was poured into 160 ml. of water. The precipitate of trinitrobenzene weighed 0.45 g. and melted at 118–120°. The yield was 75%; corrected for the recovery of trinitrobenzene when 0.6 g. of that material is dissolved in 25 ml. of acetone and the solution poured into 150 ml. of water, the yield is better than 95%.

Colored complexes from aromatic nitro compounds and sodium iodide. Our procedure for these tests is to add to an approximately 0.2*M* acetone solution of the aromatic nitro compound an equal volume of an approximately 0.2*M* stock solution of sodium iodide. About 0.2 g. of the nitro compound, enough to make 1 or 2 ml. of solution, is used. It is weighed to about ±0.03 g. The following nitro aromatic compounds have been tried with the results described in the discussion above.

A. Mononitro compounds: Nitrobenzene, *p*-nitrotoluene.

B. Dinitro compounds: *o*- and *m*-Dinitrobenzene, the 2,4-dinitrohalobenzenes (X = F, Cl, Br, I), 2,6-dinitroiodobenzene, 2,6-dinitroaniline, 3,5-dinitrobenzoic acid, methyl 2-chloro-4,6-dinitrobenzoate, methyl 4-chloro-2,6-dinitrobenzoate, 1,5- and 1,8-dinitronaphthalene.

C. Trinitro compounds: 1,3,5-Trinitrobenzene, TNT, picric acid, 2,4,6-trinitrobenzoic acid, picryl chloride, bromide, and iodide.

2,4,7-Trinitro- and 2,4,5,7-tetranitro-fluorenone gave deep purple solutions, while 2,2′-dinitrobiphenyl at 0.2*M* behaved like a mononitro aromatic at about 0.4*M*.

Stabilization of hydriodic acid by sodium or potassium acetate. Samples of hydriodic acid were diluted with water or acetone until 5.56 millimoles of hydriodic acid was present in 50 ml. of solution. The solutions were analyzed for iodine by titration with thiosulfate (a) immediately or shortly after they had been prepared and (b) after they had been left standing for varying lengths of time in glass stoppered flasks. The results are given below as the per cent of hydriodic acid decomposed and, in parentheses, as the millimoles of iodine found per 5.56 millimoles of hydriodic acid originally present:

	Per Cent of Hydriodic Acid Decomposed (Millimoles of Iodine Present)		
	Initially		After 2 months
Commercial hydriodic acid diluted with acetone	3% (0.09)		50% (1.5)
As above with one equivalent of CH_3CO_2Na added	3% (0.08)		15% (0.4)
	Initially		After 20 Days
Commercial hydriodic acid freshly distilled in carbon dioxide atmosphere and diluted with water	1.5% (0.04)		25% (0.71)
As above with one equivalent of CH_3CO_2Na added	0.5% (0.01)		4% (0.1)
As above with one equivalent of CH_3CO_2K added	0.4% (0.01)		4% (0.1)
	After 30 min.	After 60 min.	After 24 hr.
Commercial hydriodic acid stabilized with H_3PO_2, diluted with acetone	2% (0.05)	7% (0.09)	54% (1.5)
As above with one equivalent of CH_3CO_2Na added	0.4% (0.01)	0.4% (0.011)	4% (0.1)
As above with one equivalent of CH_3CO_2K added	0.3% (0.007)	0.4% (0.012)	4% (0.1)

The addition of less than one equivalent of sodium or potassium acetate also inhibits the decomposition, but less effectively.

FLUSHING 67, N. Y.

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Synthesis of Iminotetrazoline Derivatives as Trichomonacidal and Fungicidal Agents[1, 2]

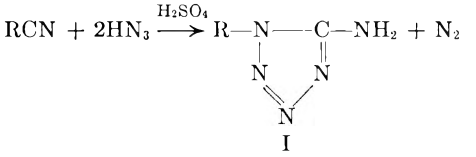
ROBERT M. HERBST AND CHARLES F. FROBERGER

Received March 14, 1957

An extensive series of 1,4-disubstituted 5-iminotetrazolines was prepared by interaction of 1-alkyl-5-aminotetrazoles with benzyl, substituted benzyl, 2-phenylethyl and 3-phenylpropyl halides. The products were usually isolated as the easily crystallizable hydrochlorides. The structure of the compounds was supported by the formation of the same product in several instances regardless of the order of introduction of the alkyl and benzyl substituents. The structure was also substantiated by the removal of the benzyl group by hydrogenolysis from a product prepared by the alkylation of 1-benzyl-5-aminotetrazole and isolation of the 1-alkyl-5-aminotetrazole.

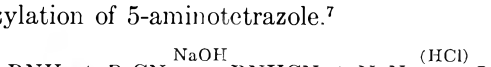
Several years ago it was observed that the salts of dialkylated 5-aminotetrazoles in which one of the alkyl groups was of moderate size were surface active agents. With the thought that these compounds might possess bacteriostatic or bactericidal activity the synthesis of a number of dialkylated aminotetrazoles was undertaken. The methylation and ethylation of 1-*n*-octyl-5-aminotetrazole gave products which exhibited a modest degree of bacteriostatic action on cultures of *Staphylococcus aureus* and *Eberthella typhosa*. The activity was markedly increased by alkylation of 1-*n*-octyl-5-aminotetrazole with benzyl chloride. For the resulting octyl benzyl aminotetrazole a phenol coefficient of about 100 was estimated. On the basis of these observations the synthesis of an extensive group of 1-alkyl-5-aminotetrazoles (I) and the products of their alkylation with benzyl and substituted benzyl halides was undertaken to determine the structural requirements for optimum bacteriostatic activity. Extensive microbiological screening[3] showed that these compounds possessed an even higher degree of cidal action against both protozoan and fungal cultures.[4]

Several methods for the synthesis of the requisite 1-alkyl-5-aminotetrazoles were used. Initially the method of von Braun and Keller[5] involving interaction of alkyl cyanides with excess hydrazoic acid in the presence of concentrated sulfuric acid was employed.



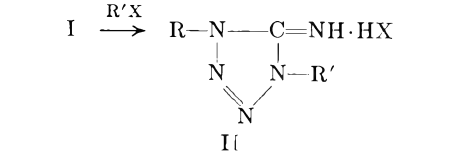
I

Subsequently, the more convenient method involving interaction of primary amines and cyanogen bromide to form monoalkylcyanamides and addition of hydrazoic acid to the latter[6] was employed. 1-Benzyl-5-aminotetrazole was prepared both from benzyl cyanide and benzylamine as well as by benzylation of 5-aminotetrazole.[7]



The 1-alkyl-5-aminotetrazoles prepared by these reactions are described in Table I.

The dialkylated products were prepared by heating without solvent to temperatures of 120–150°, the 1-alkyl-5-aminotetrazoles (I) with slightly more than an equimolar amount of the alkylating agent. Purification of the crude product was effected by several recrystallizations or by way of the free base. The latter procedure was often advantageous for the elimination of small quantities of unreacted starting materials. Most of the bases were liquids, but in several instances they could be isolated as low melting solids. The solubility of the 1-alkyl-4-aralkyl-5-iminotetrazoline hydrochlorides in both aromatic hydrocarbons and in aqueous alcohols is striking. The iminotetrazoline hydrochlorides (II) prepared in this way are described in Table II.



II

R = $CH_3(CH_2)_n$, n = 4 to 16

R′ = CH_3, CH_3CH_2, and

(1) Presented before the Division of Medicinal Chemistry at the Spring Meeting of the AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 1956.

(2) Based in part on a thesis presented by Charles F. Froberger in partial fulfillment of the requirements for the degree of Master of Science at Michigan State University.

(3) The alkyl benzyl iminotetrazolines were screened in the Parke, Davis Laboratories. The results have been published elsewhere.[4] The cooperation of Drs. C. F. Reutner, P. E. Thompson, and A. B. Hillegas in the extensive microbiological screening is gratefully acknowledged.

(4) E. F. Elslager, T. F. Reutner, and J. C. Peters, Abstracts of papers presented before the Division of Medicinal Chemistry at the Spring Meeting of the AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 1956. p. 7M.

(5) J. von Braun and W. Keller, *Ber.*, **65**, 1677 (1932).

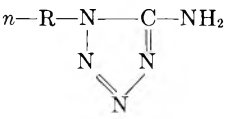
(6) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1014 (1953).

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

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

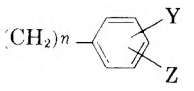
TABLE I

1-ALKYL-5-AMINOTETRAZOLES



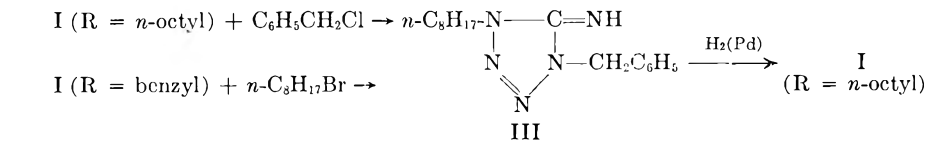
n-R	Method	Yield[a] %	M.P.°C.	Formula	Analyses % N Calcd.	Found	Reference
C_5H_{11}	B	52	165–166	$C_6H_{13}N_5$	45.1	45.6	6, 8
C_6H_{13}	B	49	166–167	$C_7H_{15}N_5$	41.4	41.7	5, 6
C_7H_{15}	B	56	164–165	$C_8H_{17}N_5$	38.2	38.5	6
C_8H_{17}	A	48	161–162	$C_9H_{19}N_5$	35.5	35.5	8
	B	64	161–162				6
C_9H_{19}	A	36	160–161	$C_{10}H_{21}N_5$	—	—	8
$C_{10}H_{21}$	A	45	161–162	$C_{11}H_{23}N_5$	31.1	31.3	
	B	51	162–163				
$C_{11}H_{23}$	A	43	158–159	$C_{12}H_{25}N_5$	—	—	8
$C_{13}H_{27}$	A	38	157–158	$C_{14}H_{29}N_5$	26.2	27.0	
$C_{14}H_{29}$	A	31	156–157	$C_{15}H_{31}N_5$	24.9	24.7	
$C_{15}H_{31}$	A	35	155–156	$C_{16}H_{33}N_5$	23.7	23.6	
$C_{17}H_{35}$	A	40	154–155	$C_{18}H_{37}N_5$	21.7	21.8	
$C_6H_5CH_2$	A	29	187–188	$C_8H_9N_5$	40.0	40.1	5
	B	72	187–188		—	—	6
	C	19[b]	189–190		—	—	7
$C_6H_5CH_2CH_2$	B	81	176	$C_9H_{11}N_5$	37.0	37.2	11

[a] Based on alkyl cyanide (Method A); Alkylamine (Method B). [b] Based on 5-aminotetrazole, other benzylated products also formed.



n = 1 to 3
Y and/or Z = H, Cl, CH_3, OCH_3, NO_2, OH.

Although the alkylation of 1-alkyl-5-aminotetrazoles (I) has been shown to lead predominantly to 1,4-dialkyl-5-iminotetrazolines (II),[9–11] the validity of these conclusions in the present instances was demonstrated by the formation of 1-*n*-octyl-4-benzyl-5-iminotetrazoline (III) by either the octylation of 1-benzyl-5-aminotetrazole (I, R = benzyl) or by the benzylation of 1-*n*-octyl-5-aminotetrazole (I, R = *n*-octyl). Similarly the methylation or ethylation of I (R = *n*-octyl) gave products identical with those obtained on octylation of I (R = CH_3 or C_2H_5).



III

Hydrogenolytic removal of the benzyl group from III formed by octylation of 1-benzyl-5-aminotetrazole gave only 1-*n*-octyl-5-aminotetrazole, a result which requires that the substituents be in equivalent positions.

(9) R. M. Herbst and D. F. Percival, *J. Org. Chem.*, **19**, 439 (1954).

(10) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).

(11) D. F. Percival and R. M. Herbst, *J. Org. Chem.*, **22**, 925 (1957).

EXPERIMENTAL[12]

1-Alkyl-5-aminotetrazoles were prepared from alkyl cyanides by interaction with excess hydrazoic acid in benzene solution in the presence of concentrated sulfuric acid,[5] Method A; by the successive addition of cyanogen bromide and hydrazoic acid to primary amines in aqueous alcoholic solution,[6] Method B; and in one case by the benzylation of 5-aminotetrazole,[7] Method C.

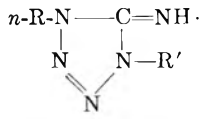
Method A. The preparation of 1-*n*-octyl-5-aminotetrazole by a modification of previously described techniques[8] serves as an example. A solution of 83 g. (0.6 mole) of *n*-octyl cyanide in 550 ml. of a 14% solution of hydrazoic acid[13] in benzene (75 g., 1.8 moles of hydrazoic acid) was treated with 175 ml. of concentrated sulfuric acid added dropwise below the surface of the liquids. The mixture was stirred vigorously throughout and the temperature was maintained at 33–38° with only intermittent cooling. After complete addition of the sulfuric acid the mixture was allowed to cool to room temperature while stirring was continued for a total of 23 hr. The layers were separated and the sulfuric acid layer was poured onto about 1.5 kg. of crushed ice, neutralized to litmus with 50% potassium hydroxide, and chilled in ice. The mixture of potassium sulfate and tetrazole was filtered by suction, washed with cold water and while still moist extracted first with 1 l. of boiling 99% isopropyl alcohol and then with 750 ml. of 90% isopropyl alcohol. The tetra-

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

(13) Reactions involving cyanogen bromide, hydrazoic acid, or sodium azide must be done in a well ventilated hood. Care must be exercised in disposing of filtrates and distillates that may contain hydrazoic acid to avoid exposure to its highly toxic vapors.

TABLE II

1-ALKYL-4-ARALKYL-5-IMINOTETRAZOLINE HYDROCHLORIDES



					Analyses			
					Calcd.		Found	
n-R	R′	Yield, %	M.P.°C.	Formula	Cl	N	Cl	N
C_5H_{11}	*p*-$ClC_6H_4CH_2$	60	151–152	$C_{13}H_{19}Cl_2N_5$	22.4	22.2	22.5	22.0
C_5H_{11}	$C_6H_5CH_2CH_2CH_2$	51	177–178	$C_{15}H_{24}ClN_5$	11.4	22.6	11.2	22.9
C_6H_{13}	*p*-$ClC_6H_4CH_2$	82	166–167	$C_{14}H_{21}Cl_2N_5$	21.5	21.2	21.3	21.1
C_6H_{13}	$C_6H_5CH_2CH_2$	43	229–230d.	$C_{15}H_{24}ClN_5$	11.4	22.6	11.6	22.4
C_6H_{13}	$C_6H_5CH_2CH_2CH_2CH_2$	55	171–172	$C_{16}H_{26}ClN_5$	11.0	21.6	11.0	21.4
C_7H_{15}	*p*-$ClC_6H_4CH_2$	90	151–152	$C_{15}H_{23}Cl_2N_5$	20.6	20.3	20.5	20.4
C_8H_{17}	$C_6H_5CH_2$	95	163–165	$C_{16}H_{26}ClN_5$	11.0	21.6	11.0	21.4
C_8H_{17}	*o*-$CH_3C_6H_4CH_2$	54	161–162	$C_{17}H_{28}ClN_5$	10.5	20.7	10.8	20.7
C_8H_{17}	*m*-$CH_3C_6H_4CH_2$	66	163–164	$C_{17}H_{28}ClN_5$	10.5	20.7	10.7	20.5
C_8H_{17}	*p*-$CH_3C_6H_4CH_2$	21	159–160	$C_{17}H_{28}ClN_5$	10.5	20.7	10.8	20.5
C_8H_{17}	*o*-$ClC_6H_4CH_2$	73	167–168	$C_{16}H_{25}Cl_2N_5$	19.8	19.5	20.0	19.7
C_8H_{17}	*p*-$ClC_6H_4CH_2$	89	165–166	$C_{16}H_{25}Cl_2N_5$	19.8	19.5	19.8	19.4
C_8H_{17}	*p*-$CH_3OC_6H_4CH_2$	42	155–156	$C_{17}H_{28}ClN_5O$	10.0	19.8	9.9	19.8
C_8H_{17}	*p*-$NO_2C_6H_4CH_2$	70	168–169	$C_{16}H_{25}ClN_6O_2$	9.6	22.8	9.5	22.8
C_8H_{17}	2,4-$Cl_2C_6H_3CH_2$	68	167–168	$C_{16}H_{24}Cl_3N_5$	27.1	17.8	27.0	17.9
C_8H_{17}	3,4-$Cl_2C_6H_3CH_2$	74	159–160	$C_{16}H_{24}Cl_3N_5$	27.1	17.8	26.9	17.7
C_8H_{17}	2-HO-5-$NO_2C_6H_3CH_2$	47	184–186	$C_{16}H_{25}ClN_6O_2$	9.2	21.8	9.1	21.9
C_8H_{17}	$C_6H_5CH_2CH_2$	64	207–208	$C_{17}H_{28}ClN_5$	10.5	20.7	10.3	20.8
C_8H_{17}	$C_6H_5CH_2CH_2CH_2CH_2$	62	153–154	$C_{18}H_{30}ClN_5$	10.1	19.9	9.9	19.7
C_9H_{19}	$C_6H_5CH_2$	86	161–162	$C_{17}H_{28}ClN_5$	10.5	20.7	10.5	20.8
C_9H_{19}	*p*-$ClC_6H_4CH_2$	79	152–153	$C_{17}H_{27}Cl_2N_5$	19.1	18.8	18.9	18.8
C_9H_{19}	2,4-$Cl_2C_6H_3CH_2$	65	143–144	$C_{17}H_{26}Cl_3N_5$	26.1	17.2	25.9	17.4
$C_{10}H_{21}$	$C_6H_5CH_2$	75	156–157	$C_{18}H_{30}ClN_5$	10.1	19.9	10.2	20.0
$C_{10}H_{21}$	*p*-$ClC_6H_4CH_2$	83	152–154	$C_{18}H_{29}Cl_2N_5$	18.4	18.1	18.3	18.1
$C_{11}H_{23}$	$C_6H_5CH_2$	90	154–155	$C_{19}H_{32}ClN_5$	9.7	19.1	9.9	19.1
$C_{11}H_{23}$	*p*-$ClC_6H_4CH_2$	90	145–146	$C_{19}H_{31}Cl_2N_5$	17.7	17.5	17.9	17.4
$C_{13}H_{27}$	$C_6H_5CH_2$	67	155–156	$C_{21}H_{36}ClN_5$	9.0	17.8	9.1	17.9
$C_{14}H_{29}$	$C_6H_5CH_2$	83	153–154	$C_{22}H_{38}ClN_5$	8.7	17.2	8.7	17.0
$C_{14}H_{29}$	3,4-$Cl_2C_6H_3CH_2$	78	139–141	$C_{22}H_{36}Cl_3N_5$	22.3	14.7	22.4	14.6
$C_{15}H_{31}$	$C_6H_5CH_2$	87	152–153	$C_{23}H_{40}ClN_5$	8.4	16.6	8.6	16.4
$C_{15}H_{31}$	*m*-$CH_3C_6H_4CH_2$	60	141–142	$C_{24}H_{42}ClN_5$	8.1	16.1	8.3	15.8
$C_{17}H_{35}$	$C_6H_5CH_2$	89	145–146	$C_{26}H_{44}ClN_5$	7.9	15.6	7.7	15.4
$C_{17}H_{35}$	*p*-$CH_3C_6H_4CH_2$	50	133–135	$C_{26}H_{46}ClN_5$	7.6	15.1	7.8	14.9
$C_{17}H_{35}$	*o*-$ClC_6H_4CH_2$	74	143–145	$C_{25}H_{43}Cl_2N_5$	14.6	14.5	14.5	14.7

zole crystallized from the alcoholic solutions on cooling and was recovered by systematic concentration of the mother liquors and recrystallization from 90% isopropyl alcohol. Appreciable amounts of low melting material, probably amide, accumulated in the last fractions obtained from the original mother liquors. Yields, physical constants and analytical data for the tetrazoles prepared in this way are given in Table I.

Method B. The preparation of 1-*n*-octyl-5-aminotetrazole by a modification of the technique of Garbrecht and Herbst[6] serves as an example. *n*-Octylamine (45 g., 0.33 mole) was dissolved in 350 ml. of 95% ethanol. Keeping the temperature of the reaction below 10° in all subsequent steps, a solution of 36 g. (0.33 mole) of cyanogen bromide in 60 ml. of water and 60 ml. of 95% ethanol was added dropwise with stirring, followed immediately by 13 g. of sodium hydroxide in 40 ml. of water. The solution was stirred for an hour at ice bath temperature after which 44 g. (0.66 mole) of sodium azide dissolved in 125 ml. of water[13] was added rapidly, followed more slowly by 57 ml. of concentrated hydrochloric acid diluted with an equal volume of water. The reaction mixture was stirred for 2 hr. at ice bath temperature when it was transferred to a steam bath and boiled under reflux for 3 hr. On chilling the solution 1-*n*-octyl-5-aminotetrazole crystallized in almost pure form. Further smaller fractions were obtained by concentrating the reaction mixture. The product was recrystallized from 90% isopropyl alcohol. Physical constants, yields, and analytical data for the tetrazoles prepared in this way are given in Table I.

Method C. The benzylation of 5-aminotetrazole followed a previously described procedure.[7] 1-Benzyl-5-aminotetrazole is formed together with other benzylation products and is described in Table I.

1,4-Dialkyl-5-iminotetrazolines. 1-n-Octyl-4-methyl-5-iminotetrazoline hydrochloride. A mixture of 19.7 g. (0.1 mole) of 1-*n*-octyl-5-aminotetrazole and 12.6 g. (0.1 mole) of methyl sulfate was heated in an oil bath at 120–125° for 3 hr. The crude methosulfate was dissolved in 75 ml. of water, the solution made alkaline with 25 ml. of 40% sodium hydroxide, saturated with potassium carbonate, and the base extracted with benzene. After drying the benzene solution over potassium carbonate, the solvent was removed on a water bath under reduced pressure and the residue taken up in 50 ml. of 99% isopropyl alcohol. The hydrochloride was precipitated by addition of 15 ml. of concentrated hydrochloric acid and 50 ml. of ether. Recrystallization was effected from 75 ml. of 99% isopropyl alcohol by addition of an equal volume of ether; yield 16.1 g., (65%), m.p. 200–201°.

Anal. Calcd. for $C_{10}H_{22}ClN_5$: N, 28.2. Found: N, 28.2.

The free base is a liquid, b.p. 147–151° at 4 mm.

A phenylthiourea was formed by interaction of the base with phenyl isothiocyanate and crystallized from 95% ethanol, m.p. 83.5–84°.

Anal. Calcd. for $C_{17}H_{26}N_6S$: N, 24.3. Found: N, 24.4.

The 3,5-dinitrobenzoyl derivative obtained from the base on treatment with 3,5-dinitrobenzoyl chloride crystallized from aqueous ethanol, m.p. 70.5–71°.

Anal. Calcd. for $C_{17}H_{23}N_7O_5$: N, 24.2. Found: N, 24.1.

The same base, hydrochloride, and derivatives were isolated after interaction of 1-methyl-5-aminotetrazole and *n*-octyl bromide in ethanol solution at 180° for 48 hr. in a sealed tube.

1-Ethyl-5-n-octyl-5-iminotetrazoline hydrochloride was prepared both by interaction of 1-*n*-octyl-5-aminotetrazole and ethyl sulfate or 1-ethyl-5-aminotetrazole[10] and *n*-octyl chloride in a similar manner. The hydrochloride crystallized from 99% isopropyl alcohol, m.p. 165–166°.

Anal. Calcd. for $C_{11}H_{24}ClN_5$: N, 26.8. Found: N, 27.1.

The free base is a liquid, b.p. 160–164° at 8 mm.

The *p*-nitrobenzoyl derivative was crystallized from aqueous ethanol, m.p. 56–57°.

Anal. Calcd. for $C_{18}H_{26}N_6O_3$: N, 22.5. Found: N, 22.7.

The 3,5-dinitrobenzoyl derivative was crystallized from aqueous ethanol, m.p. 57–58°.

Anal. Calcd. for $C_{18}H_{25}N_7O_5$: N, 23.4. Found: N, 23.5.

1-Alkyl-4-aralkyl-5-iminotetrazolines. The 1,4-disubstituted 5-iminotetrazolines were prepared by interaction of 1-alkyl-5-aminotetrazoles and benzyl, substituted benzyl, 2-phenylethyl, and 3-phenylpropyl halides as illustrated by the following examples.

1-n-Octyl-4-benzyl-5-iminotetrazoline hydrochloride. A mixture of 15 g. of 1-*n*-octyl-5-aminotetrazole and 11.4 g. of benzyl chloride was heated in an oil bath at 120–125° for 8 hr. A homogeneous melt formed which resolidified after a mildly exothermic reaction. The solid product was dissolved in 100 ml. of hot 95% ethanol, the solution diluted with 300 ml. of warm water, decolorized with charcoal and chilled. The crude hydrochloride which crystallized was filtered by suction, washed with cold aqueous ethanol, air dried, and washed again with benzene to remove unreacted benzyl chloride. Recrystallization from a mixture of 170 ml. of water, 85 ml. of 95% ethanol and 2.5 ml. of concentrated hydrochloric acid gave pure hydrochloride as colorless needles. Physical constants, yield, and analytical data are given in Table II.

The hydrobromide was prepared in a similar manner from benzyl bromide and 1-*n*-octyl-5-aminotetrazole. It was crystallized from 50% aqueous ethanol; yield 81%, m.p. 165–166°.

Anal. Calcd. for $C_{16}H_{26}BrN_5$: Br, 21.7; N, 19.0. Found: Br, 21.8; N, 19.0.

1-n-Octyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride. A mixture of 15 g. of 1-*n*-octyl-5-aminotetrazole and 15 g. of *p*-chlorobenzyl chloride was heated in an oil bath at 120–125° for 4 hr. during which a homogeneous melt formed and resolidified after a mildly exothermic reaction. The crude hydrochloride was taken up in the minimum amount of hot 95% ethanol, the solution diluted with 500 ml. of water and distilled to remove unreacted *p*-chlorobenzyl chloride. The residual aqueous solution was made strongly alkaline to litmus with 25% sodium hydroxide solution and the organic base was extracted with several portions of benzene. The benzene solutions were combined and dried over potassium carbonate, and the solvent was removed under reduced pressure on a water bath. The residual base was taken up in 75 ml. of 95% ethanol and converted into hydrochloride by addition of 15 ml. of concentrated hydrochloric acid. The mixture was heated to boiling, diluted with 75 ml. of hot water and allowed to crystallize. The hydrochloride was recrystallized from aqueous ethanol from which it separates as colorless needles. Physical constants, yield, and analytical data are given in Table II.

In another preparation the free base left on evaporation of the benzene solutions crystallized on chilling and could be recrystallized from *n*-hexane, m.p. 52–53°.

Anal. Calcd. for $C_{16}H_{24}ClN_5$: Cl, 11.0; N, 21.6. Found: Cl, 11.0; N, 21.8.

In a number of instances, particularly when the crude hydrochlorides were pigmented, it was advantageous to recrystallize the salts from toluene or benzene before the final recrystallization from aqueous ethanol. The hydrochlorides are quite soluble in the hot aromatic hydrocarbon solvents but almost insoluble in the cold. Pigments generally remain in the solvents. In addition to their solubility in hot aqueous alcohol and hot benzene or toluene, most of the hydrochlorides are also soluble in chloroform, ethyl acetate and hot ethylene chloride, but almost insoluble in cold water and aliphatic hydrocarbons. Physical constants, yields, and analytical data for all the iminotetrazoline hydrochlorides prepared as just described are given in Table II.

1-n-Octyl-4-benzyl-5-iminotetrazoline hydrochloride was also prepared by heating a mixture of 8.7 g. of 1-benzyl-5-aminotetrazole and 10.5 g. of *n*-octyl bromide at 135° for 8 hr. The crude hydrobromide was converted into base and hydrochloride as described in the preceding preparations. The hydrochloride was identical with the material made by benzylation of 1-*n*-octyl-5-aminotetrazole.

The position of the octyl group was further established by hydrogenolysis of a solution of 1.6 g. of 1-*n*-octyl-4-benzyl-5-iminotetrazoline hydrochloride (prepared by octylation of 1-benzyl-5-aminotetrazole) in 75 ml. of 95% ethanol in presence of 0.05 g. of palladium oxide catalyst at 50 p.s.i. hydrogen at room temperature. Hydrogenolysis was complete in 1 hr. The catalyst was filtered off, washed with 95% ethanol, then water. The combined filtrates were evaporated to incipient crystallization, neutralized with potassium carbonate, and the solid product recrystallized twice from 50% ethanol; yield 0.9 g., m.p. 161–162°, no depression on admixture of 1-*n*-octyl-5-aminotetrazole.

EAST LANSING, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Reaction of 5-Amino-1,2,3,4-Thiatriazole with Benzylamine

EUGENE LIEBER AND C. N. PILLAI

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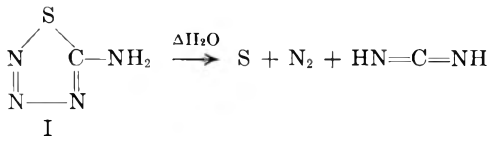
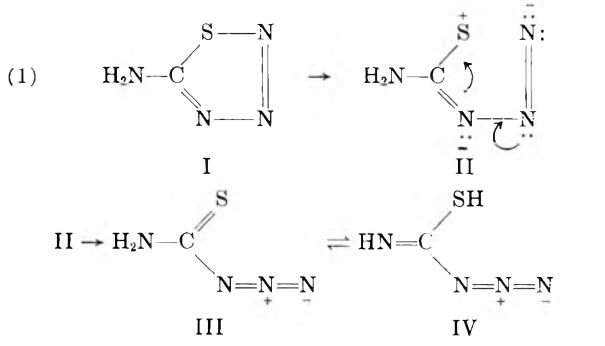
The reaction of 5-amino-1,2,3,4-thiatriazole with benzylamine proceeds by two modes, *viz.*, (*a*) a complete collapse of the ring with the elimination of sulfur, nitrogen, and cyanamid, the latter being isolated as benzylguanidine; and, (*b*) a decomposition to thiocyanic and hydrazoic acids, as evidenced by the isolation of benzylthiourea, *sym*-dibenzylthiourea and benzylammonium azide. The extent of modes (*a*) and (*b*) are dependent on the molar ratio of benzylamine, mode (*a*) predominating at low molar ratios, whereas mode (*b*) increases with increase in the mole ratio of benzylamine used. Mode (*a*) parallels the thermal degradation of 5-amino-1,2,3,4-thiatriazole and is ascribed to an explosive internal oxidation-reduction; whereas mode (*b*) is ascribed to a degradation of the anion of 5-amino-1,2,3,4-thiatriazole in which the azido ion is ejected. These theories are discussed.

One of the marked properties of 5-amino-1,2,3,4-thiatriazole (I) is the remarkable instability of its aqueous solution.[1] On standing at room temperature, even for a short period, the familiar whitish opalescence of colloidal sulfur sets in, the process being much accelerated by warming. One mole proportion of pure nitrogen is liberated along with the precipitation of sulfur and the formation of cyanamid:

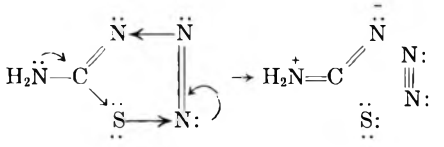


I

The above aqueous degradation is so startingly similar to the external reduction of an organic azide by hydrogen sulfide[2] as to suggest that the reaction proceeds by an internal oxidation-reduction involving the sulfur atom and the three sequentially linked nitrogen atoms of the heterocyclic ring. This can occur in one of two ways; *viz.* (1) a heterolytic bond breaking I to II (III and IV) in which



the internal oxidation-reduction takes place through the *geminal* thiol and azido groups[3] of structures III or IV; and, (2) an intramolecular oxidation-reduction movement of electrons *prior to the disintegration of the ring*, initiated by the movement of the lone pair of electrons of the 5-amino group into the ring followed by the ejection of a sulfur atom, a molecule of nitrogen, and the polarized form of cyanamid.



It should be noted that the thermal decomposition of I from the solid state exactly parallels its decomposition in water, the same products being obtained. Depending on the quantity involved, the thermal degradation of I proceeds more or less explosively. Freund and Schander[1] further showed that the same mode of degradation of I prevails in boiling aniline, the cyanamid being isolated as dicyandiamide. This has been confirmed in the present study.

Freund and Schander[1] observed that I was soluble in excess of aqueous alkali and could be recovered unchanged provided that the neutralization was immediately effected. Under these conditions they qualitatively reported the precipitation of a small quantity of sulfur and an odor of hydrazoic acid. By heating with aqueous alkali Freund and Schander[1] stated that the decomposition of I was more complete, and that on subsequent acidification, sulfur, hydrogen sulfide, and hydrazoic acid were formed. They failed to report the evolution of any gas on the reaction of I with aqueous alkali. We have confirmed these observations with the important exception that *sulfur precipitates prior to neutralization*. While this latter observation points to a similarity in the mode of decomposition in such disparate solvents as water, aqueous alkali, and aniline, the presence of sulfide and azide ions in the aqueous alkali points to a second mode of decomposition:

$$I + OH^- \rightarrow NCS^- + N_3^-$$

(1) M. Freund and A. Schander, *Ber.*, 29, 2500 (1896).

(2) Hydrogen sulfide reduces guanylazide nitrate to guanidine and nitrogen, sulfur being precipitated, J. Thiele, *Ann.*, 270, 1 (1892).

(3) A very closely related example is the spontaneous decomposition of azidothiocarbonic acid, $HSC(S)N_3$ to thiocyanic acid, nitrogen, and sulfur [H. E. Williams, *Cyanogen Compounds*, Edward Arnold and Co., London, 1949, page 321]. A reexamination of the structure of azidodithiocarbonates is in progress in this laboratory.

followed by alkaline hydrolysis of the thiocyanate ion to sulfide ion and ammonia. It was the objective of this investigation to explore this latter mode of decomposition by a study of the decomposition of I in benzylamine as solvent.

When a mixture of one mole proportion each of I and benzylamine was warmed on the steam bath a vigorous reaction ensued with copious evolution of nitrogen followed by the precipitation of sulfur in 70% yield and the isolation of benzylguanidine also in 70% yield. As the mole proportion of the benzylamine increased, the violence of the reaction, under the same initial conditions, moderated. This was paralleled by a decrease in the yield of sulfur. The products isolated depended on the method of working up the reaction mixture. Benzylammonium azide, a new compound, was readily isolated by sublimation from the reaction mixture due to the heat of reaction. The yield increased from 27 to 85% as the mole proportion of benzylamine to I increased from 2 to 4. The isolation of benzylammonium azide indicated that the following mode of decomposition was taking place:

$$I \rightarrow HNCS + HN_3$$

and that the reaction products of benzylamine and thiocyanic acid should also be present. Again, the method of recovery determined the type of product isolated. By heating a 1:4 mole mixture of I and benzylamine at the boiling point of benzylamine (185°), the only product isolated was 1,3-dibenzyl-2-thiourea, the benzylammonium azide being lost by thermal decomposition. Under milder conditions of reaction, and the removal of the excess benzylamine by steam distillation, sulfur, benzylthiourea, 1,3-dibenzyl-2-thiourea and benzylammonium azide were all isolated from the reaction mixture. The experimental results show that I undergoes two modes of decomposition:

$$\text{I} \begin{cases} \xrightarrow{\text{(a)}} S + N_2 + HN{=}C{=}NH \\ \xrightarrow{\text{(b)}} HNCS + HN_3 \end{cases}$$

mode (*a*) being the same as in its thermal decomposition from the solid state, whereas mode (*b*) is initiated under environmental conditions that will create the anion of I (Structure V, Chart I) which then undergoes a heterolytic bond breaking to structure VI, the conjugate base of III or IV. The thiocyanic acid (VII) thus produced reacts with the benzylamine to initially produce the monobenzylated product (VIII) which in turn undergoes reaction with the excess of benzylamine to produce the dibenzylated product (IX). This latter point was demonstrated independently by heating an authentic sample of benzylthiourea (VIII) with benzylamine. The change in the mode of decomposition from (*a*) to (*b*) with increasing molar proportion of benzylamine can be simply accounted for by an increase in the proportion of the anion (V) as a greater quantity of I dissolves in the solvent medium.

EXPERIMENTAL[4,5]

5-Amino-1,2,3,4-thiatriazole (I) was prepared by a modification[6] of the method of Freund and Schander.[1]

Decomposition of I *in water.* The observations reported by Freund and Schander[1] were confirmed. A weighed sample of I gave very nearly one mole proportion of a gas. A mass spectrometric analysis[7] showed the gas to be pure nitrogen.

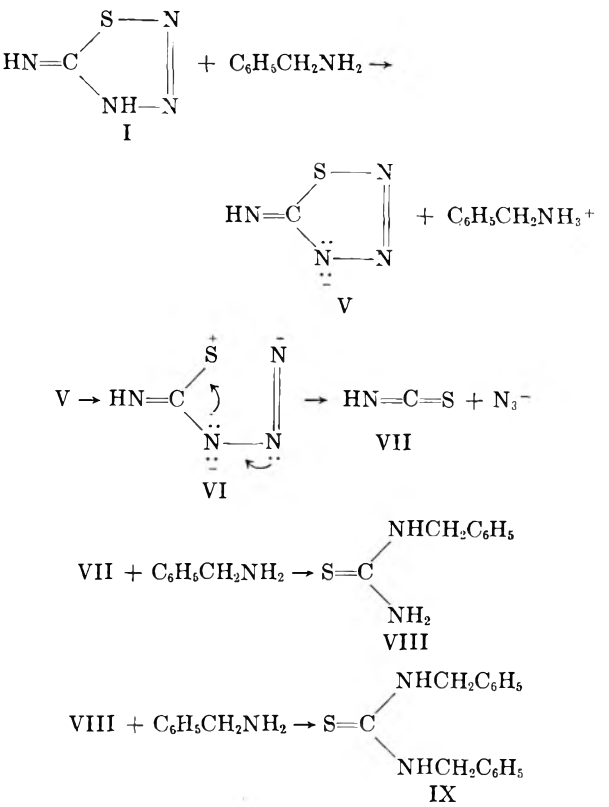


CHART I: Reaction of 5 Amino-1, 2, 3, 4-Thiatriazole in Excess Benzylamine

Reaction of I *with aqueous sodium hydroxide.* On warming I in 4% aqueous sodium hydroxide, sulfur was precipitated without the evolution of a gas. Acidification of the solution resulted in the evolution of hydrogen sulfide and hydrazoic acid, the latter being detected by the blood-red coloration it produces with a solution of ferric chlorides.[8]

Reaction of I *with aniline.* A mixture of 2 g. of I and 5 g. of aniline was boiled until the evolution of gas ceased. The mixture was diluted with 5 ml. of ethanol and the precipitated sulfur removed by filtration. The ethanol was removed by evaporation, whereupon the addition of ether precipitated a white crystalline material, m.p. 209–210°. It was

(4) All melting points are uncorrected.

(5) Microanalyses by Dr. C. Weiler and Dr. F. B. Strauss, Oxford, England.

(6) E. Lieber, E. Oftedahl, C. N. Pillai, and R. D. Hites, *J. Org. Chem.*, **22**, 441 (1957).

(7) Consolidated Engineering Corporation, Pasadena, Calif.

(8) L. M. Dennis and A. W. Browne, *J. Am. Chem. Soc.*, **26**, 577 (1904).

identified as dicyandiamide by mixed melting point technique.

Reaction of I *with benzylamine.* (*a*) *One molar proportion of benzylamine.* A mixture of 1.02 g. (0.01 mole) of I and 1.07 g. (0.01 mole) of benzylamine was heated on a steam bath. A violent reaction, reminiscent of the behavior of I on melting,[3] took place. After 5 min. heating the evolution of gas had practically ceased. The mixture in the flask was mixed with 5 ml. of ethanol and cooled. The yellow precipitate, after filtration and washing with ether, was identified as sulfur, yield 0.24 g. (70%). The mother liquor was evaporated at room temperature to remove the ethanol, and the resulting oil washed thoroughly with ether to remove any unreacted benzylamine. A pale yellow sirup, yield, 1.1 g. (73%), was obtained. The oil was found to be very soluble in water and to yield a strongly basic solution. It could not be induced to crystallize. It was identified as *benzylguanidine* by conversion to the corresponding picrate and nitrate.

Benzylguanidine picrate was obtained by reaction of the pale yellow sirup obtained above with an aqueous solution of picric acid. Recrystallized from ethanol, m.p. 185–186°. This compound has been reported to melt at 185.5°[9] and at 190–191°.[10] Accordingly, it was analyzed.

Anal. Calcd. for $C_{14}H_{14}N_6O_7$: C, 44.43; H, 3.73; N, 22.23. Found: C, 44.91; H, 3.93; N, 22.20.

Benzylguanidine nitrate was obtained by reaction of the pale yellow sirup obtained above with an aqueous solution of nitric acid. The nitrate salt on recrystallization from water melted at 151–152°. This compound has been reported to melt at 149–150°[10] and at 165°.[9]

Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.25; H, 5.70; N, 26.41. Found: C, 44.96; H, 5.88; N, 26.6.

(*b*) *Two-mole proportion of benzylamine.* A mixture of 5.1 g. (0.05 mole) of I and 10.7 g. (0.1 mole) of benzylamine was warmed on the steam bath. The mixture which contained undissolved I, began to undergo visible reaction almost immediately, as evidenced by vigorous effervescence and frothing, accompanied by the deposition of light glistening crystals in the upper cooler portion of the reaction flask. The evolution of gas was complete in approximately 10 min. The reaction mixture was diluted with 20 ml. of ethanol and cooled. The yellow crystalline sulfur was removed by filtration, yield, 0.5 g. (31%). The filtrate was mixed with enough ether to produce a milky appearance and stored in the refrigerator for several hours. The colorless crystals which had separated were filtered and washed with ether. It was identified as *benzylammonium azide*, yield 2 g. (27%). It was purified by reprecipitation from ethanolic solution with ether, m.p. 156–157°.

Anal. Calcd. for $C_7H_{10}N_4$: C, 55.96; H, 6.71; N, 37.33. Found: C, 56.61; H, 6.84; N, 36.80.

The identification was completed by mixture melting point technique with an authentic specimen of *benzylammonium azide* prepared by distilling hydrazoic acid into an ethanolic solution of benzylamine and precipitating with ether.

Benzylammonium picrate, prepared by double decomposition of *benzylammonium azide* with picric acid solution, was recrystallized from aqueous ethanol, m.p. 194°.

Anal. Calcd. for $C_{13}H_{12}N_4O_7$: N, 16.67. Found: N, 16.30.

(*c*) *Four-mole proportion of benzylamine.* A mixture of 5.1 g. (0.05 mole) of I and 21.4 g. (0.2 mole) of benzylamine was heated on the steam bath. There was a slight, but detectable, effervescence and the solution, which was originally clear, became thick with white crystalline material. The mixture was cooled and diluted with 10 ml. of ether. The glistening platelike crystals weighed 6.4 g. (85%) and were identified as benzylammonium azide. The ether was removed from the filtrate by distillation and the residue steam-distilled in order to remove the excess of benzylamine. The aqueous solution in the distilling flask was filtered to remove about 0.1 g. (about 5%) of sulfur. The filtrate was concentrated by evaporation of the water on a steam bath until a sirupy residue was obtained and cooled. The crystalline precipitate obtained was recrystallized twice from ethanol to yield 3 g. (25%), m.p. 147–148°. It was identified as *1,3-dibenzyl-2-thiourea* by mixed melting point with an authentic specimen.[11]

The mother liquor resulting from the recovery of the 1,3-dibenzyl-2-thiourea was concentrated on the steam bath. A crystalline material was obtained which, on recrystallization from hot water, melted at 161–162°. It was identified as *benzylthiourea*, yield 1 g. (12%), by mixed melting technique with an authentic specimen prepared from benzylisothiocyanate and ammonia.

Direct preparation of 1,3-dibenzyl-2-thiourea from I. A mixture of 1.02 g. (0.01 mole) of I and 4.32 g. (0.04 mole) of benzylamine was heated on the steam bath until evolution of gas had ceased (about 5 min.) and then boiled for 10 min. The thick dark sirup was cooled and diluted with 5 ml. of ether. On cooling in the refrigerator overnight, a quantity of pale yellow crystals had precipitated. Recrystallization from ethanol yielded 0.5 g. (20%) of material, m.p. 147–148°. Mixed melting point with an authentic specimen[11] of 1,3-dibenzyl-2-thiourea gave no depression.

Reaction of benzylthiourea with benzylamine. A mixture of 0.9 g. (0.05 mole) of benzylthiourea (from benzylisothiocyanate and ammonia) and 0.9 g. (0.08 mole) of benzylamine was boiled for 5 min. After cooling, the product was recovered as described above; yield about 0.3 g. (about 20%), m.p. 147–148°; no depression of melting point with an authentic specimen of 1,3-dibenzyl-2-thiourea.

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CHICAGO 14, ILL.

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[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

1,2,2-Triarylethylenes Containing *o*- and *m*-Substituents

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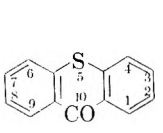
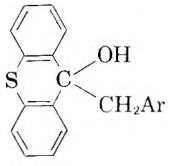
A number of new 1,2,2-triarylethylenes bearing substituents in the *ortho* and *meta* positions have been synthesized from thiaxanthone and from *o*- and *m*-substituted benzophenones. The bromination of these ethylenes has been investigated, and the products thus obtained are being tested as potential inhibitors of the secretions of the anterior pituitary.

Many derivatives of 1,2,2-triphenylethylene show more or less pronounced estrogenic activity,[1] or possess other interesting biological properties, such as inhibition of the secretions of the anterior pituitary,[2] or antagonistic action towards mammary gland hypertrophy induced by more potent estrogens.[3] As these various activities are not necessarily present in the same degree in any one triarylethylene, it was hoped that substitution in the *ortho* and *meta* positions, known to be unfavorable to estrogenic activity, would result in compounds useful for their other biological properties. The present work records the synthesis of a number of *o*- and *m*-substituted 1,2,2-triarylethylenes.

One of the intermediates used was thiaxanthone (I), which was condensed with the Grignard reagents from benzyl chloride and several of its substitution products. The tertiary thiaxanthydrols of general formula II obtained readily underwent dehydration to give the ethylenes of general formula

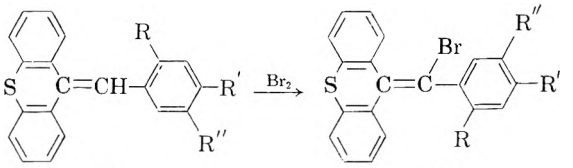


I



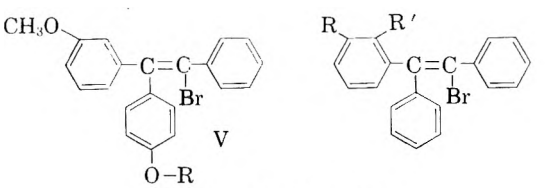
II

III. In this series, 10-benzalthiaxanthene and 10-(4-chlorobenzal)thiaxanthene have already been described in the literature;[4] 10-(2-chlorobenzal)-, 10-(2,4-dichlorobenzal)-, 10-(3,4-dichlorobenzal)-, and 10-(2,5-dimethylbenzal)-thiaxanthene are new compounds. As is the case with 10-arylidenexanthenes,[5] bromination of these 10-arylidenethiaxanthenes resulted in substitution on the ethylene bond, with formation of a series of 10-(ω-bromoarylidene)thiaxanthenes (IV), in excellent yield.



III IV

It is known that in the 1,2,2-triphenylethylene group, the presence of alkyloxy groups in *para* positions results in potent estrogens, as is the case of 1-bromo-1-phenyl-2,2-bis(*p*-ethoxyphenyl)-ethylene,[6] which has found clinical application. The synthesis of similar compounds in which one alkyloxy group has been shifted to a *meta* position has now been performed, starting from *m*-methoxybenzoic acid, whose chloride underwent Friedel-Crafts reactions with anisole and phenetole to give 3,4′-dimethoxybenzophenone and 3-methoxy-4′-ethoxybenzophenone respectively; interaction of the substituted benzophenones with benzylmagnesium chloride, and dehydration of the tertiary alcohols obtained, yielded the corresponding liquid ethylenes which underwent bromination to the well-crystallized 1-bromo-1-phenyl-2-(*m*-methoxyphenyl)-2-(*p*-methoxyphenyl)ethylene (V; R = CH_3) and 1-bromo-1-phenyl-2-(*m*-methoxyphenyl)-2-(*p*-ethoxyphenyl)ethylene (V; R = C_2H_5). In view of the interesting biological properties found in many fluorine-containing molecules,[7] 2- and 3-fluorobenzophenone were condensed with benzylmagnesium chloride to give 1,2-diphenyl-2-(2-fluorophenyl)- and 1,2-diphenyl-2-(3-fluorophenyl)ethyl-



V

VI; R = H, R′ = F
VII; R = F, R′ = H

(1) J. M. Robson and A. Schönberg, *Nature*, **140**, 196 (1937); J. M. Robson, A. Schönberg, and W. Tadros, *Nature*, **150**, 22 (1942); A. Lacassagne *et al.*, *Experientia*, **2**, 70 (1946); *Bull. soc. chim. biol.*, **29**, 1087 (1947); **30**, 674 (1948); **32**, 255 (1950).

(2) *Cf.* N. P. Buu-Hoï, N. D. Xuong, and A. Beauvillain, *Experientia*, **13**, 20 (1957).

(3) *Cf.* N. P. Buu-Hoï, International Symposium on Chemotherapy of Cancer (Oslo, 1956); to be published in *Acta Unio Intern. contra Cancrum.*

(4) E. Bergmann, *et al.*, *Bull. soc. chim. France*, 262 (1952).

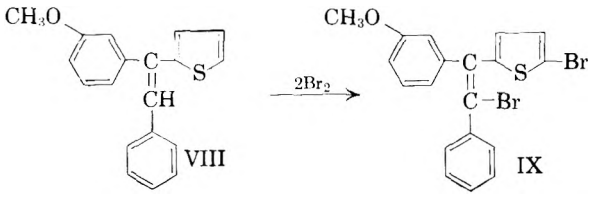
(5) Cf. N. P. Buu-Hoï and N. D. Xuong, *J. Org. Chem.*, **16**, 1633 (1951).

(6) R. Greene, *Brit. Med. J.*, **1**, 9 (1946).

(7) *Cf.* N. P. Buu-Hoï, L. Corre-Hurst, and N. D. Xuong, *Bull. soc. chim. biol.*, **37**, 867 (1955); N. P. Buu-Hoï, D. Lavit, and N. D. Xuong, *J. Org. Chem.*, **19**, 1617 (1954).

ene, and these compounds underwent bromination to form the bromo derivatives VI and VII.

In the group of thiophene analogs of triarylethylene, an interesting case is that of compound VIII, prepared from 2-(*m*-methoxybenzoyl)thiophene, whose bromination afforded, not the expected monobrominated derivative, but a dibromo compound of formula IX. The structure of this latter product was determined by an independent synthesis from 2-bromo-5-(*m*-methoxybenzoyl)-thiophene, thus proving that one bromine atom had entered the heterocyclic nucleus.[8]



All the ethylenes prepared are very weak estrogens or are inactive in this respect, and are currently being tested for inhibitory activity towards the secretions of the anterior pituitary.

EXPERIMENTAL

Preparation of 10-arylidenethiaxanthenes. To a water-cooled solution in anhydrous ether of a Grignard reagent prepared from magnesium shavings (1.2 g.-atoms) and benzyl chloride or one of its substitution derivatives (1.1 moles), thiaxanthone[9] (1 mole, suspended in ether) was added in small portions, and the mixture refluxed for 30 min. on a bath. After cooling, and decomposition with an ice-cooled dilute aqueous solution of sulfuric acid, the ether solution of the appropriate tertiary alcohol (II) was washed with water, the solvent removed, and the residue dehydrated by refluxing for 5 min. with pure formic acid (3 parts). After dilution with water the dehydration product was taken up in benzene, the benzene solution washed with water and dried over calcium chloride, the solvent removed, and the residue vacuum-fractionated. The yields of 10-arylidenethiaxanthenes thus obtained ranged from 70 to 80%. *10-(2-Chlorobenzal)thiaxanthene* (III; R = Cl, R′ = R″ = H), thus prepared from *o*-chlorobenzyl chloride, boiled at 275–285°/20 mm., and crystallized from acetic acid in fine, yellowish needles, m.p. 121°.

Anal. Calcd. for $C_{20}H_{13}ClS$: C, 74.9; H, 4.1. Found: C, 74.7; H, 3.8.

10-(2,4-Dichlorobenzal)thiaxanthene (III; R = R′ = Cl, R″ = H), b.p. 295–305°/20 mm., prepared with 2,4-dichlorobenzyl chloride, crystallized from acetic acid in pale yellow prisms, m.p. 128°.

Anal. Calcd. for $C_{20}H_{12}Cl_2S$: C, 67.7; H, 3.4. Found: C, 67.4; H, 3.5.

The isomeric *10-(3,4-dichlorobenzal)thiaxanthene* (III; R = H, R′ = R″ = Cl), b.p. 280–290°/16 mm., prepared with 3,4-dichlorobenzyl chloride, crystallized from acetic acid in shiny, yellowish prisms, m.p. 134°.

Anal. Calcd. for $C_{20}H_{12}Cl_2S$: C, 67.7; H, 3.4. Found: C, 68.0; H, 3.3.

10-(2,5-Dimethylbenzal)thiaxanthene (III; R = R″ = CH_3, R′ = H), b.p. 285–288°/25 mm., prepared with 2,5-dimethylbenzyl chloride, crystallized from ethanol in pale yellow prisms, m.p. 111°.

Anal. Calcd. for $C_{22}H_{18}S$: C, 83.8; H, 5.9. Found: C, 84.0; H, 5.8.

Bromination of 10-arylidenethiaxanthenes. To a solution of 1 g. of 9-(4-chlorobenzal)thiaxanthene[1] in 20 ml. of dry chloroform, 1.5 g. of bromine (in chloroform solution) was added in small portions, and, after decoloration, the solvent was distilled off. The residue was crystallized twice from acetic acid, giving 1.2 g. of *10-(ω-bromo-4-chlorobenzal)-thiaxanthene* (IV; R = R″ = H, R′ = Cl), as fine colorless prisms, m.p. 147°.

Anal. Calcd. for $C_{20}H_{12}BrClS$: C, 60.3; H, 3.0. Found: C, 60.2; H, 3.1.

The following compounds were similarly prepared:

(*a*) *10-(ω-Bromo-2-chlorobenzal)thiaxanthene* (IV; R = Cl, R′ = R″ = H), shiny colorless prisms, m.p. 157°.

Anal. Calcd. for $C_{20}H_{12}BrClS$: C, 60.3; H, 3.0. Found: C, 60.0; H, 3.1.

(*b*) *10-(ω-Bromo-2,4-dichlorobenzal)thiaxanthene* (IV; R = R′ = Cl, R″ = H), fine colorless prisms, m.p. 141°.

Anal. Calcd. for $C_{20}H_{11}BrCl_2S$: C, 55.4; H, 2.5. Found: C, 55.7; H, 2.6.

(*c*) *10-(ω-Bromo-3,4-dichlorobenzal)thiaxanthene* (IV; R = H, R′ = R″ = Cl), shiny, colorless prisms, m.p. 181°.

Anal. Calcd. for $C_{20}H_{11}BrCl_2S$: C, 55.4; H, 2.5. Found: C, 55.7; H, 2.8.

(*d*) *10-(ω-Bromo-2,5-dimethylbenzal)thiaxanthene* (IV; R = R″ = CH_3, R′ = H), fine, colorless prisms, m.p. 136°.

Anal. Calcd. for $C_{22}H_{17}BrS$: C, 67.2; H, 4.3. Found: C, 66.9; H, 4.6.

3,4′-Dimethoxybenzophenone. Aluminum chloride (28 g.) was added, in small portions to an ice-cooled solution of 20 g. of anisole and 31 g. of *m*-methoxybenzoyl chloride in 150 ml. of dry carbon disulfide; after 8 hr. at room temperature, followed by the usual treatment, 42 g. of product, b.p. 240–241°/15 mm., n_D^{27} 1.6099, was obtained, which solidified and crystallized from ethanol in colorless prisms, m.p. 60°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.8. Found: C, 74.3; H, 6.0.

The same procedure, applied to 22 g. of phenetole, yielded 34 g. of *3-methoxy-4′-ethoxybenzophenone*, b.p. 248–250°/15 mm., n_D^{27} 1.5979, which crystallized from ethanol in fine, colorless prisms, m.p. 51°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.1; H, 6.3. Found: C, 75.0; H, 6.3.

2-(3-Methoxybenzoyl)thiophene. Prepared from 20 g. of thiophene, 37.3 g. of *m*-methoxybenzoyl chloride, and 31 g. of aluminum chloride in 150 ml. of carbon disulfide (the reaction mixture was worked up after 3 hr.), this *ketone* was a yellow, viscous oil, b.p. 210–212°/24 mm., yield: 30 g.

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.1; H, 4.6. Found: C, 66.0; H, 4.5.

1-Bromo-1-phenyl-2-(m-methoxyphenyl)-2-(p-methoxyphenyl)ethylene (V; R = CH_3). To an ethereal solution of a Grignard reagent prepared from 15 g. of benzyl chloride and 1.8 g. of magnesium shavings, 15 g. of 3,4′-dimethoxybenzophenone (in ether solution) was added in small portions, with cooling, and the mixture was then refluxed for 1 hr. After the usual treatment and dehydration of the crude tertiary carbinol with formic acid, 18 g. of the *ethylene* was obtained as a viscous yellow oil, b.p. 286–288°/30 mm., which was dissolved in 35 ml. of chloroform, and treated directly with 11 g. of bromine. After evaporation of the solvent, the residue was recrystallized twice from ethanol, giving 15 g. of the *bromo compound* as fine, colorless prisms, m.p. 132–133°.

Anal. Calcd. for $C_{22}H_{19}BrO$: C, 66.9; H, 4.9. Found: C, 67.0; H, 4.8.

1-Bromo-1-phenyl-2-(m-methoxyphenyl)-2-(p-ethoxyphenyl)-ethylene (V; R = C_2H_5). The *ethylene* obtained from 3-methoxy-4′-ethoxybenzophenone (15 g.) and benzylmagnesium chloride was a viscous, yellow oil (17 g.), b.p. 270–273°/20 mm.; treatment with 7.5 g. of bromine in chloroform afforded the *bromo compound*, which crystallized from acetic acid in fine, colorless needles, m.p. 136°; yield: 16 g.

(8) For other instances, see N. H. Nam, N. P. Buu-Hoï, and N. D. Xuong, *J. Chem. Soc.*, 1690 (1954).

(9) K. Ziegler, *Ber.*, **23**, 2471 (1890).

Anal. Calcd. for $C_{23}H_{21}BrO_2$: C, 67.5; H, 5.2. Found: C, 67.8; H, 5.1.

1-Bromo-1-phenyl-2-(m-methoxyphenyl)-2-(5-bromo-2-thienyl)ethylene (IX). The *ethylene* obtained from 2-(*m*-methoxybenzoyl)thiophene (15 g.) and benzylmagnesium chloride was a pale yellow, viscous oil (24 g.), b.p. 251–252°/20 mm.; treatment of this substance with 24 g. of bromine (in chloroform) yielded 25 g. of the *dibromo compound*, which crystallized from acetic acid in cream-colored needles, m.p. 94°.

Anal. Calcd. for $C_{19}H_{14}Br_2OS$: C, 50.7; H, 3.2. Found: C, 50.6; H, 3.1.

This compound was found to be identical with the monobromination product of the ethylene prepared from 5-bromo-2-(*m*-methoxybenzoyl)thiophene and benzylmagnesium chloride.

m-Fluorobenzophenone. To a solution of 30 g. of benzene and 12.5 g. of *m*-fluorobenzoyl chloride in 50 ml. of dry carbon disulfide, 15 g. of aluminum chloride was added in small portions with stirring, and the mixture left for 8 hrs. at room temperature, then refluxed for 1 hr. The usual treatment afforded 12 g. of *m-fluorobenzophenone*, which crystallized from ligroin as lustrous, colorless leaflets, m.p. 55°; the corresponding 2,4-dinitrophenylhydrazone crystallized from acetic acid in orange-yellow needles, m.p. 260°.

Anal. Calcd. for $C_{13}H_9FO$: C, 78.1; H, 4.5. Found: C, 77.9; H, 4.5.

o-Fluorobenzophenone. Similarly prepared from *o*-fluorobenzoyl chloride, this *ketone* is a pale yellow oil, b.p. 190°/29 mm., n_D^{22} 1.5898, which formed a 2,4-dinitrophenylhydrazone, m.p. 220°.

Anal. Calcd. for $C_{13}H_9FO$: C, 78.1; H, 4.5. Found: C, 77.8; H, 4.6.

The starting material for this synthesis, *o*-fluorobenzoyl chloride, was characterized by its condensation product with *p*-phenylenediamine in pyridine medium; *1,4-bis(o-fluorobenzoylamino)benzene* crystallized from acetic acid in shiny colorless prisms, m.p. 273°.

Anal. Calcd. for $C_{20}H_{14}F_2N_2O_2$: N, 8.0. Found: N, 7.9.

1,2-Diphenyl-2-(m-fluorophenyl)ethylene. Prepared from 10 g. of *m*-fluorobenzophenone and benzylmagnesium chloride (10 g.) in ether, this compound, b.p. 229–230°/16 mm., n_D^{22} 1.6502, crystallized from ethanol in shiny colorless prisms, m.p. 55°; yield: 10 g.

Anal. Calcd. for $C_{20}H_{15}F$: C, 87.7; H, 5.5. Found: C, 87.6; H, 5.7.

1-Bromo-1,2-diphenyl-2-(m-fluorophenyl)ethylene (VII), prepared by treating 11 g. of the above ethylene with 6.4 g. of bromine in chloroform medium, crystallized from ethanol in shiny, colorless needles, m.p. 97°.

Anal. Calcd. for $C_{20}H_{14}BrF$: C, 68.1; H, 4.0. Found: C, 68.1; H, 4.3.

1,2-Diphenyl-2-(o-fluorophenyl)ethylene. This compound crystallized from ethanol as lustrous, colorless leaflets, m.p. 73°. Yield: 10 g.

Anal. Calcd. for $C_{20}H_{15}F$: C, 87.7; H, 5.5. Found: C, 88.0; H, 5.3.

Bromination of the foregoing compound yielded *1-bromo-1,2-diphenyl-2-(o-fluorophenyl)ethylene* (VI), which crystallized from ethanol in shiny, colorless prisms, m.p. 100°.

Anal. Calcd. for $C_{20}H_{14}BrF$: C, 68.1; H, 4.0. Found: C, 68.4; H, 4.0.

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[CONTRIBUTION FROM THE COLLEGE OF ENGINEERING, RUTGERS UNIVERSITY]

Matrix-Formed Adsorbing Polymers

HERMAN B. WAGNER

Received March 27, 1957

A method is described wherein the pore volume of dry silica gel particles is filled with a low viscosity, catalyzed epoxide prepolymer, this being subsequently polymerized. Following polymerization the siliceous matrix material is removed from the solid polymer by solution in aqueous hydrofluoric acid. The porous, resinous particles thus produced exhibited a capacity for adsorbing water vapor and for complexing copper, zinc, and hydrogen ion.

Conventional ion-exchanging polymers, in the usual particulate form, impose a permeability requirement on the polymer structure. This requirement, coupled with the needed inclusion of specific chemical groups for ion-exchange activity, has placed definite limitations on such compositions. The method described here provides an alternative route to securing the required permeability through casting of the polymer in a microcapillary form at the time of polymerization.

In the work described here silica gel particles were employed as a parent, matrix substance. Silica gel particles having a pore volume of 0.80 ml./g. were saturated with the required volume of the epoxide prepolymer, catalyzed with diethylene triamine. Following completion of the polymerization the silica gel matrix was removed by solution in a 27% hydrofluoric acid solution and washed thoroughly with distilled water. Detailed experimental procedure is given below.

The resinous particles thus prepared have been termed "gel replicas."

The water vapor adsorption measured for the material prepared above, and determined after drying the washed particles for two hours at 85–90° C., is given in Table I. A bulk polymerized material, of

TABLE I

WATER VAPOR ADSORPTION OF GEL-REPLICAS

Relative Humidity, 25°C., %	Adsorbed Water, gm. water/g. gel replica
100	0.48
81	0.26
51	0.069

corresponding composition, showed a water adsorption of only 0.007 gm./gm. polymer.

When the material was treated for a period of about 10 min. with a 5% sodium hydroxide solution, followed by washing with distilled water, ion-complexing of copper and zinc ions was observed, a preferential adsorption of the zinc ion being noted. The ratio of nitrogen atoms, derived from the amine, to metal-ion complexed, was calculated to be 3.8, thus corresponding approximately to the normal coordination number of 4.0. Adsorption of hydrogen ion was also observed.

As noted above, the weight of water vapor adsorbed by 1 g. of the gel replica, at saturation, was 0.48 gram. A calculation of this value was made independently, on a theoretical basis, from the concept that the void space in the resinous material corresponds to the solid space in the parent silica gel matrix. Taking the densities of the epoxide prepolymer, solid silica, and diethylene triamine as 1.23, 2.2, and 0.96 g./ml., respectively, gives a calculated value of 0.46 gram of water/g. of gel replica.

Similar gel replicas have been prepared using silica gel particles of spherical shape (bead form). Here the polymer particles obtained were of spherical shape and of density equal to 0.74 g./ml; the reduction below the density of the bulkpolymerized epoxide resin (1.16 g./ml), together with the water adsorptive values measured, is evidence of the porous structure of the gel replica particles.

This technique has been extended now to preparation of additional adsorbing polymers, and it is believed that the general method opens a new field in adsorption technology.

EXPERIMENTAL

Preparation of an epoxide-type gel replica Diethylene triamine (5.7 g.) was added to 19.3 g. of a liquid, low-molecular weight epoxide prepolymer. Dried silica gel particles (24.8 g.) were then added to this solution and agitated for approximately 15 min. At the end of this period the initially liquid, organic phase was imbibed within the silica gel particles and a free-flowing mass of discrete solid particles obtained. These were heated at 100° for 1 hr. to complete the polymerization reaction, cooled to room temperature, and then placed in a 27% hydrofluoric acid solution. Within 20 min. the siliceous portion of the mass was dissolved, leaving an organic, particulate residue. These particles were thoroughly washed with distilled water and dried at 85°. This material was designated as "I" and exhibited the water adsorption properties shown above in Table I.

Hydrogen-ion adsorption of gel replica. A 5.00 g. portion of the material "I" was placed for approximately 5 min. in 200 ml. of 5% sodium hydroxide solution, washed with 200 ml. of distilled water, and then placed again for 5 min. in a fresh 200 ml. portion of 5% sodium hydroxide solution. Repeated washing with distilled water was then given until a *p*H of approximately 7.0 was obtained. This material was then dried for 1 hr. at 80–85°, and designated as II. Seven hundred seventeen thousandths gram of II was then added to 26.0 ml. of a 0.100*N* hydrochloric acid solution. The *p*H of this solution (glass electrode determination, 25°) before addition of the resinous particles, was 0.97. The *p*H was then followed as a function of elapsed time. This varied as indicated in Table II.

TABLE 2

Time, Min.	*p*H
0	0.97
5	2.10
10	2.40
15	2.65
30	3.20
60	3.75
90	3.95
120	4.20

Copper-ion complexing. A 0.507 g. sample of II was placed in a solution of 0.228 g. of $CuSO_4.5H_2O$ contained in 91 ml. of water. Decoloration of the copper sulfate solution was noted, and the originally colorless resinous particles assumed a pronounced blue color, indicating adsorption of the copper ion. Contact was allowed for 3 hr., with occasional agitation. The supernatant solution then showed 0.0097 gram of $CuSO_4.5H_2O$, corresponding to 0.218 gram adsorbed. A ratio of 3.86 gram-atoms of nitrogen/g.-ion copper adsorbed are calculated from these data and from the original polymer/amine composition.

Displacement of adsorbed copper ion by zinc ion. The pronounced blue coloration of the copper ion adsorbing gel replica particles noted above persisted visually unchanged after repeated washing with distilled water; when, however, the resinous particles, holding the adsorbed copper ion, were shaken with a 10 ml. portion of 0.30*N* zinc sulfate solution the blue color of the resinous particles disappeared, and the originally colorless zinc sulfate solution assumed a blue color, this indicating qualitatively a displacement of the copper ion.

NEW BRUNSWICK, N. J.

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

Synthesis of Derivatives of Alkylated and Arylated Piperidones and Piperidinols

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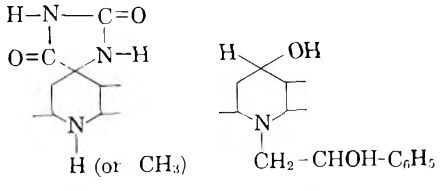
Received April 5, 1957

A number of new derivatives of substituted 4-piperidones have been prepared, including spirohydantoins, 1-phenacyl and 1-(2-hydroxyethyl) derivatives and quaternary compounds.

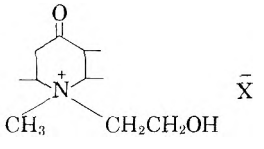
Earlier work has shown that spirohydantoins prepared from menthone and carvomenthone had marked anticonvulsant action in experimental animals.[1] In man, however, the compounds were ineffective. It is possible that this loss of activity in man may be due to lack of ability to absorb the material from the digestive tract. On this assumption it was decided to prepare spirohydantoins having other functional groups present which might facilitate their absorption. With this in mind, it seemed of interest to use a number of 4-piperidones as the starting ketones for the preparation of spirohydantoins (A), since the piperidone nucleus in a molecule may enhance nerve depressant action. This nucleus is present in such physiologically active compounds as cocaine, morphine and Demerol.

Although the preparation of spirohydantoins from 4-piperidones was the primary purpose of this investigation, several other compounds of possible physiological interest were made also. The main types prepared are shown below:



A

B



C

Types B and C were prepared as potential adrenergic or cholinergic compounds.

The 2,2,6,6-tetramethyl-4-piperidone was prepared from phorone and ammonia by the method of Guerschi.[2] 1,2,2,6,6-Pentamethyl-4-piperidone was similarly prepared from phorone and methylamine.[2,3] 2,2,6-Trimethyl-4-piperidone was prepared from diacetoneamine acid oxalate and acetal.[4] 1-Methyl-3-carbethoxy-4-piperidone[5] was prepared by the Dieckmann condensation of methyldi(β-carbethoxyethyl)amine.[6] 1-Methyl-4-piperidone was prepared from the carbethoxy derivative by heating with hydrochloric acid.

The 2,6-diphenyl-4-piperidones were all prepared by the method of Noller and Baliah.[7] Benzaldehyde, the appropriate ketone, and ammonium acetate were heated in glacial acetic acid solution.

The spirohydantoins were prepared from the piperidones by the method of Bucherer.[8] In general the spirohydantoins from *N*-methylpiperidones melted slightly above 200° while those derived from piperidones having no substituents on nitrogen melted above 300°. All melted with decomposition.

The 4-piperidinols required in this study were obtained from the corresponding piperidones by hydrogenation with platinum as the catalyst or by reduction with lithium aluminum hydride. When 2,2,6-trimethyl-4-piperidone was reduced with lithium aluminum hydride it gave the *alpha* form of the alcohol, m.p. 137–138°. This had previously been obtained by a sodium amalgam reduction.[9] When 2,2,6-trimethyl-4-piperidone was hydrogenated over platinum at room temperature, the corresponding *beta* form was obtained, m.p. 158–159°. This form had also been isolated previously from a sodium amalgam reduction.[9] The remaining piperidinols were obtained in one form only.

The *N*-phenacyl derivatives of the piperidinols were prepared by heating with phenacyl bromide in ethanol or benzene solution. The *N*-phenacyl piperidinols were reduced with lithium aluminum

(1) E. S. Rothman and A. R. Day, *J. Am. Chem. Soc.*, **76**, 111 (1954).

(2) J. Guerschi, *Ber.*, **28**, 160 (1895).

(3) L. Orthner, *Ann.*, **456**, 251 (1927).

(4) A. T. King, F. A. Mason, and S. B. Schryver, British Patent **101,739** (1916).

(5) S. M. McElvain and K. Rorig, *J. Am. Chem. Soc.*, **70**, 1829 (1948); S. M. McElvain, *J. Am. Chem. Soc.*, **46**, 1725 (1924).

(6) R. Mozingo and J. H. McCracken, *Org. Syntheses*, Coll. Vol. III, 258 (1955).

(7) C. R. Noller and V. Baliah, *J. Am. Chem. Soc.*, **70**, 3853 (1948).

(8) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, (2), **141**, 5 (1934).

(9) C. Harries, *Ann.*, **294**, 373 (1896).

hydride to the corresponding *N*-(2-hydroxy-2-phenylethyl)-4-piperidinols.

For the preparation of type C, the appropriate piperidine compound was heated with ethylene oxide to form the *N*-β-hydroxyethylpiperidine and the latter was converted to a quaternary compound by heating with methyl iodide.

EXPERIMENTAL

The melting points recorded are uncorrected. They were taken in an apparatus similar to the one described by Wagner and Meyer[10] except that instead of using external heat an internal electrically heated coil made of Nichrome wire was used.

Preparation of 4-piperidones. See Table I. *2,2,6,6,-Tetramethyl-4-piperidone* (I). This compound, also known as triacetoneamine, was made from phorone and ammonia by the method of Guerschi.

TABLE I
SUBSTITUTED 4-PIPERIDONES

Compound	Substituents	Yield, %	M.P., °C.	B.P., °C.
I	2,2,6,6-Tetramethyl[2]	75	58–59[a]	
II	1,2,2,6,6-Pentamethyl[2,3]	57		78–82 at 2 mm.
III	2,2,6-Trimethyl[4]	87[b]	181–183[c]	
IV	1-Methyl-3-carbethoxy[5]	58		82–84 at 0.2 mm.
V	1-Methyl[5]	52		43–44 at 6 mm.
VI	2,6-Diphenyl-3-methyl[7]	40	91–92[d]	
VII	2,6-Diphenyl-3,3-dimethyl[7]	50	114–115	
VIII	2,6-Diphenyl-3,5-dimethyl[7]	72	131–133	
IX	1,3-Dimethyl-2,6-diphenyl[7]	42	130–131	

[a] Melting point of monohydrate. [b] As acid oxalate. [c] Melting point of acid oxalate. [d] Literature gives 86–87°.

1,2,2,6,6-Pentamethyl-4-piperidone (II). The methods of Guerschi[2] and Orthner[3] were slightly modified for the preparation of this compound from phorone and methylamine. The initial reaction was carried out in an atmosphere of nitrogen. The removal of solvent, prior to fractionation of the reaction products, was also carried out in a stream of nitrogen.

2,2,6-Trimethyl-4-piperidone (III). It was prepared from diacetoneamine acid oxalate and acetal and isolated as its acid oxalate.[4] The free base was obtained by dissolving the oxalate salt in water and with cooling the solution was made strongly alkaline with 12*N* sodium hydroxide solution. The yellow oil was extracted with ether and the ethereal solution dried over potassium carbonate.

1-Methyl-3-carbethoxy-4-piperidone (IV). The procedures of McElvain and Rorig[5] and McElvain[5] were used to prepare this compound.

1-Methyl-4-piperidone (V). This compound was prepared from compound IV by a previously reported decarboxylation procedure.[5]

The following compounds were prepared by the method of Noller and Baliah:[7] *2,6-Diphenyl-3-methyl-4-piperidone* (VI), *2,6-diphenyl-3,3-dimethyl-4-piperidone* (VII), *2,6-diphenyl-3,5-dimethyl-4-piperidone* (VIII), *1,3-dimethyl-2,6-diphenyl-4-piperidone* (IX).

(10) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem. Anal. Ed.*, **10**, 584 (1939).

Preparation of spirohydantoins from 4-piperidones. These compounds were prepared from the 4-piperidones, ammonium carbonate and potassium cyanide in aqueous alcohol solution by the method of Bucherer.[8] Minor modifications were necessary in certain cases. In most cases it was found that the addition of more ammonium carbonate and potassium cyanide to the reaction mixture after 4 hr. of heating improved the yields. The following spirohydantoins were prepared for the first time (see Table II).

7,7,9,9-Tetramethyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (X) *from Compound* I. The mixture was heated at 55–60° for 8 hr. White crystals appeared after 4–5 hr. After 8 hr., the mixture was cooled and the crystals removed. The crude hydantoin was dissolved in dilute sodium hydroxide solution and reprecipitated by the addition of hydrochloric acid. After filtering and drying, the hydantoin was finally recrystallized from a large volume of 50% aqueous ethanol.

The hydrochloride was prepared by heating the hydantoin with a minimum amount of water and concentrated hydrochloric acid until the solid dissolved. The solution was filtered and the filtrate cooled to precipitate the hydrochloride. The conversion was nearly quantitative. The hydrochloride was recrystallized from water.

7,7,8,9,9-Pentamethyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (XI) *from Compound* II. In this case the mixture was heated at 55–60° for 18 hr. No crystals separated after 8 hr. Small amounts of ammonium carbonate and potassium cyanide were added and the heating continued for an additional 10 hr. The solution was reduced to about one-half its volume *in vacuo* and cooled to precipitate the hydantoin. The crude product was washed with water and recrystallized from 50% aqueous ethanol.

7,7,9-Trimethyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (XII) *from Compound* III. The mixture was heated at 55–60° for 8 hr. After cooling, the product was removed and washed with water. It was dissolved in dilute sodium hydroxide solution and, after filtering, the filtrate was neutralized with hydrochloric acid to precipitate the hydantoin. The product was removed, washed thoroughly with water, and dried. The hydrochloride was prepared in the same way as the hydrochloride of X.

6-Carbethoxy-8-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (XIII) *from Compound* IV. In this case after heating the mixture at 55–60° for 1 hr., it separated into 2 layers and 50% aqueous ethanol was added until a homogeneous solution was obtained. The heating was then continued for 7 hr. The solvents were removed *in vacuo* and the residue recrystallized from 50% aqueous ethanol.

8-Methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (XIV) *from Compound* V. The mixture was heated at 60–65° for 8 hr. The volume was then reduced about 50% *in vacuo* and the mixture cooled. The crude product was removed, washed with water, and dried. It was then recrystallized from 95% ethyl alcohol.

The same compound was obtained when 1-methyl-3-carbethoxy-4-piperidone was used in place of compound V and the mixture heated for 18 hr. Decarboxylation occurred during the reaction.

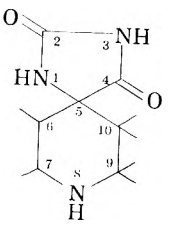
6-Methyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (XV) *from Compound* VI. The mixture was heated at 60–65° for 8 hr. After cooling, the product was removed, washed thoroughly with water, and recrystallized from a large volume of 50% aqueous ethanol.

6,6-Dimethyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (XVI) *from Compound* VII. The mixture was heated at 100° under pressure for 8 hr. After cooling, the product was removed, washed with 50% aqueous ethanol and with a little hot benzene. The dried product was dissolved in glacial acetic acid and heated with decolorizing carbon. After filtering, the filtrate was cooled and diluted with water to 3 times its volume. Aqueous ammonia was then added dropwise with cooling and stirring. The white solid, so obtained, was removed, washed, and dried.

6,10-Dimethyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane

TABLE II

1,3,8-TRIAZASPIRO[4.5]DECANE-2,4-DIONES (SPIROHYDANTOINS)



Compound	Substituents	Yield, %	M.P., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
X	7,7,9,9-Tetramethyl	80	360–365 dec.	58.64	8.50	18.65		58.39	8.63	18.48	
	Hydrochloride of X		>360 dec.	50.47	7.70	16.05	13.55	50.56	7.71	16.04	13.46
XI	7,7,8,9,9-Pentamethyl	46	209–211	60.21	8.84	17.56		60.00	9.11	17.39	
XII	7,7,9-Trimethyl	95	360 dec.	56.84	8.11	19.88		56.69	8.22	20.04	
	Hydrochloride of XII		>360 dec.	48.49	7.32	16.96	14.32	48.64	7.42	17.06	14.14
XIII	6-Carbethoxy-8-methyl	50	230–232	51.75	6.71	16.46		51.83	6.76	16.31	
XIV	8-Methyl	34	254–256	52.45	7.15	22.94		52.25	7.07	22.92	
XV	6-Methyl-7,9-diphenyl	80	363–365 dec.	71.63	6.31	12.56		71.77	6.47	12.45	
XVI	6,6-Dimethyl-7,9-diphenyl	79	323–325 dec.	72.20	6.63	12.03		72.44	6.64	11.86	
XVII	6,10-Dimethyl-7,9-diphenyl	76	>360 dec.	72.20	6.63	12.03		72.14	6.39	11.89	
XVIII	6,8-Dimethyl-7,9-diphenyl	69	370–373 dec.	72.20	6.63	12.03		71.97	6.48	11.97	

TABLE III

SUBSTITUTED 4-PIPERIDINOLS

Compound	Substituents	Yield, %	M.P., °C.	Analyses, % Calcd. C	H	N	Found C	H	N
XIX[11]	2,2,6,6-Tetramethyl	89	128–128.5[a]						
XX[9]	2,2,6-Trimethyl								
	Alpha form	79	137–138						
	Beta form	97	160–161[a]						
XXI	2,6-Diphenyl-3-methyl	82	125–126[b]						
XXII	2,6-Diphenyl-3,5-dimethyl	83	133–134	81.10	8.23	4.98	81.30	8.05	4.75
XXIII	2,6-Diphenyl-3,3-dimethyl	89	136.5–137.5	81.10	8.23	4.98	81.21	8.30	4.93
XXIV	1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl	74	186–186.5	77.51	8.37	4.31	77.39	8.34	4.27

[a] Literature reports 158–159°. [b] Baliah and Ekambaram [*J. Indian Chem. Soc.*, **32**, 274 (1955)] report 123–124°.

2,4-dione (XVII) *from Compound* VIII. This compound was prepared in the same manner as XVI. The crude product was washed with 60% aqueous ethanol until colorless. The dry product was dissolved in a minimum amount of hot *6N* acetic acid. After filtering, the filtrate was diluted with water and treated with aqueous ammonia as in the case of XVI.

6,8-Dimethyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (XVIII) *from Compound* IX. The reaction mixture was heated at 60–65° for 18 hr. After cooling, the product was removed, washed with water, and dried. It was then recrystallized from 95% ethyl alcohol.

Preparation of 4-piperidinols (see Table III). *2,2,6,6-Tetramethyl-4-piperidinol* (XIX). 2,2,6,6-Tetramethyl-4-piperidone monohydrate in 95% ethyl alcohol was hydrogenated in the presence of platinum. The product was obtained by evaporating the alcohol solution *in vacuo* and recrystallizing the residue from benzene.[11]

2,2,6-Trimethyl-4-piperidinol (XX) (*α-form*). Lithium aluminum hydride (1.52 g., 0.04 mole) was added to 100 ml. of dry ether and the mixture stirred and refluxed for 30 min. Drying tubes were used to prevent moisture from reaching the reaction mixture. The external heat was removed and 14.1 g. (0.10 mole) of 2,2,6-trimethyl-4-piperidone in 100 ml. of dry ether was added dropwise. The mixture was then refluxed for an additional 15 min. Water (25 ml.) was added carefully to decompose the excess lithium aluminum hydride and then 100 ml. of *6N* hydrochloric acid added to dissolve the basic aluminum precipitate. The two layers were separated and the aqueous layer made strongly alkaline with *12N* sodium hydroxide solution. The alkaline solution was extracted with seven 100 ml. portions of butanol-1. The butanol was removed *in vacuo* and the residue was recrystallized from ethyl acetate. The product melted at 137–138°.[9]

2,2,6-Trimethyl-4-piperidinol (*β-Form*). The β-form was obtained by hydrogenating the ketone in 95% ethyl alcohol solution in the presence of platinum as a catalyst. After removing the ethyl alcohol *in vacuo*, the residue was recrystallized from ethyl acetate. The product melted at 160–161°.[9]

A mixture of the α- and β-forms melted at 121–123°.

2,6-Diphenyl-3-methyl-4-piperidinol (XXI). This compound was prepared from 2,6-diphenyl-3-methyl-4-piperidone hydrochloride by hydrogenation with platinum as the catalyst in 95% ethyl alcohol. The catalyst was removed

(11) E. Fischer, *Ber.*, **17**, 1789 (1884).

TABLE IV

SUBSTITUTED 1-PHENACYL-4-PIPERIDINOLS

Compound	Substituents	Yield, %	M.P., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XXV	2,2,6,6-Tetramethyl	23	116.5–117.5	74.15	9.15	5.09	74.24	9.18	5.04
XXVI	2,6-Diphenyl-3,3-dimethyl	75	124–126	81.19	7.32	3.51	81.35	7.38	3.48
XXVII	2,6-Diphenyl-3,5-dimethyl	55	129.5–130	81.19	7.32	3.51	81.00	7.52	3.56
	SUBSTITUTED 1-(2-HYDROXY-2-PHENYLETHYL)-4-PIPERIDINOLS								
XXVIII	2,2,6,6-Tetramethyl	80	124–124.5	73.60	9.81	5.05	73.77	9.76	5.10
XXIX	2,6-Diphenyl-3,3-dimethyl	57	197–198	80.76	7.78	3.49	80.88	7.95	3.54
XXX	2,6-Diphenyl-3,5-dimethyl	40	303–305	80.76	7.78	3.49	80.98	7.93	3.50
XXXI	2,6-Diphenyl-3-methyl	43	227–229.5	80.60	7.54	3.62	80.69	7.57	3.58

and the filtrate was made basic with ammonium hydroxide. The hot solution was then diluted with water to about 3 times its volume and allowed to cool. The product was collected, dried, and recrystallized from petroleum ether (65–100°).

The same compound was obtained by reduction with lithium aluminum hydride.

2,6-Diphenyl-3,5-dimethyl-4-piperidinol (XXII). The low solubility of 2,6-diphenyl-3,5-dimethyl-4-piperidone in ether led to the use of a Soxhlet extractor as a means of carrying out the reduction. Lithium aluminum hydride (3.8 g., 0.1 mole) was added to 500 ml. of dry ether. After refluxing for 30 min., a thimble containing 50 g. (0.18 mole) of the ketone was placed in the Soxhlet and refluxing was continued for 45 min. after all of the ketone had dissolved. The Soxhlet condenser was replaced with a straight condenser and 30 ml. of water was added very carefully to destroy the excess lithium aluminum hydride. Hydrochloric acid (200 ml., 6*N*) was then added and the solid removed by filtration. The solid was treated with 200 ml. of 95% ethyl alcohol and concentrated ammonium hydroxide added dropwise with stirring until a clear solution was obtained. After filtering, the filtrate was diluted with water to about 3 times its volume to precipitate the product. The latter was dried and recrystallized from petroleum ether (65–110°).

2,6-Diphenyl-3,3-dimethyl-4-piperidinol (XXIII). This piperidinol was prepared from 2,6-diphenyl-3,3-dimethyl-4-piperidone by the method described for XXI. The crude product was recrystallized from methanol.

1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol (XXIV). 1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidone was hydrogenated in glacial acetic acid using platinum as catalyst. After removing the solvent *in vacuo*, the residue was recrystallized from benzene.

Preparation of N-Phenacyl Compounds (see Table IV). *1-Phenacyl-2,2,6,6-tetramethyl-4-piperidinol* (XXV). A mixture of 10.5 g. (0.067 mole) of 2,2,6,6-tetramethyl-4-piperidinol, 6.66 g. (0.034 mole) of phenacyl bromide and 25 ml. of dry benzene was heated at 90–95° under pressure for 2 hr. After cooling, 50 ml. of dry benzene was added and the mixture was cooled overnight. The amine hydrobromide was removed and washed with a little dry benzene. The benzene solution was then extracted with 2*N* hydrochloric acid. The acid solution was cooled and while stirring was made alkaline by the addition of 6*N* sodium hydroxide. The precipitated phenacyl compound was either removed by filtration or by extraction with benzene, the benzene subsequently being removed *in vacuo*. The dried product was recrystallized from petroleum ether (65–110°).

1-Phenacyl-2,6-diphenyl-3,3-dimethyl-4-piperidinol (XXVI). The procedure for XXV was used for this preparation except that 2,6-diphenyl-3,3-dimethyl-4-piperidinol was used as the starting piperidinol and dry ethanol was used as the solvent. The filtrate from the hydrobromide was evaporated to dryness *in vacuo*. The residue was extracted with dry ether, the ether removed under reduced pressure, and the residue recrystallized from aqueous ethyl alcohol. The compound was dried *in vacuo* over phosphorus pentoxide.

1-Phenacyl-2,6-diphenyl-3,5-dimethyl-4-piperidinol (XXVII). This compound was prepared from 2,6-diphenyl-3,5-dimethyl-4-piperidinol and phenacyl bromide by heating in dry ethanol at 95°, under pressure, for 25 hr. The mixture was evaporated to dryness *in vacuo* and the residue extracted with dry ether. After removing the ether from the extract, the residue was recrystallized from aqueous ethyl alcohol.

Reduction of N-phenacyl Compounds (see Table IV). *1-(2-Hydroxy-2-phenylethyl)-2,2,6,6-tetramethyl-4-piperidinol* (XXVIII). Lithium aluminum hydride (0.38 g., 0.01 mole) in 100 ml. of dry ether was refluxed for 15 min. and 4.6 g. (0.0167 mole) of 1-phenacyl-2,2,6,6-tetramethyl-4-piperidinol in 100 ml. of dry ether was added dropwise. After the addition the mixture was heated to boiling for an additional 30 min. Water (25 ml.) was then cautiously added to destroy excess lithium aluminum hydride and finally 100 ml. of 6*N* hydrochloric acid was added and the mixture stirred for 15 min. The acid layer was separated and washed with ether. With cooling, the solution was then made strongly alkaline with 12*N* sodium hydroxide and extracted with ether. After removing the ether, the residue was recrystallized from 1:1 benzene-petroleum ether (65–110°).

1-(2-Hydroxy-2-phenylethyl)-2,6-diphenyl-3,3-dimethyl-4-piperidinol (XXIX). This compound was prepared from 1-phenacyl-2,6-diphenyl-3,3-dimethyl-4-piperidinol by the procedure used for making XXVIII up to the point where the 6*N* hydrochloric acid was added. After the addition of the acid, the solid was removed by filtration. It was mixed with 100 ml. of 95% alcohol; concentrated ammonium hydroxide was then added to neutralize the hydrochloride. The solution was diluted with water and cooled overnight. The precipitate so obtained was recrystallized from ethanol.

1-(2-Hydroxy-2-phenylethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol (XXX). This product was prepared from 1-phenacyl-2,6-diphenyl-3,5-dimethyl-4-piperidinol by the same method used for XXIX.

1-(2-Hydroxy-2-phenylethyl)-2,6-diphenyl-3-methyl-4-piperidinol (XXXI). In this case the 1-phenacyl-4-piperidinol was not isolated but was reduced directly to XXXI. 2,6-Diphenyl-3-methyl-4-piperidinol was condensed with phenacyl bromide in ethanol solution by the method used for making XXVII. The final ether extract of the phenacyl derivative was reduced directly with lithium aluminum hydride as described for the preparation of XXIX, except that the final product was recrystallized from methanol.

Preparation of 1-(2-hydroxyethyl)-4-piperidones, 1-(2-hydroxyethyl)-4-piperidinols, and quaternary compounds. 1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidone (XXXII). 2,6-Diphenyl-3,5-dimethyl-4-piperidone (14 g., 0.05 mole), 3.1 g. (0.07 mole) of ethylene oxide, and 19 ml. of methanol was heated at 90–95° under pressure for 24 hr. The solvent was removed *in vacuo* and the residue was

recrystallized from petroleum ether (65–110°). The yield was 68%, m.p. 149–159°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.00; H, 7.79; N, 4.33. Found: C, 78.09; H, 7.64; N, 4.26.

1-(2-Hydroxyethyl)-2,6-diphenyl-3,3-dimethyl-4-piperidone (XXXIII). A mixture of 14 g. (0.05 mole) of 2,6-diphenyl-3,3-dimethyl-4-piperidone, 3.52 g. (0.08 mole) of ethylene oxide, and 20 ml. of methanol was heated at 95–100° under pressure for 24 hr. After removing the solvent *in vacuo*, the viscous residue was covered with petroleum ether and allowed to stand in a refrigerator until the material crystallized. It was recrystallized from petroleum ether. The yield was 81%, m.p. 104–104.5°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.00; H, 7.79; N, 4.33. Found: C, 77.90; H, 7.59; N, 4.30.

1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol (XXXIV). Compound XXXII was hydrogenated in glacial acetic acid with platinum as a catalyst. The acetic acid was removed *in vacuo* and the residue was recrystallized from benzene. The yield was 74%, m.p. 186–186.5°.

Anal. Calcd. for $C_{21}H_{27}NO_2$: C, 77.51; H, 8.37; N, 4.31. Found: C, 77.39; H, 8.34; N, 4.27.

1-(2-Hydroxyethyl)-1-methyl-2,6-diphenyl-3,5-dimethyl-4-ketopiperridinium iodide (XXXV). A mixture of 0.5 g. (0.0015 mole) of 1-(2-hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidone and 3 g. (0.021 mole) of methyl iodide was heated at 100° under pressure for 68 hr. Excess methyl iodide was removed *in vacuo* and the residue was recrystallized from 95% ethyl alcohol. The yield was 46%, m.p. 203.5–204.5°.

Anal. Calcd. for $C_{22}H_{28}NO_2I$: C, 56.76; H, 6.06; N, 3.01; I, 27.26. Found: C, 56.90; H, 6.15; N, 3.02; I, 27.19.

1-(2-Hydroxyethyl)-1-methyl-2,6-diphenyl-3,3-dimethyl-4-ketopiperridinium iodide (XXXVI). A mixture of 9.6 g. (0.03 mole) of 1-(2-hydroxyethyl)-2,6-diphenyl-3,3-dimethyl-4-piperidone and 21.1 g. (0.15 mole) of methyl iodide was heated at 100° under pressure for 72 hr. Excess methyl iodide was removed *in vacuo* and the residue was recrystallized from ethanol-ether. The yield was 30%, m.p. 209.5–210.5°.

Anal. Calcd. for $C_{22}H_{28}NO_2I$: C, 56.76; H, 6.06; N, 3.01; I, 27.26. Found: C, 57.00; H, 6.07; N, 3.07; I, 27.06.

1-(2-Hydroxyethyl)-1-methyl-2,6-diphenyl-3,5-dimethyl-4-hydroxypiperidinium iodide (XXXVII). A mixture of 8.1 g. (0.025 mole) of 1-(2-hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol and 21.1 g. (0.15 mole) of methyl iodide was heated at 100° under pressure for 96 hr. Excess methyl iodide was removed *in vacuo* and the residue was recrystallized from dry ethanol. The yield was 53%, m.p. 219–220°.

Anal. Calcd. for $C_{22}H_{30}NO_2I$: C, 56.54; H, 6.47; N, 3.00; I, 27.15. Found: C, 56.43; H, 6.40; N, 2.88; I, 27.32.

Preparation of p-nitro and p-aminobenzoates of XIX *and* XX. These derivatives were prepared by the usual procedures, namely *p*-nitrobenzoylation in pyridine solution and subsequent reduction of the nitro group with hydrogen and palladium.

p-Nitrobenzoate of 2,2,6,6-tetramethyl-4-piperidinol (XXXVIII). The product was recrystallized from 95% ethyl alcohol; yield 49%, m.p. 128.5–129.5°.

Anal. Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.71; H, 7.12; N, 9.18.

p-Aminobenzoate of 2,2,6,6-tetramethyl-4-piperidinol (XXXIX). The product was recrystallized from water; yield 95%, m.p. 146–147°.

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.30; H, 8.86; N, 9.96.

p-Nitrobenzoate of 2,2,6-trimethyl-4-piperidinol (XL). This compound was recrystallized from 95% ethyl alcohol; yield 48%, m.p. 93–94°.

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.89; N, 9.58. Found: C, 61.50; H, 6.95; N, 9.47.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Some Derivatives of ϵ-Caprolactam[1,2]

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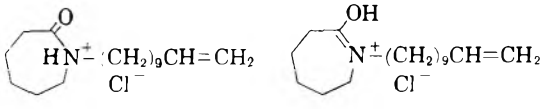
A method for the *N*-alkylation of ϵ-caprolactam has been developed and used to produce the *N*-*n*-butyl, *N*-*n*-hexyl and the *N*-undecenyl derivatives. All of these amides showed markedly basic properties. Hydrolysis of *N*-undecenyl-ϵ-caprolactam with hydrochloric acid solution led to the formation of *N*-10(11?)-chloroundecyl-ϵ-aminocaproic acid which was characterized as the *N*-*p*-toluenesulfonyl derivative. *N*-*p*-Toluenesulfonyl-ϵ-aminocaproic acid was prepared and found to undergo cyclization forming *N*-*p*-toluenesulfonyl-ϵ-caprolactam when treated with either phosphorus pentachloride or sulfuric acid. The benzyl esters of *N*-benzoyl-ϵ-aminocaproic acid and *N*-formyl-ϵ-aminocaproic acid were synthesized.

In connection with the synthesis of a polyampholyte of regular structure, work was directed toward the preparation of a suitable intermediate from ϵ-caprolactam. Although this route to a polyampholyte proved to be infeasible, a number of previously unreported derivatives of ϵ-caprolactam were made.

A general procedure for the *N*-alkylation of ϵ-caprolactam was developed and the properties of the *N*-alkyl-ϵ-caprolactams were briefly investigated. All were found to have a pronounced basic character, forming perbromide and hygroscopic hydrogen chloride salts readily. In the case of *N*-undecenylcaprolactam a crystalline hydrochloride was isolated and the infrared absorption of this compound indicated it to be a mixture of the two isomers shown below. While ϵ-caprolactam itself and *N*-methyl-ϵ-caprolactam are easily hydrolyzed,



(1) Abstracted from a portion of the Ph.D. thesis of Wendell W. Moyer, Jr., University of Illinois, 1957.

(2) The work discussed herein was performed as a part of the synthetic rubber research project sponsored by the National Science Foundation.

the higher *N*-alkyl derivatives may be hydrolyzed only with difficulty.

A somewhat surprising cyclization was found to occur when *N*-*p*-toluenesulfonyl-ϵ-aminocaproic acid was treated with either catalytic amounts of sulfuric acid under esterification conditions or with phosphorus pentachloride in benzene. *N*-*p*-Toluenesulfonyl-ϵ-caprolactam was recovered in both cases as the primary reaction product.

EXPERIMENTAL[3]

N-n-Butyl-ϵ-caprolactam. 1. *Sodium hydride alkylation method of Fones.*[4] Into a 500-ml. three-necked flask, fitted with a stirrer, reflux condenser with calcium chloride drying tube, and dropping funnel, were placed 2.40 g. (0.10 mole) of sodium hydride and 11.32 g. (0.10 mole) of ϵ-caprolactam in 200 ml. of dry xylene. The stirrer was started and the mixture was heated under reflux in an atmosphere of nitrogen for 10 hr. After cooling somewhat, a mixture of 27.4 g. (0.2 mole) of *n*-butyl bromide and 50 ml. of dry xylene was added and the reaction mixture was heated under reflux with stirring for 4 hr. The hot mixture was filtered, the residual sodium bromide was washed with 50 ml. of dry benzene, and the filtrate and washings were combined. Distillation of the solvent under diminished pressure followed by fractionation of the residual liquid yielded 11.85 g. (70%); b.p. 137–140° (17 mm.); n_D^{20} 1.4782.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.98; H, 11.32. Found: C, 70.24; H, 11.06.

The infrared spectrum contains a significant band at 1645 cm.$^{-1}$ indicating the presence of a disubstituted amide and is consistent with the expected structure. A hydrochloride derivative was prepared but was not characterized because of its hygroscopic nature.

2. *Sodium method.* Into a 500-ml. three-necked flask fitted with a stirrer, reflux condenser with a calcium chloride drying tube, and dropping funnel, were placed 200 ml. of dry xylene, 2.30 g. (0.10 g.-atom) of powdered sodium and 11.32 g. (0.10 mole) of ϵ-caprolactam. The mixture was heated under reflux with stirring for 4 hr. After cooling slightly, 20.6 g. (0.15 mole) of *n*-butyl bromide was added dropwise to the reaction mixture. The mixture was then heated under reflux with stirring for 8 hr., cooled to room temperature, and filtered in order to remove the precipitated sodium bromide. The precipitate was washed several times with dry benzene and the combined filtrate and washings were evaporated. Distillation of the residual liquid through a 10-inch Vigreux column yielded 13.23 g. (78.1%); b.p. 130–137° (15 mm.).

N-n-Hexyl-ϵ-caprolactam. The sodium hydride procedure was carried out using 19.8 g. (0.12 mole) of *n*-hexyl bromide in place of the *n*-butyl bromide. Distillation of the residual liquid yielded 14.9 g. (75% of theory); b.p. 190–197° (30 mm.); 167–174° (20 mm.) n_D^{20} 1.4754.

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.04; H, 11.75. Found: C, 73.29; H, 11.50.

The infrared spectrum of this compound is almost identical with that of N-*n*-butyl-ϵ-caprolactam and is in agreement with the expected structure. Impure hydrochloride and perbromide salts were prepared but were not characterized.

N-Undecenyl-ϵ-caprolactam. This compound was prepared by the sodium alkylation procedure used for the preparation of the *N*-butyl derivative. The only modifications were the use of an equivalent amount, 23.3 g. (0.10 mole), of undecylenyl bromide, and an allowance for longer heating under reflux. The crude product was purified by distillation under reduced pressure yielding 16.65 g. (63%); b.p. 160–165° (0.8 mm.); 165–168° (1 mm.); n_D^{20} 1.4797.

Anal. Calcd. for $C_{17}H_{31}NO$: C, 76.92; H, 11.77. Found: C, 76.65; H, 11.51.

The infrared spectrum contains bands assignable to a disubstituted amide (1645–50 cm.$^{-1}$) and to a terminal vinyl group (978, 910 cm.$^{-1}$).

The hydrogen chloride salt was prepared by bubbling dry hydrogen chloride gas into an ethereal solution of the *N*-alkyl derivative. The derivative had a melting point of 74.5–77.5°. The infrared spectrum of a Nujol mull gave principal bands at 3080, 2905, 2840, 2530, 2065, 1965–80, 1765, 1632, 1477, 1435, 1390, 1325, 991 and 912 cm.$^{-1}$ indicating a mixture of the two salts mentioned before. The product loses hydrogen chloride on drying in a vacuum and a good analysis was not obtained on the product. A 10,11-dibromoundecenyl-ϵ-caprolactam perbromide salt was prepared by adding bromine to an ice-cold ethereal solution of the *N*-undecenyl compound. The perbromide salt precipitated from the ethereal solution as an orangish red viscous oil. The infrared spectrum contains a band assignable to a disubstituted amide salt (1732 cm.$^{-1}$).

N-p-Toluenesulfonyl-N-10(or 11?)-chloroundecyl-ϵ-aminocaproic acid. In a 500-ml. flask fitted with a reflux condenser were placed 15.0 g. (0.057 mole) of *N*-undecenyl-ϵ-caprolactam and 200 ml. of 18% hydrochloric acid. After heating under reflux continuously for seven days, the hot solution was transferred to a 500-ml. beaker and allowed to cool to room temperature. An oily layer separated and solidified on standing. This product was presumably the hydrogen chloride salt of *N*-10(or 11)-chloroundecyl-ϵ-aminocaproic acid.

This acid solution was neutralized with sodium hydroxide pellets, and then 2.25 g. (0.057 mole) of sodium hydroxide was added in excess. The resulting solution was transferred to a 1-l. Erlenmeyer flask and an ethereal solution of 10.83 g. (0.057 mole) of *p*-toluenesulfonyl chloride was added. The mixture was then shaken mechanically for 6 hr., acidified with concentrated hydrochloric acid, and extracted several times with ether. The combined ethereal solution was evaporated to dryness and the resulting straw-colored, viscous liquid was dried for one day in a vacuum desiccator. A yield of 24.6 g. was obtained (91%); $n_D^{19.75}$ 1.5093. All attempts to induce crystallization of this compound were unsuccessful. An analysis of the crude compound gave the following results:

Anal. Calcd. for $C_{24}H_{40}NO_4SCl$: C, 60.79; H, 8.52; N, 2.96. Found: C, 62.56; H, 8.58; N, 3.14.

The infrared spectrum contains bands assignable to an aliphatic acid (1710, 2600–3200 cm.$^{-1}$), to a sulfonamide (1159, 1338 cm.$^{-1}$), and to a *para* substituted aromatic group (1604, 1503, and 813 cm.$^{-1}$).

In order to obtain a characterizable solid derivative of this compound, the *S*-benzyl thiuronium salt was prepared according to the direction of Donleavy.[5] The derivative was isolated in 93% yield having a crude melting point of 94.5–95.5°. After three recrystallizations from 80% ethanol, a product was obtained which melted at 97–97.5°.

Anal. Calcd. for $C_{32}H_{50}N_3O_4S_2Cl$: C, 60.02; H, 7.87; N, 6.56; Cl, 5.54. Found: C, 60.74; H, 8.04; N, 6.31; Cl, 4.73.

The infrared spectrum of a Nujol mull contains bands assignable to a carboxylic acid salt (1576, 1409 cm.$^{-1}$), to a sulfonamide (1340, 1160 cm.$^{-1}$), to *mono* and *para* substituted aromatic rings (1604, 1503, 695 and 813 cm.$^{-1}$), and to a thiuronium salt (1670, 2700–3100, 3200 and 3540 cm.$^{-1}$).

(3) The microanalyses were performed by Jozsef Nemeth, Lucy Chang, Maria Benassi, R. J. Nesset, and Ruby Ju, of the University of Illinois; Clark Microanalytical Laboratories, Urbana, Illinois; and Micro-Tech Laboratories, Skokie, Illinois. The infrared spectra were determined and interpreted by James Brader of the University of Illinois.

(4) W. S. Fones, *J. Org. Chem.*, **14**, 1099 (1949).

(5) J. J. Donleavy, *J. Am. Chem. Soc.*, **58**, 1004 (1936).

N-p-Toluenesulfonyl-ϵ-aminocaproic acid. Sodium ϵ-aminocaproate was prepared according to the method of Galat.[6] Into a 500-ml. flask fitted with a reflux condenser were placed 67.8 g. (0.60 mole) of ϵ-caprolactam, 300 ml. of water, and 48.0 g. (1.2 moles) of sodium hydroxide. The solution was heated under reflux for 1 hr. and then cooled in an ice bath.

The sodium ϵ-aminocaproate was then converted into *N-p*-toluenesulfonyl-ϵ-aminocaproic acid by means of the general method of McChesney and Swann.[7] The alkaline solution of sodium ϵ-aminocaproate was transferred to a 1-l. Erlenmeyer flask and an ethereal solution, 114.4 g. (0.60 mole), of *p*-toluenesulfonyl chloride was added. After shaking the mixture mechanically for 6 hr., the ethereal layer was separated from the aqueous layer, and the aqueous solution was acidified to Congo red with dilute hydrochloric acid. The tosyl derivative, which crystallized immediately, was collected on a filter and dried overnight in a vacuum desiccator; yield 158 g. (92.4%). Recrystallization of the product from 25% ethanol yielded 141 g.; m.p. 106.5–108°; (reported 104–106°[8]).

Formation of N-p-toluenesulfonyl-ϵ-caprolactam in the attempted preparation of N-p-toluenesulfonyl-ϵ-aminocaproyl chloride. In a 100-ml flask fitted with a reflux condenser were placed 28.5 g. (0.10 mole) of *N-p*-toluenesulfonyl-ϵ-aminocaproic acid and 41.65 g. (0.20 mole) of phosphorus pentachloride. The mixture was heated in an oil bath at 100° for 6 hr. After cooling, the reaction mixture was extracted with low petroleum ether. Evaporation of the petroleum ether, followed by distillation of the residual liquid under diminished pressure yielded a crude product which boiled from 150 to 180° at 5 mm. The distillation was accompanied by decomposition. The crude product solidified upon cooling and after two recrystallizations from cyclohexane an analytically pure sample was obtained which melted at 123–124.5°.

Anal. Calcd. for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.32; H, 6.23; N, 5.35.

The infrared spectrum of a chloroform solution contains bands assignable to an imide (1696 cm.$^{-1}$), to a sulfonamide group (1358, 1172 and 676 cm.$^{-1}$), and to a para substituted aromatic ring (1604, 1502, and 813 cm.$^{-1}$).

Formation of N-p-toluenesulfonyl-ϵ-caprolactam in the attempted preparation of benzyl N-p-toluenesulfonyl-ϵ-aminocaproate. In a 500-ml. flask fitted with a Dean-Stark trap were placed 50.0 g (0.175 mole) of *N-p*-toluenesulfonyl-ϵ-aminocaproic acid, 100 g. (0.93 mole) of benzyl alcohol, 200 ml. of dry benzene, and 1.0 g. of *p*-toluenesulfonic acid monohydrate. The solution was heated under reflux for one day, during which 1.9 ml. of water was expelled. After cooling to room temperature, the resulting solution was washed successively with six 50-ml. portions of 5% sodium bicarbonate solution, twice with 50 ml. of water, and once with 50 ml. of saturated sodium chloride solution. Solvent and benzyl alcohol were removed by distillation at reduced pressure and the residual liquid was fractionated through a 12-inch Vigreux column under diminished pressure. The distillation resulted in considerable decomposition; however, a crude product was isolated which boiled from 140–180° at 2.5 mm. Upon cooling, this material solidified. After two recrystallizations from 95% ethanol, an analytically pure sample was obtained which melted at 123–124.5°. The infrared spectrum of a chloroform solution is identical with that of the compound proved to be *N-p*-toluenesulfonyl-ϵ-caprolactam. A mixed melting point with the known compound showed no depression in melting point.

Benzyl N-benzoyl-ϵ-aminocaproate. *N*-Benzoyl-ϵ-aminocaproic acid was prepared from ϵ-caprolactam according to the method of Galat.[6]

In a 500-ml. flask fitted with a Dean-Stark trap were placed 50.0 g. (0.21 mole) of *N*-benzoyl-ϵ-aminocaproic acid, 100 g. (0.93 mole) of benzyl alcohol, 200 g. of dry benzene, and 2 ml. of concentrated sulfuric acid. The solution was heated under reflux for 12 hr. and then allowed to cool to room temperature. The solution was then washed successively with three 50-ml. portions of 5% sodium bicarbonate solution, four 50-ml. portions of water, and once with 50 ml. of saturated sodium chloride solution. Solvent and excess benzyl alcohol were removed by distillation at reduced pressure, using the water aspirator. Final distillation of the residual liquid under diminished pressure yielded 63.0 g. (91%); b.p. 250–255° (0.3 mm.); m.p. 62–65°; $n_D^{21.25}$ 1.5568. After four recrystallizations from 80-20 cyclohexane-benzene solution, an analytically pure sample was obtained; m.p. 64.5–66°.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 74.06; H, 7.08; N, 4.35.

The infrared spectrum of a chloroform solution contains bands assignable to an amide (1660, 3455 cm.$^{-1}$), and to an aliphatic ester (1728, 1220–40 cm.$^{-1}$).

Benzyl N-formyl-ϵ-aminocaproate. ϵ-Aminocaproic acid was prepared from ϵ-caprolactam according to the method of Meyers and Miller.[9] The amino acid was then converted to the *N*-formyl derivative by the procedure of Coffman, Cox, Martin, Mochel, and Van Natta.[10]

In a 500-ml. flask fitted with a Dean-Stark trap were placed 25.0 g. (0.157 mole) of *N*-formyl-ϵ-aminocaproic acid, 50.0 g. (0.46 mole) of benzyl alcohol, 200 ml. of dry benzene, and 1.5 ml. of concentrated sulfuric acid. The reaction mixture was heated under reflux for one day during which 2.7 ml. of water was expelled. After cooling to room temperature, the resulting solution was washed successively with five 50-ml. portions of 5% sodium bicarbonate solution, three 50-ml. portions of water, and finally once with saturated sodium chloride solution. Solvent and excess benzyl alcohol were removed by distillation at reduced pressure. The remaining liquid was distilled under diminished pressure yielding 8.85 g. (23%); b.p. 235° (8 mm.); $n_D^{22.5}$ 1.5210. (Extensive decomposition occurred during the distillation making it almost impossible to maintain a constant pressure.)

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 68.28; H, 7.95; N, 5.41.

The infrared spectrum contains bands assignable to a formamide (1670, 3270 cm.$^{-1}$) and an aliphatic ester (1735, 1163 cm.$^{-1}$).

In an effort to obtain an analytically pure product, the above crude sample was refractionated through a 10-inch Vigreux column under diminished pressure. Complete decomposition of the ester occurred. Benzyl alcohol and ϵ-caprolactam were shown to be the products of the decomposition.

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(6) A. Galat, *J. Am. Chem. Soc.*, 69, 86 (1947).

(7) E. W. McChesney and W. K. Swann, Jr., *J. Am. Chem. Soc.*, 59, 1116 (1937).

(8) K. Thomas and M. G. H. Goerne, *Hoppe-Seyler's Z physiol. Chem.*, 104, 73 (1918).

(9) C. Y. Meyers and L. E. Miller, *Org. Syntheses*, 32, 13 (1952).

(10) D. D. Coffman, N. L. Cox, E. L. Martin, W. E. Mochel, and F. J. Van Natta, *J. Polymer Sci.*, 3, 85 (1948).

[CONTRIBUTION NO. 764 FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Reduction of Schiff Bases with Sodium Borohydride

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A new method has been developed for the selective reduction of the Schiff base linkage occurring in compounds of the *N*-benzylidenaniline type. This method involves the use of sodium borohydride under a variety of conditions with the yields of secondary amines generally ranging from 91–99%. Reducible groups such as the nitro and chloro groups are not affected during the course of the reduction. The Schiff base, *N*-benzylidene-*p*-aminophenol failed to yield any detectable amount of its corresponding secondary amine under the conditions employed probably due to a tautomerization involving a quinoid-type structure.

In connection with some other work on di-secondary amines, it was found desirable to prepare secondary amines from their corresponding Schiff bases, some of which contained groups which are usually reducible. The need for nitro substituted secondary amines eliminated the possible use of catalytic hydrogenation of the corresponding Schiff base. All other methods of reduction thus far reported in the literature were eliminated as possibilities on the basis of this need. Since sodium borohydride is such a highly selective reducing agent and normally will not attack the nitro group, attention was focused on its potential use for the reduction of Schiff bases.

The Schiff bases which were studied were the nitro, chloro, methoxy, and hydroxy derivatives of the parent compound, *N*-benzylidenaniline. Their preparation generally involved reacting equimolar amounts of the aldehyde and amine using standard procedures.

The general reaction by which this series of Schiff bases was reduced is given by the following equation in which Ar and Ar′ may be a phenyl group or a nitro-, chloro-, methoxy-, or hydroxyphenyl group. Table I contains a list of secondary amines

$$\mathrm{Ar{-}CH{=}N{-}Ar'} \xrightarrow{\mathrm{NaBH_4}} \mathrm{Ar{-}CH_2{-}NH{-}Ar'}$$

which were prepared by this method. In Table II are listed the benzoyl derivatives of these secondary amines.

The yields of secondary amines obtained by this method were quite high, generally being in the range of 91–99%. The slightly low yields of the nitro-containing compounds (VII) and (IX) were due to the ready decomposition which these two compounds underwent. In both of these cases, a 6–7% yield of a high-melting decomposition product was obtained in addition to the expected secondary amine.

It was found that the reduction conditions were not very critical. All of the reactions were accompanied by a color change which served to indicate that a reduction was taking place. In general, one of the two techniques was used to effect a reduction. Technique A involved the addition of a solution of sodium borohydride to a refluxing solution of the Schiff base. A reverse order of addition did not prove to be very satisfactory. The concentrations of the solutions were not very critical. A simpler technique, B, involved the portionwise addition of solid sodium borohydride to a solution of the Schiff base. In this case it was generally more desirable to have the Schiff base solution at a temperature below the refluxing point of the solvent in order to moderate the vigorous reaction.

Absolute methanol proved to be a convenient medium for the reaction in spite of the increased rate of decomposition of sodium borohydride in this solvent. Ethanol was found to be superior to methanol in that the rate of decomposition of sodium borohydride in ethanol was considerably reduced. However, the rate of dissolution of the hydride in ethanol was also reduced as well as the rate of reduction. It was also found that it was not necessary for the Schiff base to be completely soluble in the solvent in order for a reduction to be effected. On the other hand, it was necessary for the sodium borohydride to be soluble in the solvent, otherwise no reduction took place. In this connection no reductions were effected in anhydrous chloroform in which the hydride was insoluble.

The secondary amines were liberated from the reaction solution by the addition of sodium hydroxide plus water or by water alone. Since (VII) and (IX) were quite susceptible to decomposition by base, these two compounds were liberated as solids by the use of water alone. In fact, some of (IX) was obtained directly from the reaction solution without the addition of water or base.

When (XVI) and (XVII) were treated with sodium borohydride under the usual conditions, no detectable amounts of the corresponding secondary amines were obtained. It is believed that the abnormal behavior of (XVI) and (XVII) may be explained on the basis of tautomerization. The location of the hydroxyl group in the ortho or para position of the aniline portion of the Schiff base molecule might result in the formation of a quinoid-type structure by means of a tautomeric shift as follows:

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TABLE I

SECONDARY AMINES

Ar—CH_2—NH—Ar′

Ar	Ar′		M.P., °C. (Corr.)	Yield, %	Analyses	Calcd.	Found
Phenyl	Phenyl	I	37–38 [a]	97.4			
p-Chlorophenyl	*p*-Chlorophenyl	II	70.5–71 [b]	92.8	Cl	28.12	27.85
o-Chlorophenyl	*p*-Chlorophenyl	III	47–47.5	93.5	Cl	28.12	27.85
p-Chlorophenyl	*m*-Chlorophenyl	IV	—	95.0 [c]			
Phenyl	*p*-Chlorophenyl	V	48.5–49 [d]	91.2	Cl	16.26	16.34
Phenyl	*o*-Chlorophenyl	VI	39.5–40 [b,d]	93.3			
p-Nitrophenyl	*p*-Nitrophenyl	VII	185–185.5 [e]	83.3	N	15.49	15.49
m-Nitrophenyl	*m*-Nitrophenyl	VIII	138.5–139	98.2	N	15.49	15.60
p-Nitrophenyl	Phenyl	IX	67–68 [f,g]	87.2			
m-Nitrophenyl	Phenyl	X	84–84.5 [h]				
Phenyl	*p*-Nitrophenyl	XI	146.5–147 [i]	90.0			
Phenyl	*m*-Nitrophenyl	XII	106–106.5 [j]	94.1			
p-Methoxyphenyl	Phenyl	XIII	46.5–47 [b]	93.2	C	78.84	78.43
					H	7.10	7.03
Phenyl	*p*-Methoxyphenyl	XIV	50–50.5 [b]	91.0			
m-Hydroxyphenyl	Phenyl	XV	103.5–104 [k]	96.0	C	79.16	78.92
					H	5.62	5.59

[a] M. Hasselblatt [*Z. anorg. Chem.*, **119**, 347 (1921)] reported m.p. 36.5–36.8°. [b] A. Roe and J. Montgomery, *J. Am. Chem. Soc.*, **75**, 911 (1953) [c] Secondary amine was high-boiling oil. Yield based on benzamide derivative. See Table II. [d] D. Peacock, *J. Chem. Soc.*, **125**, 1979 (1924). [e] C. Paal and C. Benker, *Ber.*, **32**, 1256 (1899). [f] J. Strakosch, *Ber.*, **6**, 1062 (1873). [g] C. Paal and Sprenger, *Ber.*, **30**, 69 (1897). [h] Purgotti and Monti, *Gazz. Chim. Ital.*, **30**, 256. [i] F. Kehrmann and M. Tichvinsky, *Ann.*, **290**, 293 (1896). [j] R. Meldola and F. W. Streatfield, *J. Chem. Soc.*, **51**, 114 (1887). [k] E. Bamberger and J. Müller, *Ann.*, **313**, 112 (1900). Analysis of corresponding Schiff base m.p. 101–102°: Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 78.92; H, 5.59.

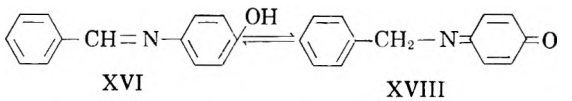
TABLE II

BENZOYL DERIVATIVES OF SUBSTITUTED *N*-PHENYLBENZYLAMINES

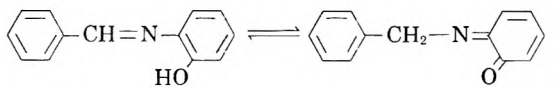
$ArCH_2—N(Ar')—COC_6H_5$

Secondary Amine	Benzamide M.P. °C. (Corr.)	Analysis % Calcd.	Found
I	107–107.5 [a]		
II	111	Cl, 19.91	Cl, 20.06
III	162.5–163	Cl, 19.91	Cl, 20.16
IV	98–98.5	Cl, 19.91	Cl, 19.95
V	137–137.5 [b]	Cl, 10.98	Cl, 10.98
VI	110.5–111 [b]		
VIII	121–121.5	C, 63.66	C, 64.27
		H, 4.01	H, 4.22
IX	118–118.5	C, 72.28	C, 72.92
		H, 4.85	H, 4.94
X	100–100.5	C, 72.28	C, 72.88
		H, 4.85	H, 4.82
XII	120–120.5	C, 72.28	C, 73.05
		H, 4.85	H, 4.83
XIII	71–71.5	C, 79.47	C, 80.18
		H, 6.03	H, 5.83
XIV	61.5–62	C, 79.47	C, 80.13
		H, 6.03	H, 6.13
XV	99.5–100	C, 79.59 [c]	C, 79.20
		H, 5.20	H, 5.19

[a] R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., p. 88, John Wiley and Sons, Inc., New York, 1948. [b] See ref. *e* of Table I. [c] Analysis for dibenzoylated secondary amine.



XVI XVIII



XVII

On the basis of this postulation, the quinoid-type structure necessarily would be favored under the basic conditions of this reduction method in order to account for the lack of a reduction. If such a tautomeric shift occurs, it would be necessary, in order for a reaction to take place, for the sodium borohydride to attack a nitrogen to carbon double bond in which the carbon atom would be involved in a quinoid ring system. However, no instance has been reported in which such a ring system has been reduced with sodium borohydride. Furthermore, such a tautomerization would involve a shift from a ring system of relatively lesser resonance to the highly resonating quinoid-type ring system. This increase in resonance might be expected to show up as a bathochromic shift in the ultraviolet spectrum of (XVI) and (XVIII). It was found that the spectrum of an alcoholic solution of (XVI) exhibited a peak at 335 mμ. When alcoholic potassium hydroxide was added to the sample solution it became pale yellow

and the peak shifted to 390 mμ and possessed about the same relative intensity. Furthermore, when the basic solution was acidified with alcoholic acetic acid, the spectrum obtained was identical with that of the initial alcoholic solution of (XVI). Although there is the possibility of phenoxide ion formation, the very large bathochromic shift of 55 mμ along with development of color, in base, and the lack of chemical reactivity tend to favor the existence of a quinoid structure and to indicate an existing tautomerization.

Conversely, when the hydroxyl group is located in a meta position on the aniline portion of the Schiff base, or in any position on the benzaldehyde portion of the molecule, there is no opportunity for such a quinoid structure to exist. A methoxyl group, in the ortho or para position of the aniline portion of the Schiff base would likewise prevent the formation of a quinoid structure. Hence reduction would be expected in such cases. This latter condition has been substantiated, though not rigorously, by the successful reduction of *N*-(*m*-hydroxybenzyliden)-aniline (XV) and *N*-benzylidene-*p*-anisidine (XVI).

EXPERIMENTAL

Reduction technique A. A 5–10% solution of the Schiff base, dissolved in absolute methanol, was placed in a 3-necked flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser. A 2–10% solution of sodium borohydride, double the molar amount of Schiff base, was dissolved in absolute methanol. When the dropwise addition of the sodium borohydride was complete, the reaction solution was refluxed an additional 15 min. and then cooled. To this solution was added an equal volume of cold tap water whereby a precipitate of the secondary amine formed. In some earlier experiments, the secondary amine was liberated by the addition of a molar amount of sodium hydroxide which was twice that of the sodium borohydride used. In these cases, the sodium hydroxide was added as a 6*N* solution; this being followed by the addition of cold tap water which was equal in volume to that of the total solution. The precipitate of secondary amine was then collected by suction filtration, washed with water, and dried. In many cases the product was of sufficient purity that no recrystallization was necessary.

Reduction technique B. A 5–10% solution of the Schiff base, dissolved in absolute methanol, was placed in a 3-necked flask fitted with two glass stoppers and a reflux condenser. This solution was warmed or left at room temperature. To this was added an equimolar amount of solid sodium borohydride. The portion-wise addition was made through one of the necks of the flask. If the reduction reaction became too vigorous, the flask was momentarily placed in cold water. When the initial reaction had subsided, the contents of the flask were refluxed for 15 min. and then cooled. The secondary amine was liberated by means of water or sodium hydroxide plus water as in technique A. The precipitate of secondary amine thus formed was collected, washed with water, and dried. In many cases no recrystallization was necessary.

Preparation of benzoyl derivatives. The benzoyl derivatives were prepared from benzoyl chloride by the usual method and recrystallized from 95% ethanol.

Ultraviolet absorption analysis. N-Benzylidene-*p*-aminophenol of concentration 5.0 mg./l. was placed in a silica cell and the ultraviolet absorption curve obtained. A Beckman DK double beam instrument with matched cells was used. The reference cell was filled with 95% ethanol, the solvent from which the spectrum was obtained. After securing this absorption curve, two drops of a 1% solution potassium hydroxide solution in 95% ethanol was added to each cell. The color of the sample solution turned pale yellow. After obtaining this spectrum, 4 drops of a 2% acetic acid solution in 95% ethanol was added to each cell and a reading again taken.

Acknowledgment. The authors wish to thank Stephen Osborn for his help in connection with the ultraviolet part of this work.

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS CHEMICAL LABORATORY, NEW YORK UNIVERSITY]

Arylation of Aromatic Compounds by the Meerwein Reaction. Evidence for Aryl Radicals from Orientation Studies[1]

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Received February 19, 1957

Benzene, nitrobenzene, and chlorobenzene have been arylated under homogeneous Meerwein reaction conditions. Isomer distributions have been determined and have been found to correspond to radical orientation. This information supports the conclusion that the Meerwein reaction involves aryl radicals.

Although the mechanism of the Meerwein reaction has been the subject of several recent investigations[2–4] the question of free aryl radical intermediates remains unanswered. This omission is primarily a result of the inapplicability of standard tests for free radicals in such complex systems. A new approach to this problem was provided by the observation that benzene was arylated under Meerwein reaction conditions.[2] Consequently, nitrobenzene and chlorobenzene have been arylated in the

(1) Presented in part at the Meeting-In-Miniature of the New York Section of the AMERICAN CHEMICAL SOCIETY, March 16, 1956.

(2) A part of the present paper has appeared in preliminary form: S. C. Dickerman, K. Weiss, and A. K. Ingberman, *J. Org. Chem.*, **21**, 380 (1956).

(3) J. K. Kochi, *J. Am. Chem. Soc.*, **78**, 1228 (1956).

(4) O. Vogl and C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **78**, 3799 (1956).

same manner; the mixtures of isomeric biphenyls have been analyzed and the results compared with those reported for recognized radical attack on these substances.[5]

A homogeneous solution of nitrobenzene (0.5*M*), *p*-nitrobenzenediazonium chloride (0.1*M*), and cupric chloride (0.1*M*) in 70% aqueous acetone gave 13% of the isomeric dinitrobiphenyls. The composition of this mixture is shown in Table I together

TABLE I

p-NITROPHENYLATION OF NITROBENZENE

Source of *p*-Nitrophenyl Group	Isomer Content (%) 2,4′	3,4′	4,4′
Meerwein reaction	65	14	21
p-Nitrobenzoyl peroxide[6]	58	13	29
Gomberg-Bachmann reaction[7]	34	23	43

with the values which have been observed by others using accepted sources of aryl radicals. These mixtures of dinitrobiphenyls are not easily analyzed and the good agreement between the results of the Meerwein reaction and arylation *via* *p*-nitrobenzoyl peroxide might have been obscured had we not used a similar isolation procedure and an identical method of analysis.[6] The discrepancy between the *p*-nitrobenzoyl peroxide decomposition and the Gomberg-Bachmann reaction is disturbing since this represents the first instance known to us of a major difference between these well-known methods of generating aryl radicals.[8]

A second arylation, the phenylation of chlorobenzene, was carried out in the same manner. The product, a mixture of chlorobiphenyls, gave an infrared tracing, Fig. 1, virtually identical with that of a mixture of chlorobiphenyl prepared by a Gomberg-Bachmann reaction. Hey and coworkers[9] have demonstrated the reliability of this method of comparison. The minor deviations between the two infrared curves represent differences in isomer content which are within experimental error.

The original example of Meerwein arylation, the 2,4-dichlorophenylation of benzene, has been investigated in some detail and results are summarized in Table II. The yield of 2,4-dichlorobiphenyl appears to be proportional to the concentration of

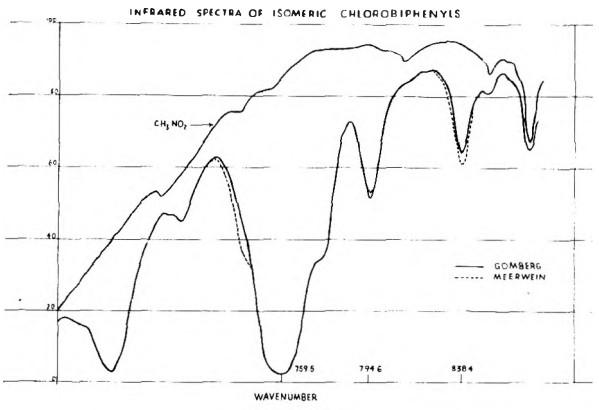

FIGURE 1.

benzene and inversely proportional to that of cupric chloride. It is significant that the addition of sodium acetate did not increase the yield of biphenyl.

TABLE II

2,4-DICHLOROPHENYLATION OF BENZENE

Run	Reactants (Molarity)[a] $ArN_2^+Cl^-$[c]	$CuCl_2$	C_6H_6	Products (%)[b] $C_{12}H_8Cl_2$	$C_6H_4Cl_2$	$C_6H_3Cl_3$
1	0.046[d]	0.051	0.80	29	18	5
2	0.10	0.050	0.50	19	37	14
3	0.10	0.050	0.50	21	36	14

[a] In 70% aqueous acetone. Homogeneous except for Run 3 to which was added sodium acetate. [b] 2,4-Dichlorobiphenyl, 1,3-dichlorobenzene, 1,2,4-trichlorobenzene. [c] 2,4-Dichlorobenzenediazonium chloride. [d] Solid diazonium salt was used.

Discussion. It is generally accepted that arylations of aromatic compounds, *via* benzoyl peroxides or Gomberg-Bachmann reactions, involve aryl radicals. The results of our isomer distribution studies clearly indicate that the same species, *p*-nitrophenyl and phenyl radicals, are produced in Meerwein reactions involving the corresponding diazonium salts. The conclusion that the Meerwein reaction proceeds by a radical mechanism is in agreement with the early suggestion of Koelsch and Boekelheide[10] and with the more comprehensive mechanism recently presented.[2] In terms of the latter mechanism the yield of biphenyl is determined by the efficiency with which arylation competes with hydrogen abstraction from acetone and halogen abstraction from cupric chloride. In addition the rate of reaction of the diazonium cation with the dichlorocuprate (I) ion is important. If this reaction is slow, solvolysis can compete with Meerwein reaction. An example of this situation is the slow reaction which gave chlorobiphenyls in low yield accompanied by phenol formation. The limited data at hand permit only the general conclusion that electron-attracting substituents favor arylation. The kinetics of the reaction of 2,4-dichlorobenzenediazonium chloride

(5) This method of detecting aryl radicals was developed and has been used extensively by Hey and coworkers; see, for example, D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.* 3963 (1955).

(6) R. T. Morrison and R. F. Sweeney, Abstracts, 130th Meeting AMERICAN CHEMICAL SOCIETY, Sept. 1956, p. 74-0. R. F. Sweeney, Ph.D. thesis, New York University, June 1956.

(7) D. F. DeTar and A. A. Kazimi, *J. Am. Chem. Soc.*, **77**, 3842 (1955).

(8) This difference may be rationalized in part by postulating that some of the 4,4′-isomer isolated from the Gomberg-Bachmann reaction arises by a coupling.

(9) D. R. Augood, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 44 (1953).

(10) C. F. Koelsch and V. Boekelheide, *J. Am. Chem. Soc.*, **66**, 412 (1944).

with benzene as well as other Meerwein reactions have been studied in the presence and absence of air and a detailed discussion of the mechanism of the Meerwein reaction will appear in that article.

EXPERIMENTAL

All melting and boiling points are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York, N. Y. Spectra were determined on Beckman Model DK-2 and Perkin-Elmer Model 112 spectrophotometers.[11]

All arylation reactions were performed in a three-necked flask, fitted with a gas-tight stirrer, connected through a condenser to a simple eudiometer, and immersed in a constant temperature bath at 35°.

p-Nitrophenylation of nitrobenzene. *p*-Nitroaniline hydrochloride (17.45 g.) was suspended in a mixture of 21 ml. of concentrated hydrochloric acid and 80 ml. of water. After heating to effect solution the mixture was cooled to 0° and diazotized in the presence of 30 g. of ice by rapid addition of a solution of 7.0 g. of sodium nitrite in 40 ml. of water. After 30 min. the turbid solution was filtered and diluted to a volume of 200 ml. with water.

This solution of the diazonium salt was mixed at 35° with 700 ml. of C.P. acetone, 75 ml. of water, 51.5 ml. of purified nitrobenzene, and 25 ml. of 2*M* cupric chloride. Gas evolution began at once and 99% of the theoretical volume of nitrogen was evolved in 9 min. The addition of solid sodium chloride produced two phases. The organic phase was extracted with saturated ammonium chloride solution and the extracts were added to the aqueous phase. The latter was exhaustively extracted with ether and the extracts were added to the original organic phase. The combined extracts were concentrated to a volume of 100 ml., dried over magnesium sulfate, and fractionated. All of the nitrobenzene and most of the *p*-nitrochlorobenzene were removed at a maximum head temperature of 81° at 2 mm. The brown, semisolid residue was dissolved in purified methylene chloride and diluted to exactly 250 ml.

The isomeric dinitrobiphenyls were isolated by a procedure similar to that of Morrison and Sweeney.[6] The residue, 208 mg., from a 10 ml. aliquot of the crude dinitrobiphenyl solution was dissolved in a 1:1 mixture of purified petroleum ether and purified methylene chloride and chromatographed on a column of Alcoa Alumina XF-21 which had been activated by heating at 450° for 5 hr. The column was prepared, developed and eluted with 5700 ml. of the 1:1 solvent mixture. A total of 37 fractions were collected after which the eluant left no residue on evaporation. The first 9 fractions contained *p*-nitrochlorobenzene which was removed by evaporation at room temperatures and 0.06 mm. for 16.5 hr. The residue which amounted to 7.5 mg. was combined with the remaining fractions to give an almost colorless, crystalline residue having a faint camphor-like odor. The unknown impurity responsible for this odor was removed by rechromatographing on a fresh column, prepared from the same sample of alumina, using 1200 ml. of methylene chloride as the eluant. Fractions 1–7 gave 120 mg. (12%) of almost colorless, odorless crystalline residue. The ultraviolet spectrum of fraction 7 identified it as 2,4′-dinitrobiphenyl. Fractions 8 and 9 gave 3.4 mg. of a yellow oil with a strong, camphor-like odor having an ultraviolet spectrum very different from that of the biphenyl.

The mixture of dinitrobiphenyls was analyzed using the procedure and the extinction coefficients of the individual dinitrobiphenyls reported by Morrison and Sweeney.[6] The mixture was dissolved in methylene chloride and diluted with "isooctane" to give a solution containing 0.8% methylene chloride and a solid content of 13 mg. per liter. The ultraviolet absorption spectrum of this solution was determined and the isomer content was calculated by the method of least squares from the optical densities at ten regularly spaced wave lengths from 230 mμ to 320 mμ. The composition was found to be 65% 2,4′, 14% 3,4′, and 21% 4,4′.

Phenylation of chlorobenzene. Freshly distilled aniline (8.9 g.) was diazotized using 17.5 ml. of concd. hydrochloric acid, 25 ml. of water, 25 g. of ice, and a solution of 6.7 g. of sodium nitrite in 20 ml. of water. The solution of diazonium salt was filtered and diluted to a volume of 100 ml. with water. This solution was mixed with 1400 ml. of C.P. acetone, 300 ml. of water, 130 ml. of chlorobenzene, and 200 ml. of 0.535*M* cupric chloride solution. Evolution of nitrogen began at once and 99% of the theoretical amount was given off in 70 min. The reaction mixture was diluted with water and exhaustively extracted with ether. The combined extracts were concentrated, dried, and fractionated at atmospheric pressure until most of the chlorobenzene had been removed. The residual oil was steam-distilled and the 5 l. of distillate was extracted with ether. The extracts were washed with 1*N* sodium hydroxide solution and then with water until neutral. The ether solution was dried, concentrated, and distilled. After a fore-run of chlorobenzene the crude chlorobiphenyls (0.35 g., 2%) were collected from 74–155° at 0.08–0.60 mm. The alkaline extracts yielded phenol which was brominated to give 4.4 g. of 2,4,6-tribromophenol. This represents a minimum yield of 14% of phenol.

The crude mixture of isomeric chlorobiphenyls contained colored impurities which were removed by chromatography on alumina with petroleum ether as eluant. A colorless sample of the chlorobiphenyls of b.p. 91–99° at 0.65–0.85 mm. was isolated. The infrared spectrum of this material in nitromethane solution[7] is compared in Fig. 1 with an authentic sample of mixed chlorobiphenyls prepared by a Gomberg-Bachmann reaction and purified as described above.

2,4-Dichlorobiphenyl. (*a*) *Using solid diazonium salt.* 2,4-Dichlorobenzenediazonium chloride (6.00 g.), prepared by the method of Knoevenagel, was dissolved in a mixture of 420 ml. of C.P. acetone, 120 ml. of water, 45 ml. C.P. benzene, and 60 ml. of 0.535*M* cupric chloride solution. Nitrogen evolution began immediately and a total of 95% of the theoretical amount was evolved in 24 min. Addition of solid sodium chloride to the homogeneous solution caused separation of two phases. The acetone-rich phase was washed with saturated ammonium chloride solution and the washings were added to the aqueous layer. This solution was exhaustively extracted with benzene and the extracts were combined with the acetone-rich phase. The resulting solution was dried with magnesium sulfate and concentrated by distillation through a short, packed column. The residue was steam-distilled up to a bath temperature of 185° and the distillate was extracted with ether. The combined and dried ether extracts were concentrated and distilled to yield 0.74 g. (18%) of 1,3-dichlorobenzene of b.p. 171–172°, 0.26 g. (5%) of 1,2,4-trichlorobenzene of b.p. 90–101° at 12.0–13.5 mm., and 1.85 g. (29%) of 2,4-dichlorobiphenyl of b.p. 90–92° at 0.13–0.14 mm., Table II.

Colored impurities in this sample of 2,4-dichlorobiphenyl were removed by chromatographing on alumina using purified petroleum ether as solvent and eluant. The colorless biphenyl was redistilled before analysis.

Anal. Calcd. for $C_{12}H_8Cl_2$: C, 64.6; H, 3.61; Cl, 31.8. Found: C, 64.8; H, 3.64; Cl, 31.6. The ultraviolet absorption spectrum of this material was identical with that of a sample of 2,4-dichlorobiphenyl prepared by the Gomberg-Bachmann reaction.

(*b*) *Using aqueous diazotization.* 2,4-Dichloroaniline hydrochloride (20.0 g.) was diazotized at 0° using 21 ml. of concd. hydrochloric acid, 80 ml. of water, 30 g. of ice, and 7.0 g. of sodium nitrite in 40 ml. of water. The solution of diazonium salt was filtered and diluted with water to a volume of 200 ml.

(11) The authors wish to thank Mr. Yugi Tajima of the Dept. of Chemical Engineering of New York University for making the infrared tracings.

The diluted solution of the diazonium salt was mixed with 700 ml. of C.P. acetone, 45 ml. of C.P. benzene, and 100 ml. of 0.50*M* cupric chloride solution. A total of 99% of the theoretical volume of nitrogen was evolved in 10 min. The procedure described above was followed with minor variations to give 5.53 g. (37%) of 1,3-dichlorobenzene, 2.63 g. (14%) of 1,2,4-trichlorobenzene, and 4.26 g. (19%) of 2,4-dichlorobiphenyl.

(c) *Using sodium acetate.* The quantities of reagents and procedure were identical with (b) except for the addition of an amount (12.8 g.) of anhydrous sodium acetate equivalent to the excess hydrochloric acid. A two phase reaction mixture resulted which evolved the theoretical volume of nitrogen in 17 min., yield 5.35 g. (36%) of 1,3-dichlorobenzene, 2.63 g. (14%) of 1,2,4-trichlorobenzene, and 4.74 g. (21%) of 2,4-dichlorobiphenyl.

(d) *By Gomberg-Bachmann reaction.* 2,4-Dichloroaniline hydrochloride (20.0 g.) was diazotized in the usual manner in a total volume of 146 ml. Excess nitrous acid was destroyed with urea and 400 ml. of C.P. benzene was added The mixture was cooled to 10°, vigorous agitation was begun, and 50 ml. of 5*N* sodium hydroxide was added over a period of 45 min. The isolation procedure previously described was followed and yielded 12.3 g. (55%) of 2,4-dichlorobiphenyl, b.p. 95–102° at 0.10–0.15 mm. A 1.49 g. sample of the biphenyl was purified by chromatography, yield 1.47 g. of colorless oil, b.p. 94–97° at 0.06–0.08 mm.

Anal. Calcd. for $C_{12}H_8Cl_2$: C, 64.6; H, 3.61; Cl, 31.8. Found: C, 64.7; H, 3.51; Cl, 31.9.

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

Competitive Metalation of Diphenyl Sulfone and 4,4′-Dimethyldiphenyl Sulfone by *n*-Butyllithium

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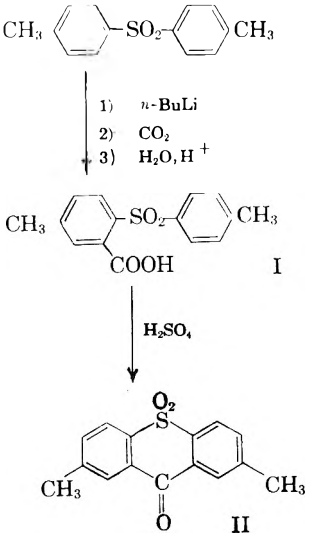
Competition between diphenyl sulfone and 4,4′-dimethyldiphenyl sulfone for an insufficient amount of *n*-butyllithium resulted in 47% metalation of diphenyl sulfone and 53% metalation of the dimethyldiphenyl sulfone. This unexpected preferential metalation of the rings supposedly deactivated by methyl groups may be due to the rapid and reversible formation of a larger concentration of the sulfone-*n*-butyllithium complex of the more basic dimethyldiphenyl sulfone. Determination of van't Hoff *i* factors in sulfuric acid for the two sulfones indicated the dimethyldiphenyl sulfone to be the more basic.

We have been studying the effect of simple alkyl substituents on the metalation of aromatic rings by *n*-butyllithium. An earlier paper[2] from this laboratory on the metalation of 4-*tert*-butyldiphenyl sulfone showed that the *tert*-butyl group caused deactivation of the ring to which it is attached, since metalation occurred predominantly in the unsubstituted ring. This result was in accord with some earlier observations by Truce[3] and Bryce-Smith[4] and the "protophilic" nature[4] of the metalation reaction. Thus, 4-methyldiphenyl sulfone was metalated[3] with *n*-butyllithium and 59% of the metalation was reported to occur in the unsubstituted phenyl ring and 41% in the ring containing the methyl group. Our work[2] with 4-*tert*-butyldiphenyl sulfone indicated an expected greater deactivating effect by the *tert*-butyl group as compared with a methyl group. These experiments were based on the intramolecular competititon of the two reactive positions adjacent to the sulfone group for the *n*-butyllithium. Intermolecular competitive metalation experiments have been used[4,5] by several workers to show relative activating and deactivating effects of functional groups toward the metalation reaction. We decided to study the intermolecular competitive metalation of diphenyl sulfone and 4,4′-dimethyldiphenyl sulfone to see how the results compared with the intramolecular competititon



experiments of Truce and Norman[3] on 4-methyldiphenyl sulfone.

(1) Present address: The Koppers Co., Monaca, Pa.

(2) D. A. Shirley and E. A. Lehto, *J. Am. Chem. Soc.*, **79**, 3481 (1957).

(3) W. E. Truce and O. L. Norman, *J. Am. Chem. Soc.*, **75**, 6023 (1953).

(4) D. Bryce-Smith, *J. Chem. Soc.*, 1079 (1954).

(5) (a) H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, **67**, 877 (1945). (b) H. Gilman, M. Van Ess, H. B. Willis, and C. G. Stuckwisch, *J. Am. Chem. Soc.*, **62**, 2606 (1940). (c) H. Gilman and F. Breuer, *J. Am. Chem. Soc.*, **56**, 1123 (1934).

We first carried out the metalation of 4,4′-dimethyldiphenyl sulfone itself with an equimolar amount of butyllithium, and after carbonation isolated the expected 2-carboxy-4,4′-dimethyldiphenyl sulfone (I) in 53% yield. The structure of I was indicated by its ready conversion to the corresponding thioxanthone-10-dioxide (II) with concentrated sulfuric acid.

The competitive metalation of an equimolar mixture of diphenyl sulfone and 4,4′-dimethyldiphenyl sulfone was carried out with one-half the *n*-butyllithium needed for complete monometalation. The reaction mixture was carbonated and the mixed monocarboxylic acids isolated in such manner that the isomer ratio was not disturbed. A neutralization equivalent on the mixed metalation acids indicated the composition to be 55 mole per cent 2-carboxy-4,4′-dimethyldiphenyl sulfone and 45 mole per cent of 2-carboxydiphenyl sulfone. We also constructed a melting point-composition diagram (data in Table I) from pure samples of the acids, and determined the composition of the mixture from these data. This indicated the composition to be 53 mole per cent of 2-carboxy-4,4′-dimethyldiphenyl sulfone.

TABLE I

FINAL MELTING TEMPERATURES OF MIXTURES OF 2-CARBOXYDIPHENYL SULFONE (A) AND 2-CARBOXY-4,4′-DIMETHYLDIPHENYL SULFONE (B)

Composition, Wt. Per Cent (A–B)	Final Melting Point, °C.
100–0	144
89–11	138
80–20	[a]
70–30	152
60–40	162
50–50	174
40–60	183
33–67	189
20–80	196
10–90	201
0–100	206
A and unknown mixture	167
B and unknown mixture	192
Unknown mixture (Run 1)	178
Unknown mixture (Run 2)	180
Unknown mixture (Average)	179

[a] This sample did not fully crystallize at room temperature in a vacuum desiccator.

The larger amount of metalation in the methyl substituted sulfone was surprising; such a result is not in accord with the results of the intramolecular competition experiment of Truce and Norman,[3] with another indication of the deactivating effect of the methyl group,[6] and with the probable mechanism of the metalation reaction.[4] Since our competitive metalation reaction occurred in the presence of the undissolved mixed sulfones, it was considered that the results might be influenced by a greater ether-solubility of the dimethyldiphenyl sulfone than the diphenyl sulfone, thus giving a higher effective concentration of the former compound. This was found not to be the case, since the diphenyl sulfone is actually more soluble in ether at 0° and at 25° than is the dimethyl substituted compound.

Another explanation seemed more plausible. The metalation of a diaryl sulfone probably involves first the formation of a coordination complex between an *n*-butyllithium molecule and an oxygen atom of the sulfone group. Such a complex should be formed rapidly and reversibly and the more basic of two competing sulfones would be present in larger concentration as its complex with the organometallic. The subsequent step of rearrangement of the complex to the metalated product[7] is probably rate determining and irreversible. Thus a steady state of higher concentration of the complex of the more basic sulfone could lead to more metalation of this sulfone, even though the decomposition of the complex into the reaction products occurred at a somewhat slower rate in comparison with the less basic sulfone.

The question remains as to which of the two sulfones used is the more basic. The inductive and hyperconjugative electron release effects of the methyl group should render the dimethyldiphenyl sulfone more basic than the diphenyl sulfone, and this fits the interpretation of the experimental results given above. However, some work of Szmant and coworkers[8] on the determination of van't Hoff *i* factors of substituted aryl sulfones in sulfuric acid indicated that electron releasing groups rendered the sulfone less basic (lower *i* factor) while electron attracting groups had the reverse effect (higher *i* factor). We determined the *i* factors of diphenyl sulfone and 4,4′-dimethyldiphenyl sulfone and observed values of 1.19 and 1.81, respectively. Szmant and Brost[8a] report a value of 1.3 for diphenyl sulfone. These *i* factors are in line with our view of the experimental results presented above. After completion of this work, the studies of Gillespie[9] came to our attention in which is reported[9b] a redetermination of the *i* factor of 4-nitro- and 4,4′-dinitrodiphenyl sulfone and values of 1.35 and 1.28, respectively, for these two compounds. Szmant's values for these same compounds were 1.5 and 2.0. The decrease in *i* factor in going from the 4-nitro to the 4,4′-dinitro compound is indicated by Gillespie to be in line with the expected effect of the nitro group in decreasing the basicity of the sulfone

(6) S. Gronowitz, *Arkiv Kemi*, **7**, 361 (1954).

(7) J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, **68**, 1658 (1946).

(8) (a) H. H. Szmant and G. A. Brost, *J. Am. Chem. Soc.*, **73**, 4175 (1951). (b) H. H. Szmant and R. L. Lapinski, *J. Am. Chem. Soc.*, **74**, 4395 (1952).

(9) (a) R. J. Gillespie, *J. Chem. Soc.*, 2542 (1950). (b) R. J. Gillespie and R. C. Passerini, *J. Chem. Soc.*, 3850 (1956).

group. Gillespie[9] has reported a value of 1.20 for diphenyl sulfone. Protonation of the nitro groups by the sulfuric acid makes difficult a direct comparison of diphenyl sulfone and the nitro derivatives, but Gillespie feels that the conclusion of Szmant that a nitro group increases the basicity of the sulfone is incorrect. The increase in the *i* factor from 1.19 to 1.81 when two methyl groups are introduced into the *para* positions of diphenyl sulfone indicates that the basicity of the sulfone group toward sulfuric acid is increased by such substitution. However, we also determined the *i* factor for 4-methyldiphenyl sulfone and found it to be 1.20. This indicates little, if any, increase in basicity by substitution of only one methyl group. The corresponding *i* factor for 4-*tert*-butyldiphenyl sulfone is 1.26, indicating a slight increase in basicity.

EXPERIMENTAL[10]

Metalation of 4,4'-dimethyldiphenyl sulfone. 4,4'-Dimethyldiphenyl sulfone, m.p. 159–160°, was prepared in 49% yield from *p*-toluenesulfonyl chloride and toluene by the general method of Buehler and Masters.[11] The reported melting point for this compound is 158°.[12]

To a well-stirred suspension of 24.6 g. (0.10 mole) of 4,4'-dimethyldiphenyl sulfone in 200 ml. of dry ether was added slowly at ice-bath temperature an equimolar amount of an ethereal solution of *n*-butyllithium. A nitrogen atmosphere was used. The mixture was stirred for 2 hr. at ice-bath temperature and then for 1 hr. after removal of the ice-bath. The mixture was carbonated by pouring over a slurry of ether and crushed solid carbon dioxide. After removal of the ether and carbon dioxide, water was added and the insoluble material was separated by filtration. The residue weighed 6.7 g. and melted at 155–157°. After recrystallization from benzene it melted at 156–157°. A mixture melting point with a sample of 4,4'-dimethyldiphenyl sulfone, m.p. 159–160°, was 157–158°. The aqueous filtrate from the above filtration was acidified with 1:1 hydrochloric acid and the resulting solid precipitate was collected by filtration. It weighed 21.8 g. and melted at 208–211°. This material was dissolved in aqueous sodium carbonate, filtered, and the filtrate was acidified with dilute hydrochloric acid. The precipitated solid was collected by filtration and recrystallized from 95% ethanol. The yield of crystalline solid melting at 205–206° was 15.3 g. (53%).

Anal. Calcd. for $C_{15}H_{14}O_4S$: C, 62.07; H, 4.83; neut. equiv., 290. Found: C, 61.87; H, 5.06; neut. equiv., 291.

Methyl ester of 2-carboxy-4,4'-dimethyldiphenyl sulfone. A mixture of 5.0 g. (0.017 mole) of 2-carboxy-4,4'-dimethyldiphenyl sulfone and 100 ml. of dry ether was treated with an excess of an ethereal solution of diazomethane. After removal of the ether and excess diazomethane, the residue was recrystallized from aqueous ethanol. There was obtained 4.3 g. (83%) melting at 95–96°. Recrystallization of a small amount of this material from aqueous methanol did not raise the melting point.

Anal. Calcd. for $C_{16}H_{16}O_4S$: C, 63.16; H, 5.26. Found: C, 63.06; H, 5.35.

Hydrazide of 2-carboxy-4,4'-dimethyldiphenyl sulfone. Two grams (0.007 mole) of the methyl ester was heated to reflux with 4 ml. of 99–100 per cent hydrazine hydrate for 15 min. and then just enough absolute ethanol was added to cause complete solution. The solution was heated to reflux for 2 hr. on the steam bath, after which the ethanol was removed by evaporation and the residue was recrystallized from very dilute aqueous ethanol. The resulting material weighed 1.5 g. (75%) and melted at 153–154°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: N, 9.21. Found: N, 9.19.

2,7-Dimethylthioxanthone-10-dioxide. II. One gram (0.003 mole) of 2-carboxy-4,4'-dimethyldiphenyl sulfone was heated at 185–195° with 20 ml. of concentrated sulfuric acid for 15 min. according to the procedure described by Ullmann and Lehner.[13] The solution was cooled and poured into an excess of cold water. Recrystallization of the resulting precipitated solid from a mixture of methanol and 95% ethanol gave 0.5 g. (61%) of a solid melting at 237–238°.

Anal. Calcd. for $C_{15}H_{12}O_3S$: C, 66.18; H, 4.41. Found: C, 66.19; H, 4.54.

Metalation of diphenyl sulfone. The procedure followed was due to Truce and Amos[14] for metalation of the same compound. A 42% yield of 2-carboxydiphenyl sulfone, m.p. 143–144° was obtained. Truce and Amos[14] report a 61% yield of acid melting at the same temperature.

Competitive metalation between diphenyl sulfone and 4,4'-dimethyldiphenyl sulfone. (*a*) *Run 1.* To a well-stirred suspension of 21.8 g. (0.10 mole) of diphenyl sulfone and 24.6 g. (0.10 mole) of 4,4'-dimethyldiphenyl sulfone in 300 ml. of dry ether under an atmosphere of nitrogen was added slowly at ice-bath temperature 0.10 mole of an ethereal solution of *n*-butyllithium. After the addition of *n*-butyllithium was complete, the reaction mixture was stirred for 2 hr. at ice-bath temperature and for 1 hr. after removal of the ice-bath. Carbonation of the reaction mixture was accomplished by pouring over a slurry of ether and crushed solid carbon dioxide. After the removal of the ether and carbon dioxide, water was added, and the resulting mixture was filtered. The insoluble residue weighed 35.1 g. and melted at 97–109°. The aqueous filtrate on acidification with 1:1 hydrochloric acid gave an oily precipitate which slowly crystallized on standing. The crystalline solid which was collected by suction filtration melted at 120–176°. It was dissolved in aqueous sodium carbonate solution, filtered, and the aqueous filtrate acidified with dilute hydrochloric acid. The precipitated crystalline material collected by filtration weighed 11.9 g. and melted at 115–178°. The neutralization equivalent of this material was found to be 278, which corresponds to a weight per cent composition of 57% of 2-carboxy-4,4'-dimethyldiphenyl sulfone and 43% of 2-carboxydiphenyl sulfone, or a mole per cent composition of 55 and 45%, respectively.

(*b*) *Run 2.* The procedure was similar to that of Run 1, except that 10.9 g. (0.05 mole) of diphenyl sulfone and 12.3 g. (0.05 mole) of 4,4'-dimethyldiphenyl sulfone in 200 ml. of dry ether were allowed to react with approximately 0.05 mole of an ethereal solution of *n*-butyllithium. The non-acidic material recovered from the reaction mixture weighed 12.1 g., while the acidic material, isolated as in Run 1, weighed 8.7 g. and melted over the range 127–180°, neutralization equivalent 278 ± 1. A mixture melting point with the acidic mixture obtained from Run 1 had a final melting point of 179°.

Mixture melting points of 2-carboxydiphenyl sulfone and 2-carboxy-4,4'-dimethyldiphenyl sulfone. Samples of these two acids were weighed together to give mixtures of varying composition. These were dissolved in acetone and the resulting solutions evaporated slowly to dryness. Melting points of these mixtures were determined by means of a Köfler micro hot stage melting point apparatus, and the final melting points (representing complete melt) were plotted *versus* composition (weight per cent). The unknown mixture (taking an average of the final melting points of the mixtures obtained from both Run 1 and Run 2) corresponded

(10) Microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(11) C. A. Buehler and J. E. Masters, *J. Org. Chem.*, **4**, 262 (1939).

(12) H. Beckurts and R. Otto, *Ber.*, **11**, 2066 (1878).

(13) F. Ullmann and A. Lehner, *Ber.*, **38**, 729 (1905).

(14) W. E. Truce and M. F. Amos, *J. Am. Chem. Soc.*, **73**, 3013 (1951).

to a 55–45, weight per cent composition (53–47 mole per cent) of 2-carboxy-4,4′-dimethyldiphenyl sulfone and 2-carboxydiphenyl sulfone, respectively, according to the plotted data of Table I. Furthermore, a mixture melting point of 2-carboxy-4,4′-dimethyldiphenyl sulfone with the unknown mixture raised the melting point, while a mixture melting point of 2-carboxydiphenyl sulfone with the unknown mixture lowered the melting point, which information supports the composition designated from the plot. The above procedure was used by Truce and Norman[3] to determine the percentage composition of a mixture of isomeric carboxylic acids resulting from the metalation of 4-methyldiphenyl sulfone with *n*-butyllithium, followed by carbonation.

Determination of i factors. The diphenyl sulfone used was Eastman White Label sample recrystallized from benzene. The 4-*tert*-butyldiphenyl sulfone was prepared as described previously.[2] The 4-methyldiphenyl sulfone was prepared from *p*-toluenesulfonyl chloride and benzene in the presence of aluminum chloride. The product melted at 124–125° (reported[11] 125–125.5°). The apparatus, technique, and solvent for the cryoscopic measurements have been described previously.[15] The solvent was prepared with care so that the freezing point of the 100% sulfuric acid was on the linear portion on the water side of the freezing point-composition curve as shown by Gillespie.[16] The apparatus was allowed to stand several hours for the sulfuric acid to absorb the moisture from the air in the cell before the initial freezing point of the acid was determined. The supercooling of the solutions was controlled to ±0.1°. The solutions in the cryostat were held below 18° throughout the period in which freezing point measurements were being made.[17] For diphenyl sulfone, three independent runs gave *i* factors of 1.19, 1.20, and 1.17, calculated from freezing points taken 15 to 20 min. after addition of the sulfone to the cryostat. Single runs gave corresponding values of 1.20 for 4-methyldiphenyl sulfone, 1.26 for 4-*tert*-butyldiphenyl sulfone, and 1.81 for 4,4′-dimethyldiphenyl sulfone.

Determination of solubilities. Samples of diphenyl sulfone and 4,4′-dimethyldiphenyl sulfone were placed in dry ether which was then refluxed for a short time. The solutions were decanted into glass-stoppered Erlenmeyer flasks which were placed in a thermostat at 25 ± 0.02° and allowed to reach temperature equilibrium. The sulfones, in excess of the amount required to saturate the ether, precipitated during this period. Samples of the clear supernatant liquid were withdrawn into a gravimetric pipet, and 10 ml. of the saturated solutions delivered into a weighing bottle. The solvent was evaporated, and the weights of the sulfones determined gravimetrically. The Erlenmeyer flasks containing the solutions were then placed in an ice bath and allowed to stand until equilibrium conditions were reached. Samples of the saturated solutions were withdrawn and their sulfone content determined as before. The results of duplicate determinations expressed in moles per liter of solution are as follows:

Diphenyl sulfone	25°	.0830, .0829
	0°	.0400, .0396
4,4′-Dimethyldiphenyl sulfone	25°	.0436, .0443
	0°	.0207, .0208

KNOXVILLE, TENN.

(15) C. M. Welch and H. A. Smith, *J. Am. Chem. Soc.*, **72**, 4748 (1950).

(16) R. J. Gillespie, *J. Chem. Soc.*, 2496 (1950).

(17) H. A. Smith and R. G. Thompson, *J. Am. Chem. Soc.*, **77**, 1778 (1955).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITY OF MARYLAND AND WAYNE STATE UNIVERSITY]

Pyrolysis of Esters. XI. A New Synthesis of α-Alkylacrylonitriles[1,2]

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The selectivity in the direction of elimination during the pyrolysis of tertiary esters has been used to prepare a series of α-alkylacrylonitriles. Thus α-ethyl-, α-*n*-propyl-, α-isobutyl-, and α-*n*-hexylacrylonitriles were prepared in 73 to 94% yields by the pyrolysis of the acetates derived from the corresponding methyl ketone cyanohydrins. Each of these monomers was polymerized by peroxide to a moderately high molecular weight polymer, with the poly-α-ethylacrylonitrile softening at 110–140°. One must conclude that previous preparations of these monomers were not free from inhibitors. These present results are additional evidence for the high degree of selectivity during the pyrolysis of esters.

Previous work in these laboratories has shown that the pyrolysis of esters proceeds in a highly selective manner to produce almost exclusively the least highly alkylated olefin according to the Hofmann rule.[6,7] For example, the pyrolysis of methylisopropylcarbinyl acetate gave almost exclusively 3-methyl-1-butene with little or no formation of the other possible isomer, 2-methyl-2-butene. It was shown that the presence of an unsaturated electron-withdrawing group in the β-position to the acyloxy group resulted in the formation of primarily the

(1) Previous paper in this series, *J. Org. Chem.*, **21**, 858 (1956).

(2) (a) Presented in part before the Division of Polymer Chemistry at the 128th National Meeting of the AMERICAN CHEMICAL SOCIETY, Minneapolis, Minn., September 1955; (b) Abstracted in part from a dissertation submitted by John J. Hewitt to the Graduate Council of Wayne State University, December 1952, and from a thesis submitted by Floyd E. Naylor to the faculty of the Graduate School of the University of Maryland, December 1955, in partial fulfillment of the requirements of the degrees of Doctor of Philosophy.

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(4) Office of Naval Research Fellow, University of Maryland, 1951–1955.

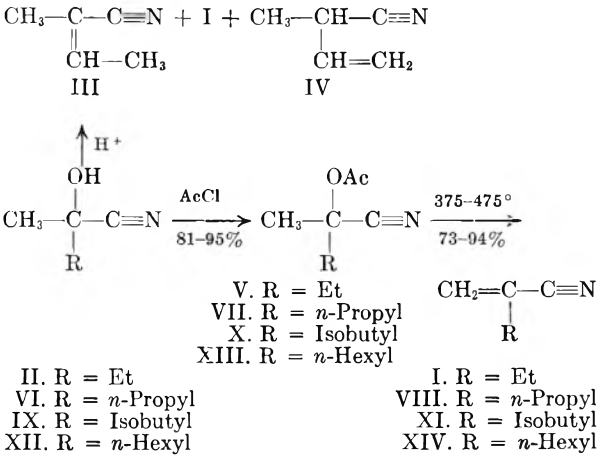
(5) Research Corporation Fellow, Wayne State University, 1951–1952.

(6) W. J. Bailey and C. King, *J. Am. Chem. Soc.*, **77**, 75 (1955).

(7) W. J. Bailey, C. King, and J. J. Hewitt, *J. Am. Chem. Soc.*, **77**, 357 (1955).

conjugated isomer.[8] However, the presence of a β-methoxy or a β-dimethylamino group did not seem to affect either the selectivity or the direction of elimination.[9] It seemed very probable that this selectivity could be used for the synthesis of interesting monomers for polymerization that are either impossible or difficult to synthesize by conventional methods. Actually, since the discovery of the new heterogeneous catalysts for the polymerization of alpha olefins,[10] many uses of this method in the hydrocarbon field are quite obvious. For example, the pyrolysis of methylisobutylcarbinyl acetate to produce 4-methyl-1-pentene is certainly the method of choice for the synthesis of this alpha olefin.

Methacrylonitrile can be prepared conveniently by the dehydration of acetone cyanohydrin. However, the corresponding dehydration of methyl ethyl ketone cyanohydrin (II)



produces a mixture containing as the main product β-methylcrotonitrile (III) plus only a small amount of α-ethylacrylonitrile (I). Furthermore, these two isomers apparently are difficult to separate by conventional distillation. Even though there are many reports of the synthesis of α-ethylacrylonitrile (I) and other α-alkyl derivatives,[11,12] there has been no report of a successful homopolymerization of any of these monomers. For these reasons, Marvel, Miller, and Chou developed a synthesis of I and other analogous α-alkylacrylonitriles from the corresponding α-alkylacroleins by dehydration of the corresponding oxime.[12] Even with this improved procedure they report,[13] "....very little success was had in obtaining homopolymers from α-ethyl- or α-*n*-pentylacrylonitrile with either free-radical or ionic initiators." One of the explanations that has been advanced for the failure of I to homopolymerize has been the steric hindrance of the ethyl group. In view of the fact that α-methylacrylonitrile homopolymerizes very readily it did not seem reasonable that the introduction of a CH_2 group should stop homopolymerization completely. In fact an examination of the models of the two monomers and their polymers did not indicate that the steric effect should be highly pronounced. It seemed possible that the failure of the previous samples of I to homopolymerize might be due to the presence of small amounts of isomeric impurities, such as III or IV, that were formed during dehydration with an acid catalyst. Any of these impurities, especially IV, could act as a chain transfer agent and prevent the formation of a high polymer. This view is further strengthened by the fact that α-phenylacrylonitrile,[14] which cannot form such isomeric impurities, does indeed homopolymerize.

Since the pyrolysis of esters has been shown to proceed in a selective manner with simple compounds, it seemed possible that this method could be used to prepare α-ethylacrylonitrile (I) from the α-acetoxy-α-methylbutyronitrile (V). If the sample of I prepared in this manner could be made to homopolymerize, this would not only serve as additional evidence concerning the selectivity of the elimination reaction but would also disprove the hypothesis that steric hindrance prevented the homopolymerization in the previous examples.

For this reason the cyanohydrin of methyl ethyl ketone (II) was esterified with acetyl chloride to produce a 95% yield of V. The use of acetic anhydride resulted in recovery of starting material even after reflux for several days, and the use of pyridine with the acetyl chloride gave products that were difficult to purify. The tertiary acetate V was then dropped through a pyrolysis tube packed with 1/8-inch borosilicate glass helices and externally heated at 475°. Conditions were carefully controlled in order that charring was virtually eliminated and that only 83% of the theoretical amount of acetic acid was liberated. Under these conditions a 73% yield of α-ethylacrylonitrile (I) was produced. Although the identity of this sample of I was established by agreement of its physical constants

(8) W. J. Bailey and C. King, *J. Org. Chem.*, **21**, 858 (1956).

(9) W. J. Bailey and L. Nicholas, *J. Org. Chem.*, **21**, 648 (1956).

(10) G. Natta, *J. Polymer Sci.*, **16**, 143 (1955); G. Natta, P. Pino, G. Mazzanti, P. Corradini, and U. Giannini, *Rend. accad. nazl. Lincei*, [8] **18**, 19 (1955).

(11) (a) P. Bruylants, L. Ernould, and M. Dekoker, *Bull. sci. acad. roy. Belg.*, [5] **16**, 721 (1930); (b) M. Vossen, *Bull. soc. chim. Belg.*, **41**, 331 (1932); (c) A. Vermeulen and L. Adriaens, *Bull. soc. chim. Belg.*, **38**, 301 (1929); (d) A. Craen, *Bull. soc. chim. Belg.*, **42**, 410 (1933); (e) P. Ceuterick, *Bull. soc. chim. Belg.*, **44**, 89 (1935); (f) G. Verbulst and C. Glorieux, *Bull. soc. chim. Belg.*, **41**, 501 (1932).

(12) C. S. Marvel, W. R. Miller, and L. C. Chou, *J. Am. Chem. Soc.*, **72**, 5408 (1950).

(13) C. S. Marvel, R. T. Stiehl, W. K. Taft, and B. G. Labbe, *Ind. Eng. Chem.*, **46**, 804 (1954); a private communication from R. T. Stiehl indicated that during a distillation of α-ethylacrylonitrile a solid polymer accidentally resulted but that this polymer was not completely characterized.

(14) A. M. Clifford and J. R. Long, U. S. Patent 2,362,049 (1944); *Chem. Abstr.*, **39**, 2296 (1945).

with the reported values as well as by its infrared spectrum, the purity of I really was established by the fact that this monomer would homopolymerize. Thus when a benzene solution of I was heated with benzoyl peroxide, a solid poly-α-ethylacrylonitrile, softening point 110–140°, resulted. Although its intrinsic viscosity was only 0.12, this is the first solid homopolymer reported from this monomer. Even though these results seem to indicate that there may be some steric hindrance to polymerization in I, the effect is not nearly as large as previously believed. Furthermore, these results indicate that the previously prepared samples of I must have contained some impurity, such as III or IV, that could act as a chain transfer agent. These results also offer additional evidence of the high degree of selectivity of the elimination in the pyrolysis of esters, provided that any charring that could cause acid-catalyzed rearrangements is eliminated.

Chapin and Smith,[15] for example, carried out the pyrolysis of the α-acetoxy-α-methylbutyronitrile (V) over clay plate and obtained a sample of impure I that could not be homopolymerized or purified by distillation. They did establish the presence of the isomeric methylcrotonitrile III in their pyrolysis product. Apparently the clay plate was acidic enough to cause either some acid-catalyzed elimination of acetic acid from V or some acid-catalyzed rearrangement of the resulting olefin I.

In order to establish more clearly the extent of steric hindrance to polymerization it seemed of interest to prepare a series of alpha-substituted acrylonitriles. It was thought that, if several acrylonitriles with fairly large alpha substituents could be prepared and made to homopolymerize, one could conclude more definitely that steric hindrance could not completely account for the failure of previously prepared α-alkylacrylonitriles to polymerize. For this reason the syntheses of α-*n*-propyl-, α-isobutyl-, and α-*n*-hexylacrylonitriles (VIII, XI, XIV) were undertaken.

Methyl *n*-propyl ketone cyanohydrin (VI) was heated with acetyl chloride to produce a 93% yield of the corresponding acetate VII. Pyrolysis of VII at 385° with care to avoid carbonization produced a 55% conversion to α-*n*-propylacrylonitrile (VIII). Since 38% of the starting ester was recovered, the yield of VIII, based on unrecovered material, was 89%. When VIII was homopolymerized in a standard peroxide-catalyzed emulsion system, a white powdery poly-*n*-propylacrylonitrile, softening at 60–64° and having an intrinsic viscosity of 0.12, was obtained.

Similarly, methyl isobutyl ketone cyanohydrin (IX) was acetylated with acetic anhydride in an 81% yield and the resulting acetate X was pyrolyzed at 375° to produce a 46% conversion to α-isobutylacrylonitrile (XI). Since a 40% recovery of X also was obtained, the yield of XI, based on unrecovered material, was 77%. Standard emulsion polymerization of XI produced a solid white polymer, softening at 50–54° and having an intrinsic viscosity of 0.1.

Methyl *n*-hexyl ketone cyanohydrin (XII) was acetylated with acetyl chloride in a 90% yield and the resulting acetate XIII was pyrolyzed at 375° to yield a 48% conversion to α-*n*-hexylacrylonitrile (XIV). Again, since 49% of the starting ester XIII was recovered, the yield of XIV, based on unrecovered material, was 92%. Standard emulsion polymerization of XIV produced a viscous oil with an intrinsic viscosity of 0.11. The polymer, on cooling, formed a solid, softening point 15–18°.

The softening-point relationships in this series are approximately what one would expect from a series of amorphous polymers with increasing size of a side chain. Rehberg and Fisher[16] found that as one increased the number of carbon atoms in the alkyl group in a series of poly-*n*-alkyl methacrylates, the brittle point dropped from 88° for the methyl ester to −35° for the dodecyl ester. (The *n*-amyl derivative softened at +3°.) Similarly, Overberger, Frazier, Mandelman, and Smith[17] found that, as the length of the side chain was increased in a series of poly-*p*-alkylstyrenes, the softening point dropped from 100° for polystyrene to about −65° for the *n*-decyl derivative. (The *n*-hexyl derivative softened at −27°.)

In order to obtain some idea of the reactivity of one of these α-substituted acrylonitriles, a copolymerization was carried out with α-isobutylacrylonitrile (XI) and methyl methacrylate. The product, softening point 115–145°, intrinsic viscosity 0.3, obtained from a monomer mixture containing 40% by weight of the nitrile XI, after a 6% conversion, contained only 33% of XI.

Even though the molecular weights of the poly-α-alkylacrylonitriles were not extremely high, this is the first report of a solid homopolymer for this series. One would conclude, therefore, that steric hindrance to polymerization must be somewhat important but not enough to prevent homopolymerization. This steric effect probably exaggerated the effect of impurities on the polymerization. Thus chain transfer agents, such as III or IV, if present in previous preparations of these monomers, probably would have had a large inhibitory effect on the homopolymerization. Apparently the amount of these inhibitors in the monomers prepared by pyrolysis was not as large. One can conclude, therefore, that the pyrolysis of esters does indeed proceed in a highly selective manner and is an excellent method for the preparation of monomers for polymerization.

(15) E. C. Chapin and R. F. Smith, *J. Am. Chem. Soc.*, **76**, 4179 (1954).

(16) C. E. Rehberg and C. H. Fisher, *Ind. Eng. Chem.*, **40**, 1429 (1948).

(17) C. G. Overberger, C. Frazier, J. Mandelman, and H. F. Smith, *J. Am. Chem. Soc.*, **75**, 3326 (1953).

EXPERIMENTAL[18]

Methyl ethyl ketone cyanohydrin (II). By a modification of the procedure for the preparation of acetone cyanohydrin,[19] 500 g. (9.7 moles) of powdered 95% sodium cyanide, 1.2 liters of water, and 887 g. (12.3 moles) of methyl ethyl ketone were placed in a 5-liter, three-necked flask equipped with a stirrer, a dropping funnel, and a thermometer. While the reaction mixture was maintained below 15°, 2.1 liters (8.5 moles) of 40% sulfuric acid was added with vigorous stirring over a 3-hr. period. After the organic layer was dried over anhydrous sodium sulfate, the excess methyl ethyl ketone was removed by distillation and the residue was fractionated through a 12-in., helix-packed column to yield 672 g. (80%) of methyl ethyl ketone cyanohydrin (II), b.p. 108.4° (40 mm.), n_D^{25} 1.4127, d_{25}^{25} 0.9212 [reported[15] b.p. 87–88° (17 mm.), n_D^{24} 1.4119].

Anal. Calcd. for C_5H_9NO: C, 60.58; H, 9.15. Found: C, 60.81; H, 9.37.

α-Acetoxy-α-methylbutyronitrile (V). To 99 g. (1 mole) of methyl ethyl ketone cyanohydrin (II) was added 79 g. (1 mole) of acetyl chloride at a rate slow enough to keep the temperature below 80°. After the reaction mixture had been heated for 12 hr., it was extracted with water, a saturated sodium carbonate solution, and again with water. The mixture was then dried over anhydrous sodium sulfate and fractionated through a 12-in., helix-packed column to yield 134 g. (95%) of α-acetoxy-α-methylbutyronitrile (V), b.p. 108–109° (40 mm.), n_D^{25} 1.4137, d_{25}^{25} 0.9808 [reported[15] b.p. 90–91° (16 mm.), n_D^{24} 1.4111].

Anal. Calcd. for $C_6H_{11}NO_2$: C, 59.55; H, 7.85. Found: C, 59.59; H, 7.70.

α-Ethylacrylonitrile (I). At the rate of 2 g. per min., 100 g. (0.71 mole) of α-acetoxy-α-methylbutyronitrile (V) was added dropwise through a vertical Vycor tube packed with 1/8-in. borosilicate glass helices and externally heated at 475°, as described previously.[20] The pyrolysate was condensed in a 6-inch spiral condenser and collected in a 300-ml., side-inlet flask cooled in a Dry Ice–chloroform–carbon tetrachloride bath. In order to prevent charring the apparatus was continuously flushed with a slow stream of oxygen-free nitrogen. The pyrolysate was extracted with water until the aqueous extracts tested neutral to litmus, and the organic layer was then dried over a mixture of anhydrous sodium sulfate and potassium carbonate. (Titration of an aliquot of the aqueous extracts with standard base indicated that 83% of the theoretical amount of acetic acid had been liberated.) Fractionation through a 6-in., helix-packed column produced 50 g. (73%) of α-ethylacrylonitrile (I), b.p. 112.5–113°, n_D^{25} 1.4120, d_{25}^{25} 0.8083 [reported[15] b.p. 111.9–112.9°, n_D^{20} 1.4118].

Anal. Calcd. for C_5H_7N: C, 74.03; H, 8.68. Found: C, 74.15; H, 8.71.

Polymerization of α-ethylacrylonitrile (I). A solution of 10 g. of α-ethylacrylonitrile (I) and 0.1 g. of benzoyl peroxide in 50 ml. of benzene was heated under reflux for 35 hr. The benzene solution was extracted with a dilute sodium hydroxide solution and then treated with Norite to remove a yellow color. Addition of an excess of petroleum ether produced a precipitate, which was removed by filtration and dried in vacuum to yield 6 g. of white poly-α-ethylacrylonitrile which began to shrink at 110° and completely softened below 140°. The polymer had an intrinsic viscosity of 0.12.

Anal. Calcd. for $(C_5H_7N)_x$: C, 74.03; H, 8.68. Found: C, 74.10; H, 8.49.

α-Acetoxy-α-methylvaleronitrile (VII). Methyl *n*-propyl ketone cyanohydrin (VI), b.p. 101° (17 mm.), n_D^{25} 1.4200 [reported[21] b.p. 100° (21 mm.), n_D^{19} 1.42065], was prepared in a 76% yield by a modification of the procedure described above for methyl ethyl ketone cyanohydrin (II). To 160 g. (1.5 moles) of the cyanohydrin VI, heated in a 500-ml., three-necked flask fitted with a dropping funnel and a reflux condenser protected with a calcium chloride tube, was added dropwise 120 g. (1.5 moles) of acetyl chloride over a 1-hr. period. After the reaction mixture had been heated under reflux for 14 hr., it was fractionated through a 10-in., helix-packed column to yield 221 g. (93%) of α-acetoxy-α-methylvaleronitrile (VII), b.p. 96° (25 mm.), n_D^{25} 1.4186.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 61.93; H, 8.38. Found: C, 61.86; H, 8.25.

α-n-Propylacrylonitrile (VIII). At the rate of 3 g. per minute, 71.5 g. (0.46 mole) of α-acetoxy-α-methylvaleronitrile (VII) was added dropwise through the same pyrolysis tube described above heated at 385°. The same procedure for the pyrolysis and treatment of the pyrolysate also was used with the exception that the pyrolysate was dissolved in 50 ml. of ether before extraction. (Titration of an aliquot of the aqueous extracts indicated that 55% of the theoretical amount of acetic acid had been liberated.) Distillation of the ether solution through a 10-inch, helix-packed column yielded 39 g. (55%) of α-*n*-propylacrylonitrile (VIII), b.p. 134° (760 mm.), n_D^{25} 1.4211 [reported[11c] b.p. 135.7° (757 mm.), n_D^{20} 1.42283], and 27.5 g. (38% recovery) of the starting acetate VII. The yield of VIII, based on unrecovered VII, was, therefore, 89%.

Anal. Calcd. for C_6H_9N: C, 75.79; H, 9.47. Found: C, 75.56; H, 9.57.

Polymerization of α-n-propylacrylonitrile (VIII). In a 2-oz. vial were placed 5.5 g. (0.058 mole) of α-*n*-propylacrylonitrile (VIII), 18 g. of water, 0.02 g. of potassium persulfate, 0.03 g. of lauryl mercaptan, and 0.5 g. of sodium stearate and the vial was carefully flushed with nitrogen. The vial was rotated end-over-end at 50° for 5 days. Additional potassium persulfate was added at 24-hr. intervals. The polymer emulsion was poured into 100 ml. of vigorously stirred methanol. After the resulting precipitate was removed by filtration, it was redissolved in 10 ml. of tetrahydrofuran and reprecipitated by the addition of this solution to an additional 100 ml. of methanol. The precipitate was removed by filtration and dried under vacuum to yield 0.9 g. (17% conversion) of a white powder of poly-α-*n*-propyl acrylonitrile, softening point 60–64°, $[\eta]_{C\to O}$ 0.12.

α-Acetoxy-α,γ-dimethylvaleronitrile (X). Methyl isobutyl ketone cyanohydrin (IX), b.p. 109° (24 mm.), n_D^{25} 1.4240 [reported[22] b.p. 109° (24 mm.), n_D^{21} 1.42595], was prepared in a 78% yield by a modification of the procedure described above for methyl ethyl ketone cyanohydrin (II). In a 1-l., 3-necked flask fitted with two reflux condensers were placed 127 g. (1 mole) of the cyanohydrin IX, 408 g. (4 moles) of acetic anhydride and 60 g. of acetic acid. After the reaction mixture had been heated under reflux for 72 hr., it was fractionally distilled through a 10-in., helix-packed column to yield 137 g. (81%) of α-acetoxy-α,γ-dimethylvaleronitrile (X), b.p. 125° (36 mm.), n_D^{25} 1.4220.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.87; H, 8.92. Found: C, 63.78; H, 8.75.

α-Isobutylacrylonitrile (XI). At the rate of 3 g. per min.,

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(20) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 543 (1956).

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85 g. (0.5 mole) of α-acetoxy-α,γ-dimethylvaleronitrile (X) was added dropwise to the pyrolysis tube heated at 375°. The pyrolysate was worked up as indicated previously for that from the pyrolysis of VII. (Titration of an aliquot of the aqueous extracts indicated that 55% of the theoretical amount of acetic acid had been liberated.) The ether extract was fractionally distilled through a 10-in., helix-packed column to yield 25 g. (46%) of α-isobutylacrylonitrile (XI), b.p. 68° (50 mm.), n_D^{25} 1.4232, and 33 g. of the starting acetate X. The yield of XI, based on unrecovered starting material, was 77%.

Anal. Calcd. for $C_7H_{11}N$: C, 77.06; H, 10.09. Found: C, 77.08; H, 9.85.

Polymerization of α-isobutylacrylonitrile (XI). By the use of a procedure similar to that described for α-*n*-propylacrylonitrile (VIII), 4 g. of α-isobutylacrylonitrile (XI) was polymerized in an emulsion system over a 4-day period. The crude polymer, formed by coagulation in methanol, was redissolved in tetrahydrofuran and was then reprecipitated by the addition of this solution to methanol. The white powder was dried under vacuum to yield 0.4 g. (10%) of poly-α-isobutylacrylonitrile, softening point 50–54°, $[\eta]_{c\to 0}$ 0.1.

Copolymerization of α-isobutylacrylonitrile (XI) *and methyl methacrylate.* By a procedure similar to that described for the polymerization of α-*n*-propylacrylonitrile (VIII), 2 g. of α-isobutylacrylonitrile and 3 g. of methyl methacrylate were copolymerized over a 52-hr. period. The emulsion was poured into 200 ml. of methanol and the mixture was made acidic to litmus. After the copolymer was collected by filtration, it was redissolved in 10 ml. of tetrahydrofuran and reprecipitated by the addition of this solution to 100 ml. of methanol. The copolymer was dried under vacuum to yield 0.3 g. of a white powder, softening point 115–145°, $[\eta]_{c\to 0}$ 0.3. Analysis showed that the copolymer contained 3.97% nitrogen, which indicated that the copolymer contained approximately 1 mole of α-isobutylacrylonitrile for every 2 moles of methyl methacrylate.

α-Acetoxy-α-methylcaprylonitrile (XIII). Methyl *n*-hexyl ketone cyanohydrin (XII), b.p. 130° (11 mm.), n_D^{25} 1.4301 [reported[11f] b.p. 131–132° (11 mm.), n_D^{20} 1.43227], was prepared in a 58% yield by a modification of the procedure described above for the preparation of methyl ethyl ketone cyanohydrin (II). By the same procedure described above for the preparation of α-acetoxy-α-methylvaleronitrile (VII), 90 g. (0.58 mole) of the cyanohydrin XII was acetylated with 70 g. (0.89 mole) of acetyl chloride to yield 100 g. (90%) of α-acetoxy-α-methylcaprylonitrile (XIII), b.p. 128° (12 mm.), n_D^{25} 1.4286.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 67.01; H, 9.65. Found: C, 66.99; H, 9.38.

α-n-Hexylacrylonitrile (XIV). At the rate of 3 g. per min., 71 g. (0.38 mole) of α-acetoxy-α-methylcaprylonitrile (XIII) was added dropwise to the pyrolysis tube heated at 375°,as described above. The pyrolysate was worked up as described for the *n*-propylacrylonitrile (VIII). (Titration of an aliquot of the aqueous extracts indicated that 48% of the theoretical amount of acetic acid had been liberated.) The ether extract was fractionally distilled through a 10-in., helix-packed column to yield 24.5 g. (48%) of α-*n*-hexylacrylonitrile (XIV), b.p. 114° (50 mm.), n_D^{25} 1.4347 [reported b.p. 80° (12 mm.),[11f] b.p. 201° (766 mm.),[11f] b.p. 112° (48 mm.),[12] n_D^{20} 1.43972,[11f] n_D^{20} 1.4350[12]], and 35 g. of the starting acetate XIII. The yield of XIV, based on unrecovered starting material, was 92%.

Anal. Calcd. for $C_9H_{15}N$: C, 78.83; H, 10.95. Found: C, 79.11; H, 10.71.

Polymerization of α-n-hexylacrylonitrile (XIV). By a procedure very similar to that described for α-*n*-propylacrylonitrile (VIII), 5 g. (0.036 mole) of α-*n*-hexylacrylonitrile (XIV) was polymerized in an emulsion system over a 4-day period. The polymer was purified as described above to yield 0.3 g. of a clear viscous poly-α-*n*-hexylacrylonitrile, $[\eta]_{c\to 0}$ 0.11, which became a hard glass at 0° and resoftened at 15–18°.

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Kinetics of Diels-Alder Reactions of Eleostearic Acids with Maleic Anhydride and Substituted Maleic Anhydrides

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The kinetics of the Diels-Alder reactions of *alpha*- and *beta*-eleostearic acids with chloromaleic, methylmaleic, and maleic anhydrides have been investigated. The reactions of chloromaleic anhydride and maleic anhydride with the eleostearic acids conformed to second order kinetics, but those of methylmaleic anhydride particularly with *alpha*-eleostearic acid, were not strictly second order. The specific rate constants for the Diels-Alder reactions of *beta*-eleostearic acid were found to be of greater magnitude than those for *alpha*-eleostearic acid, and the reactions of the former were found to be less temperature-dependent than the reactions of the latter. Energies of activation for the systems in which *beta*-eleostearic acid was a reactant were markedly lower than those for systems containing *alpha*-eleostearic acid, while the magnitude of the frequency factors of the respective systems was reversed. Substitution of either a methyl group or chlorine atom into maleic anhydride resulted in diminished dienophilic activity. The influences of structure, steric requirements, and group inductive effects on the specific rate constants of the various reactions have been considered.

In continuing the study of the Diels-Alder reactions of *alpha*- and *beta*-eleostearic (octadecatrienoic) acids[2,3] we have now investigated the kinetics of their reactions with maleic anhydride, chloromaleic anhydride, and methylmaleic anhydride (citraconic anhydride). This series of dienophiles

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

(2) J. S. Hoffman, R. T. O'Connor, F. C. Magne, and W. G. Bickford, *J. Am. Oil Chemists' Soc.*, **32**, 533 (1955).

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is of particular interest, because it provides a means of comparing the effects of electron-withdrawing and electron-releasing substituents on the rates of Diels-Alder addition. Of further interest is a comparison of the relative rates of addition of such dienophiles to *alpha*-eleostearic acid, which contains only one pair of conjugated, *trans,trans* ethylenic bonds, with rates of addition to *beta*-eleostearic acid, which contains two pairs of such double bonds—having one ethylenic bond in common.

Previous work has shown that the 9-*cis*, 11-*trans*, 13-*trans* conjugated system of *alpha*-eleostearic acid forms a single maleic anhydride adduct across carbons 11–14. However, two maleic anhydride adducts are produced with the all *trans* system of *beta*-eleostearic acid, addition occurring either across carbons 9–12 or carbons 11–14.[4]

Accordingly, an investigation was undertaken to determine the influence of temperature, diene configuration, dienophile structure, and group inductive effects on the specific rate constants of the various reactions.

EXPERIMENTAL

Preparation of materials. Alpha- and beta-eleostearic acids. Pure *alpha*- and *beta*-eleostearic acids were prepared by the method of Hoffman, *et al.*[5] *Alpha*-eleostearic acid: m.p. 49.2–49.4°, absorptivity (a) = 176.7 at 271.5 mμ in cyclohexane. *Beta*-eleostearic acid: m.p. 71–72°, absorptivity (a) = 201.8 at 269.0 mμ in cyclohexane.

Maleic anhydride. Maleic anhydride was crystallized from chloroform (2 g./ml.) at room temperature (m.p. 51–53°).

Chloromaleic anhydride. Chloromaleic anhydride was placed in the refrigerator until it partially solidified. The crystals were filtered, washed with petroleum ether, dissolved in ethyl ether (1 g./ml.), and allowed to crystallize at −20° (m.p. 31–32°).

Methylmaleic anhydride. Methylmaleic anhydride was purified by high vacuum distillation (b.p. 35°/100μ).

Xylene. Reagent grade xylene was washed with concentrated sulfuric acid until no discoloration was produced, then with water, and finally with a solution of potassium hydroxide. The washed xylene was dried first with anhydrous sodium sulfate, and then with solid potassium hydroxide before it was distilled (b.p. 137–138°).

Determination of reaction rates. A 2.78-g. sample of pure eleostearic acid (0.01 mole) was dissolved in approximately 40 ml. of purified xylene. To this solution was added 50.0 ml. of a 0.20*M* solution of the dienophile, and the volume made up to 100.0 ml., thus resulting in an equimolar mixture of reactants (0.10*M*).

After the reactants were mixed thoroughly, aliquots (*ca.* 5 ml.) were poured rapidly into a number of small screw cap test tubes. The caps, which contained fresh aluminum foil liners over their rubber gaskets, were tightened, and the tubes immediately immersed in a constant temperature bath controlled within ±0.1° of the desired temperature.

The tubes were removed at regular intervals, rapidly cooled to room temperature, and the contents immediately analyzed. The course of the reaction was followed by the disappearance of eleostearic acid, as determined spectrophotometrically.[5]

Using the above described procedure, at least three independent experiments, employing freshly prepared reagents, were carried out at each of two temperatures[6] for the various diene-dienophile systems. Generally, seven eleostearic acid determinations were made for each run at various time intervals during the course of each reaction, thereby providing a minimum of 21 values for use in determining the specific rate constants for each system at a given temperature. Conversion of the reactants into Diels-Alder adducts ranged from about 30–55%, depending upon the temperature and system employed.

Treatment of data. Since the diene and dienophile were employed in equimolar concentrations, it was possible to examine the data for conformity to a second order reaction by plotting the reciprocal of the concentration *vs.* time. Such graphs of the data obtained for the reactions of the eleostearic acids with maleic anhydride and chloromaleic anhydride were linear, indicating the reactions to be second order. However, the methylmaleic anhydride reactions, particularly with *alpha*-eleostearic acid, showed deviations from second order kinetics. All of the data obtained for each diene-dienophile system at a given temperature were combined, and the method of least squares was applied to the data. In these equations of the form $\frac{1}{C} = at + b$, where C is the molar concentration and t is time in minutes, the slope, a, gave the specific reaction rate constant, k. These constants are tabulated in Table I. For each diene-dienophile system, the values of the specific rate constants at two different temperatures were used to calculate the energies of activation from the Arrhenius equation. The energy of activation, E, was obtained from the slope of the equation $\ln k = \frac{-E}{RT} + \ln A$. These energies of activation and A parameters are presented in Table II. Even though five rate runs were made at each of two temperatures for the methylmaleic anhydride–*alpha*-eleostearic acid system, no significant differences could be found in the rates at these two temperatures.

TABLE I

SECOND ORDER RATE CONSTANTS FOR DIELS-ALDER REACTIONS

Reaction	Reaction Temp., °C.	10^5k[a]
Maleic anhydride + α-eleostearic acid	70	20
	85	56
Maleic anhydride + β-eleostearic acid	55	34
	70	74
	85	153[b]
Chloromaleic anhydride + α-eleostearic acid	85	21
	100	62
Chloromaleic anhydride + β-eleostearic acid	85	117
	100	244
Methylmaleic anhydride + β-eleostearic acid	85	8[b]
	100	15
	115	27

[a] Units for k are l. mole^{-1} sec.$^{-1}$ [b] Value calculated for 85°.

DISCUSSION

Diels-Alder reactions are first order with respect to both diene and dienophile components,[7,8] al-

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(5) J. S. Hoffmann, R. T. O'Connor, D. C. Heinzelman, and W. G. Bickford, *J. Am. Oil Chemists' Soc.*, **34**, 338 (1957).

(6) Data obtained at two temperatures were considered adequate for the close approximation of the Arrhenius parameters for the various reactions.

TABLE II

ARRHENIUS PARAMETERS FOR THE DIELS-ALDER REACTIONS

Reaction	E_1 kcal. mole^{-1}	log A^a
Maleic anhydride + α-eleostearic acid	17	7.0
Maleic anhydride + β-eleostearic acid	12	4.3
Chloromaleic anhydride + α-eleostearic acid	19	8.0
Chloromaleic anhydride + β-eleostearic acid	13	5.0
Methylmaleic anhydride + β-eleostearic acid	12	3.0

[a] Units for A are l. mole^{-1} sec.$^{-1}$

though recent work has shown that this is not strictly the case in instances where a large excess of dienophile is employed in the reaction.[9] Diene syntheses are reversible, and the reverse reaction is unimolecular.[10] The pre-exponential factor of the Arrhenius Equation, $k = Ae^{-E/RT}$, is of the order of 10^{12} sec.$^{-1}$ for the reverse reaction, which is of the same magnitude as that of "normal" first order reactions. For Diels-Alder reactions the magnitude of the parameter, A, of the Arrhenius Equation is generally many powers of 10 lower than the collision frequency of 10^{11} l. mole^{-1} sec.$^{-1}$, which is characteristic of "normal" bimolecular reactions. Since the probability of electron transition from one quantum state to another is the same for both forward and reverse reactions,[10] it may be concluded that the low values of A found for Diels-Alder reactions are due to structural complexities of the molecules employed in these reactions rather than to rate-restricting transitions.

It may be presumed *a priori* that structural variations among closely related dienes or dienophiles will be reflected in the relative magnitudes of the pre-exponential factors for related Diels-Alder reactions. That is, the fraction of collisions between activated molecules resulting in adduct formation will be dependent upon the internal degrees of freedom and steric requirements of the reactants.

Theories of electronic effects in Diels-Alder reactions have been applied chiefly to the interpretation of the structures of unsymmetrical adducts. However, recent investigations have shown that electronic effects in both the diene and dienophile components markedly influence the rate of the Diels-Alder reaction.[9,11] Substitution of strongly electron-withdrawing groups into the dienophile enhances dienophilic activity, while a similar effect is observed on the reaction rate through substitution of electron-releasing groups in the diene. Although the process by which electrons are transferred from the diene to the dienophile is not fully understood as yet, it is apparent that the transition state intermediate has some polar characteristics, that the reactants lie in parallel planes,[9,12] and that the two new *sigma* carbon to carbon bonds are formed simultaneously.[13,14] In this connection, it is of particular interest to note the sensitivity of the energy of activation to inductive effects of substituents in both the diene and dienophile as observed by Andrews and Keefer.[9] It may be presumed that electronic effects in the Diels-Alder reaction due to variation of substituents may be reflected in differences found in the energies of activation for closely related systems.

An increase in temperature has a greater effect on the change of reaction rate in those system employing *alpha*-eleostearic acid than in the *beta*-eleostearic acid systems. It was observed that, on raising the reaction temperature 15°, the rates of reaction for *beta*-eleostearic acid with the dienophiles employed are approximately doubled, while those for *alpha*-eleostearic acid are about trebled (see Table I).

The Arrhenius parameters for the various reactions are presented in Table II. Inspection of these data reveals that the energies of activation for all the systems containing *beta*-eleostearic acid are lower than those for the corresponding *alpha*-eleostearic acid systems.

The energies of activation for systems in which chloromaleic anhydride was a reactant are somewhat higher (1–2 kcal./mole) than for those systems employing maleic anhydride. It is of interest to note that differences in E of a similar magnitude were obtained with these same dienophiles when employed with anthracene and dimethylanthracene.[9] The energy of activation of the reaction of methylmaleic anhydride with *beta*-eleostearic acid appears to be equivalent to that of the analogous reaction with maleic anhydride, although the accuracy of the former value is questionable for reasons previously mentioned.

In considering the pre-exponential factor A for the various reactions, it is well to bear in mind that this factor contains an entropy term. The A factors for the *alpha*-eleostearic acid systems are definitely higher than those for the corresponding *beta*-eleostearic acid systems. This indicates that there are more successful collisions between activated molecules in systems containing *alpha*-eleostearic acid than in systems containing *beta*-eleostearic acid.

The fundamental difference between *alpha*- and *beta*-eleostearic acids lies in the fact that the 9, 10

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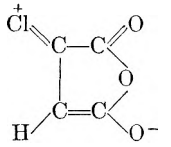
ethylenic linkage of the former has a *cis* configuration, while that of the latter has a *trans* configuration. This structural difference has a marked effect on the relative rates of reaction of the two acids. The data in Table I illustrate this point in that the presence of an additional *trans* ethylenic bond in *beta*-eleostearic acid results in higher values of k (*ca.* 4 times as great) for the reacting systems than does the presence of a corresponding *cis* bond in *alpha*-eleostearic acid. A similar observation has been made in the dimerization of eleostearic acids through a Diels-Alder mechanism.[15] The probability of the occurrence of an s-*cis* configuration in *beta*-eleostearic acid, owing to the all *trans* arrangement of its conjugated triene system, is without doubt greater than that for a similar occurrence in the *cis*, *trans*, *trans* conjugated system of *alpha*-eleostearic acid, thus enhancing the rate of adduct formation of the former. However, this explanation does not appear entirely adequate to account for the observed differences in the rates of addition of these two acids to the dienophiles. It is possible that the replacement of a *cis* ethylenic bond by a *trans* in the triene systems of the acids results in a lower "para-localization energy"[16] in the localization of two *pi* electrons in the 1, 4 positions of the remaining conjugated diene.

The dienophiles employed are closely related structurally, and the effect of substituent groups on the rate of reaction may be observed most readily by a comparison of the relative rates of reaction at one given temperature. Thus, the relative k values (in parentheses, and derived from data in Table I) are in the order maleic anhydride + *beta*-eleostearic acid (19.1), chloromaleic anhydride + *beta*-eleostearic acid (14.6), maleic anhydride + *alpha*-eleostearic acid (7.0), chloromaleic anhydride + *alpha*-eleostearic acid (2.6), methylmaleic anhydride + *beta*-eleostearic acid (1.0). Introduction of either chlorine or a methyl group into maleic anhydride reduces dienophilic activity. This type of phenomenon has been attributed, in part, to space restrictions imposed by the substituent groups 6, 16, 17.[7,17,18] However, inspection of scale models shows that the facile approach of the substituted maleic anhydrides to the eleostearic acids is not less favored than that of maleic anhydride itself. Moreover, the steric requirements of the methyl group and chlorine are approximately the same, hence it does not seem reasonable to account for the lower activity of methylmaleic anhydride on a steric basis. The influence of the methyl group on the reaction rate is that which would be expected from group inductive effects. On the other hand, it would be expected that the effect of substitution of a chlorine atom into maleic anhydride would result in an enhancement of its dienophilic activity over that of maleic anhydride. The diminished activity of chloromaleic anhydride has been attributed to a contribution of a resonance form, thus reducing the electrophilic nature of the dienophile.[9] Further support for this viewpoint is



to be found in our observation (unpublished data) that dichloromaleic anhydride is practically inactive as a dienophile when employed with the eleostearic acids. It would be expected that dichloromaleic anhydride would be more highly resonance-stabilized and consequently less active as a dienophile than the mono-chloro compound.

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Physical Properties of the Aminoazobenzene Dyes. VIII. Absorption Spectra in Acid Solution[1]

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The absorption spectra in acid solution of approximately eighty azo dyes and, in particular, the long wave-length band of the monocationic salts has been investigated. In 4-substituted azobenzene derivatives the λ_{max} of the band associated with the cationic resonance structure, $C_6H_5—N^+H=N—C_6H_4—X \longleftrightarrow C_6H_5—NH—N=C_6H_4=X^+$, shifts to the red in the order: $H < OH < NH_2 < NHMe < NHEt < NMe_2 < SMe < NHC_6H_5$.

In 4-dimethylaminoazobenzene, DAB, there is a gradual shift toward the red with the substitution in the 4′-position of the following electron-donor groups: $H < Me < C_6H_5 = NHAc = OMe = N=N—C_6H_5 < SMe < NH_2 < NMe_2$. This red shift is believed to be due to the greater importance of structures involving electronic oscillation from one end of the molecule to the other. As there is a definite red shift for the monocationic salts of 2′- and 4′-alkoxy and amino derivatives of DAB and none for 3′-derivatives, as compared to DAB, the red shift must be due to an extraconjugative effect. The spectral red shift in a homologous series of monocationic salts of dyes such as 4-hydroxyazobenzene, 4-phenylazo-1-naphthol and 9-phenylazo-10-anthrol is postulated to be due to the increase in stability of the *p*-quinonic excited state structures and a consequent decrease in the change of energy involved in the transition of the molecule from the ground to the excited state on the absorption of light energy. The C_ϵ/A_ϵ ratios of some of the dyes were also discussed.

The presence and the relative proportion of the monocationic tautomers of the 4-aminoazobenzene dyes in acid solution has been investigated.[3-6] Many of these azo dyes have been shown to cause cancer in the rat.[7] In this paper a study is presented of the effect of various substituents on the long-wave-length band stemming from the cationic resonance structure of the C tautomer, I. In an organic compound which is capable of zwitterionic resonance, addition of a proton to the positive resonance terminal will usually cause a violet shift (toward the ultraviolet) of the long wave length band; addition of the proton to the negative resonance terminal will usually cause a red shift (toward the infrared). For example, in the aminoazobenzene dyes where an amino group is the positive resonance terminal, addition of a proton to this group shortens the chain of conjugation and causes a strong violet shift in the long-wave-length band. This new band is called an ammonium, or A, band.[5] Addition of a proton to the negative resonance terminal, *e.g.*, the β-azo nitrogen, causes a red shift. The new long-wave-length band has been called the cationic resonance, or C, band.[5] In a previous paper[8] it was shown that the fairly intense long-wave-length band of the azo dyes in neutral solution stems from a zwitterionic resonance structure. Increasing the electron-donor strength at the positive end of the molecule and/or increasing the electron-acceptor strength at the negative end of the molecule was found to cause a red shift in the spectrum. As this type of structure involves

I

the expenditure of energy in the separation of charge, the addition of a proton to the negative resonance terminal would form a lower energy cationic resonance structure which would absorb at longer wave length.

The C band of 2′-, 3′- and 4′- nitro and acetyl derivatives of 4-dialkylaminoazobenzenes absorb at approximately 509 mμ. As 4-dimethylaminoazobenzene has its comparable band at 516 mμ, the effect of the electronegative groups on the C band is practically nil. In the simple 4-substituted azobenzene derivatives the wave-length maximum of the C band shifts to the red in the order: $H < OH < NH_2 < NHMe < NHEt < NMe_2 < SMe < NHC_6H_5$, Table I. Usually the bathochromic effect of a methylthio group is stronger than that of the hydroxyl group and weaker than that of the amino group, although it must be emphasized that in the present case, the spectra of azobenzene and its 4-hydroxy and 4-methylthio derivatives were determined in strongly acid solution while the amino compounds were determined in weakly acid solution. The absorption at a longer wave length of the 4-phenylaminoazobenzenes as compared to the analogous dimethylamino dyes is probably due to the following type of extraconjugation:

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

(2) Present address: Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio.

(3) A. Hantzsch and A. Burawoy, *Ber.*, **63**, 1760 (1930).

(4) G. Badger, R. Buttery, and G. Lewis, *J. Chem. Soc.*, 1954, 1888.

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

(6) G. Cilento, J. Miller, and E. Miller, *J. Am. Chem. Soc.*, **78**, 1718 (1956).

(7) J. Miller and E. Miller, *Advances in Cancer Research*, Academic Press, Inc., New York, N. Y., 1953, Vol. I, p. 339.

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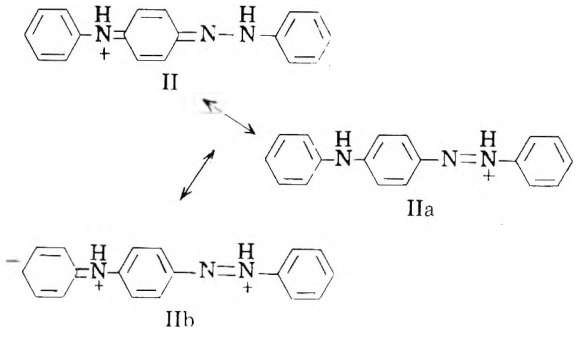


II

IIa

IIb

TABLE I

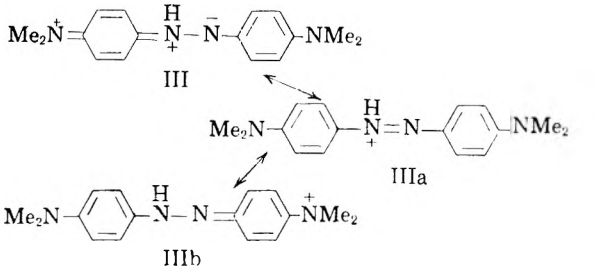
LONG WAVE-LENGTH BAND OF THE MONOCATIONIC SALTS OF 4-SUBSTITUTED AND 4,4′-DISUBSTITUTED AZOBENZENE DYES[a]

4-	4′-	λ_{max}	4-	4′-	λ_{max}
H	H	430[b]	NHC_6H_5	SCN	540
OH	H	476	NMe_2	C_6H_5	544
NH_2	H	500	NMe_2	NHAc	545
NHMe	H	505	NMe_2	OMe	548
NHEt	H	514	NMe_2	$N{=}NC_6H_5$	548
NMe_2	H	516	NMe_2	SMe	559
NMe_2	SCN	516	SMe	SMe	588[c]
NMe_2	Me	531	NHC_6H_5	SMe	590
SMe	H	532[c]	NMe_2	NH_2	610[d]
NHC_6H_5	H	540[e]	NMe_2	NMe_2	664[d]

[a] In 50% alcoholic 1*N* HCl. [b] In concentrated sulfuric acid.[10] [c] In a solution containing 25 ml. of 95% ethanol diluted to 100 ml. with concentrated sulfuric acid. [d] In glacial acetic acid. [e] In 50% alcoholic 6.8*N* sulfuric acid.[4]

This same type of extraconjugative effect is found in many types of compounds, *e.g.* R-N⁺H=CH-(CH=CH)$_2$-NHR,[9] where R = Et, λ_{max} 400 and R = C_6H_5, λ_{max} 480 mμ. In any cationic resonance structure there are two positive resonance terminals separated by a chain of conjugated atoms. In the monocationic salts of the 4-aminoazobenzenes the two limiting resonance structures involve a positive charge on the amino nitrogen, *e.g.* II, and a positive charge on the β-azonium nitrogen, *e.g.* IIa. By extraconjugation is meant any additional conjugation which essentially lengthens the chain of conjugated atoms, *e.g.* IIb.

Another type of extraconjugative effect is shown by 4-aminoazobenzenes substituted in the 2′- and 4′-positions by electron donor groups. For example, in 4-dimethylaminoazobenzene there is a gradual shift toward the red with the substitution in the 4′-position of the following electron donor groups: H < Me < C_6H_5 = NHAc = OMe = $N{=}NC_6H_5$ < SMe < NH_2 < NMe_2, Table I. In 4,4′-bis-dimethylaminoazobenzene the extraconjugative resonance shown in III wherein the positive charge resonates from one amino group to the other apparently causes the strong red shift in the spectrum of the monocation of the compound. A similar type of bathochromic effect is postulated for 4-aminoazobenzene dyes containing 2′- and 4′-electron donor substituents.



III

IIIa

IIIb

There is a definite red shift for the 2′- and 4′-alkoxy and amino derivatives of DAB and none for the 3′- derivatives as compared to DAB, Table II. This indicates that the red shift must be due to an extraconjugative effect. The fused benzene ring in both 4′-dimethylaminophenylazonaphthalenes shows an extraconjugative effect equivalent to that of a 2′- or 4′- methoxy group.

2-Methoxy-, 2-methylthio-, 4-methoxy- and 4-methylthio-azobenzene exhibit a very strong red shift in acid solution, Table II. On the other hand the 3-methoxy and 3-methylthio derivatives, like azobenzene, give only a yellow color in strong acid solution. In all cases the proton has added to an azo nitrogen causing the formation of a cationic resonance system. In the 2- and 4- substituted derivatives the positive charge can resonate between the β-azonium nitrogen and the methoxy or methylthio hetero atoms. In the 3-substituted derivatives no such resonance can take place. Consequently the color and the spectra of these latter compounds closely resemble the color and spectra of azobenzene in the same solvent. The spectra of the much more basic 2- and 3-aminoazobenzenes in acid solution resemble that of azobenzene showing that the proton has gone to the amino nitrogen, Table II.

Points of resemblance have been found between the tautomerism of 4-hydroxyazobenzene derivatives and higher homologues and the tautomerism of the monocationic salts of the 4-aminoazobenzenes.[14] In this respect in alcohol solution 4-hydroxyazobenzene exists only as the azo dye, 4-phenylazo-1-naphthol exists as a mixture of azo and phenylhydrazone tautomers while '9-phenylazo-10-anthrol' exists wholly as the phenylhydrazone. These results parallel the reduction potentials[15,16] in alcohol of *p*-benzoquinone, 0.71 v.; α-naphthoquinone, 0.49 v.; 1,4-anthraquinone, 0.40 v.; and 9,10-anthraquinone, 0.15 v. These results mean that

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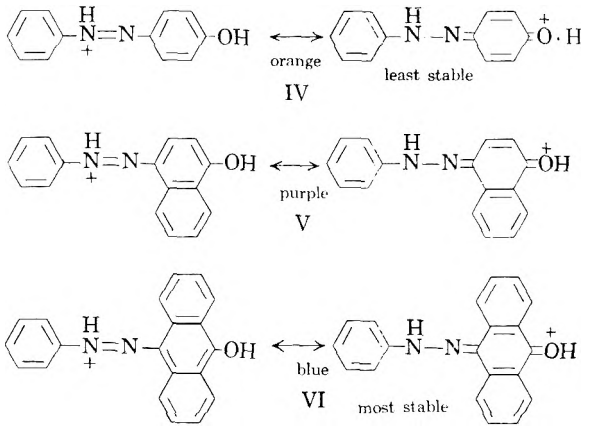
TABLE II

VISIBLE ABSORPTION SPECTRAL DATA OF MISCELLANEOUS AZO DYES

Compound	Color[a]	λ_{max}, mμ	Solvent	Compound	Color	λ_{max}, mμ	Solvent
2-Methoxy AB[b]	O	474	S[c]	4′-Methoxy DAB	V	548	[g]
3-Methoxy AB	Y	—	S	2′-Amino DAB	B	643	[h]
4-Methoxy AB	O	470	S	3′-Amino DAB	O	520s[i]	[h]
2-Methylthio AB[11]	G	—	S	4′-Amino DAB	B	610	[h]
3-Methylthio AB[11]	Y	—	S	4-Hydroxy AB	O	476	S
4-Methylthio AB	V	532	S	4-Phenylazo-1-naphthol	P	578	S
2-Amino AB	Pale P	570[d]	[e]	9-Phenylazo-10-anthrol	B[j]	—	S
3-Amino AB	Light Y	[d]	[e]	4-Phenylazo-1-naphthylamine[12]	V	545	[k]
4-Amino AB	R	502	[e]	4-Phenylazo-1-anthrylamine[13]	B	—	[l]
2′-Methoxy DAB	V	540	[g]	1,4′-Dimethylaminophenylazonaphthalene	V	540	[g]
3′-Ethoxy DAB	R	521	[g]	2,4′-Dimethylaminophenylazonaphthalene	V	545	[g]

[a] O = orange; Y = yellow; G = green; V = violet; P = purple; R = red; B = blue. [b] AB is azobenzene. [c] S is concentrated sulfuric acid. [d] The band for 2-amino AB at 570 mμ may be due to a slight amount of impurity or a very small amount of the C tautomer.[5] Otherwise the spectra in acid of 2- and 3-aminoazobenzene closely resemble the spectrum of azobenzene. [e] In 50% alcoholic 6*N* hydrochloric acid. [f] DAB is 4-dimethylaminoazobenzene. [g] In 50% alcoholic 1.2*N* hydrochloric acid. [h] In 95% acetic acid. [i] s = shoulder. [j] Unstable color. [k] In alcoholic 0.1*N* hydrochloric acid. [l] In "acid solution."[13]

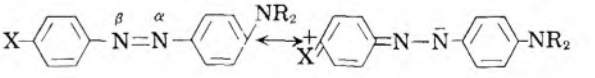
p-quinone structures increase in stability in the following order: *p*-benzoquinone < α-naphthoquinone < 1,4-anthraquinone < 9,10-anthraquinone. A somewhat similar explanation can be given for the spectral red shift in the two series; 4-hydroxyazobenzene, IV < 4-phenylazo-1-naphthol, V < 9-phenylazo-10-anthrol, VI and 4-aminoazobenzene < 4-phenylazo-1-naphthylamine < 4-phenylazo-1-anthrylamine, Table II. In these compounds an increase in the stability of the *p*-quinonic excited state structure parallels the increasing red shift, *e.g.*



A shift toward longer wave length would naturally result from any decrease in the change in energy involved in the transition of a molecule from the ground to the excited state on the absorption of light energy.

An investigation of the absorption spectra of azobenzene dyes containing a 4-alkylthio or a 4-phenylamino substituent in acid solution indicates the probably complete predominance of the C tautomer, Table III. The weak band at approximately 350–370 mμ in the acid spectra of 4-alkylthioazobenzenes has, as yet, not been satisfactorily diagnosed.

As the electron-donor strength of a group in the 4′-position of a 4-dialkylaminoazobenzene increases from hydrogen to methoxy, the C_ϵ/A_ϵ ratio decreases and the C band shifts toward the visible.[5] DAB has a C_ϵ/A_ϵ ratio of 3.6 while 4′-methoxyDAB has a C_ϵ/A_ϵ ratio of 1.0 in 50% alcoholic 1.2 N hydrochloric acid. The decrease in the C_ϵ/A_ϵ ratio is believed to be due to a decrease in the electron density at the β-nitrogen because of the following type of competitive resonance

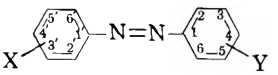


In 4′-methylthioDAB, C_ϵ/A_ϵ 2.0, an additional factor is probably present. This is the presence of the B tautomer involving proton addition to the α-azo nitrogen. The C and B tautomers would both be expected to absorb near 560 mμ. In the 4′-amino-DAB derivatives and possibly 2′-aminoDAB four monocationic tautomers, involving proton addition to the amino and azo nitrogens, should be present. The base-strengthening effect of the 2-methyl group on the β-nitrogen is shown by the increased C_ϵ/A_ϵ ratios on addition of a 2-methyl group to 4′-methylthioDAB and 4′-amino-DAB. This is in line with previous work.[5]

The spectra of 2′-, 3′- and 4′-aminoDAB derivatives in acetic acid show the presence of a long-wave-length C band and a shorter-wave-length band which may be due to the A tautomer (involving proton addition to the primary amino group)

TABLE III

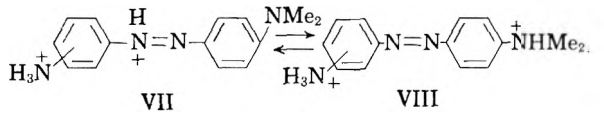
THE C_ϵ/A_ϵ RATIO OF 4-AMINO- AND 4-ALKYLTHIO- AZOBENZENE DYES



X[a]	Y[a]	λ_{max} ($\epsilon \times 10^{-3}$) C Band	A Band	Solvent[b]	C_ϵ/A_ϵ
H	4-SMe	532 (57.3)[c]	—	75% H_2SO_4	∞
H	2-Me-4-SEt	540 (42.6)[c]	—	75% H_2SO_4	∞
4′-SMe	4-SMe	588 (55.9)[d]	—	50% H_2SO_4	∞
4′-SCN	4-NHC_6H_5	540 (50.8)	—	1.2*N* HCl	∞
4′-SMe	4-NHC_6H_5	590 (54.3)[e]	—	1.2*N* HCl	∞
4′-SMe	4-NMe_2	559 (22.2)	380 (14.2)	0.06*N* HCl	1.6
		559 (27.5)	375 (13.8)	1.2*N* HCl	2.0
4′-N^+HMe_2	4-SMe	554 (57.0)[f]	—	95% H_2SO_4	—
4′-SMe	2-Me-4-NMe_2	553 (44.1)	374 (8.48)	1.2*N* HCl	5.2
2′-NH_2	4-NMe_2	643 (18.7)	472 (8.72)[g]	95% AcOH	—
2′-N^+H_3	4-NMe_2	488 (2.38)[h]	322 (28.2)	1.2*N* HCl	0.11
		503 (4.15)[i]	320 (19.8)	6*N* HCl	0.21
3′-NH_2	4-NMe_2	520s (9.40)	430 (20.0)[g]	95% AcOH	—
3′-NH_2	4-NMe_2	504 (38.1)	316 (9.28)	1.2*N* HCl	4.1
4′-NH_2	4-NMe_2	610 (21.5)	414 (14.5)[g]	95% AcOH	—
4′-N^+H_3	4-NMe_2	504 (40.4)	315 (9.20)	1.2*N* HCl	4.4
4′-NH_2	2-Me-4-NMe_2	595 (28.3)	415 (8.48)[g]	95% AcOH	—
4′-N^+H_3	2-Me-4-NMe_2	505 (50.9)	323 (4.60)	1.2*N* HCl	11.1
4′-NMe_2	4-NMe_2	664 (35.2)	430 (13.1)[g]	95% AcOH	2.7
4′-N^+HMe_2	4-NMe_2	505 (50.5)	309 (6.9)	1.2*N* HCl	7.3
4′-N^+HMe_2	4-N^+HMe_2	405 (33.2)[j]		95% H_2SO_4	

[a] X represents a 2′-, 3′-, or 4′-substituent in the prime ring, while Y represents the 4- or 2,4- substituent(s) in the other ring. [b] All solutions were 50% alcoholic except 75% sulfuric acid (75 ml. of concentrated sulfuric acid diluted to 100 ml. with 95% ethanol) and 95% sulfuric acid and acetic acids (5 ml. of 95% ethanol diluted to 100 ml. with the appropriate commercial acid). [c] Also a shoulder at 360–370 mμ. [d] Also λ_{max} 355, ϵ 1680. [e] Also λ_{max} 425, ϵ 5840 which may be due to the presence of some base. [f] Also λ_{max} 370, ϵ 3400. [g] This band could be due to the presence of base in solution. [h] A shoulder at about 440, ϵ 1630 stems from the R band of the A tautomer. [i] A shoulder present at 440, ϵ 1250 stems from the R band of the A tautomer. [j] Shoulders present at 485, ϵ 6250 and 319, ϵ 10900 stem from the two dicationic tautomers also present.

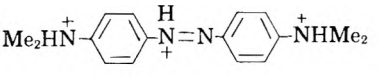
and/or the base itself. The spectra of these derivatives in 50% alcoholic 1.2 *N* hydrochloric acid show the presence of a C Band with one proton added to the 2′-, 3′- or 4′-amino nitrogen and the other added to the β azo nitrogen, VII, and an A band with a proton attached to each amino group, VIII. The



VII VIII

spectra of the 3′- and 4′-aminoDAB derivatives in 50% alcoholic 1.2 *N* hydrochloric acid are closely similar to the spectrum of DAB[5] in the same solvent. The spectrum of 2′-aminoDAB, C_ϵ/A_ϵ 0.11, in 50% alcoholic 1.2 *N* hydrochloric acid resembles that of 2′-methylDAB,[5] C_ϵ/A_ϵ 0.29, in the same solvent. Some of the factors which probably contribute to the very small proportion of C tautomer present in the acid solution are the steric hindrance and proton repulsion of the 2′-N^+H_3 group, and the decrease in the electron density of the β- azo nitrogen due to the inductive effect of the $-N^+H_3$ group.

The spectrum of 4,4′-bisdimethylaminoazobenzene in 95% sulfuric acid consists of the tricationic dye, IX, λ_{max} 405 mμ, iso-*pi*-electronic with the monocationic salt of azobenzene, λ_{max} 430 mμ. The bands at 485 and 319 mμ are due to the presence of the dicationic tautomers, Fig. 1.



IX

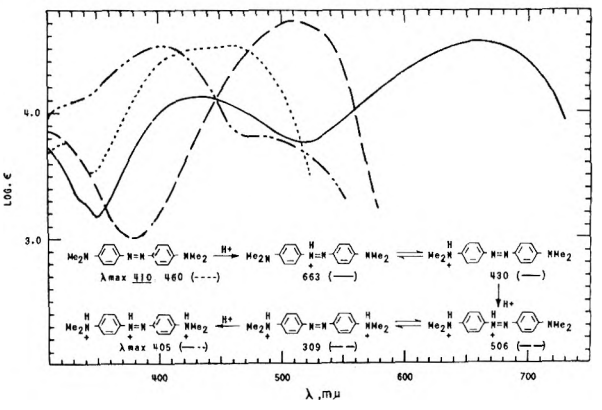
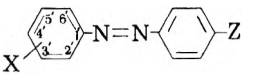


FIG. 1. VISIBLE ABSORPTION SPECTRA: 4,4′-Bisdimethylaminoazobenzene in 95% ethanol (.....); in 95% acetic acid (———); in 50% alcoholic 1.2 *N* hydrochloric acid (– – – –); in 95% sulfuric acid (— · · — · ·).

Comparison of the A bands (arising from the tautomer involving proton addition to the amino

TABLE IV

BANDS DUE TO ISO-PI-ELECTRONIC STRUCTURES



X[b]	λ_{max} ($\epsilon \times 10^{-3}$) 95% EtOH Z = H	50% EtOH[a] Z = N^+HMe_2	X	λ_{max} ($\epsilon \times 10^{-3}$) 95% EtOH Z = H	50% EtOH[a] Z = N^+HMe_2
4′-NO_2	332 (24.0)[10]	332 (7.1)	4′-OEt	349 (26.1)[17]	354 (18.8)
4′-F	323 (20.3)[17]	320 (14.4)	4′-N=N—C_6H_5	359 (44.0)	355 (17.1)
H	318 (21.3)	320 (9.8)	2′-OMe	311 (12.5)[21]	320 (8.9)
3′,4′-$(CH)_4$[c]	328 (19.0)[18]	325 (14.1)		360 (8.4)	360 (7.2)
2,2′-diMe	332 (17.4)[18]	332 (13.8)	4′-SMe	362 (23.7)[e]	375 (13.8)
4′-Me	333 (23.5)[17]	332 (12.3)	2′,3′-$(CH)_4$	372 (12.6)[18]	380 (11.9)
4′-OMe	343 (36.0)[d,20]	352 (18.3)	4′-NH_2	408 (27.5)	414 (14.5)
4′-NHAc	348 (31.6)[19]	352 (15.2)		~440s (19.0)	~447s (12.2)

[a] 1.2*N* hydrochloric acid. The acid solutions of these compounds also contain the C tautomer (see Tables I and II) which absorbs at a much longer wave length. [b] X refers to substituents in the prime ring except for X = 2,2′-diMe which, in the case of Z = H, refers to 2,2′-dimethylazobenzene and in the case of Z = N^+HMe_2 refers to the A tautomer of the monocationic salt of 2,2′-dimethyl-4-dimethylaminoazobenzene. [c] The compound, X = 3′,4′-$(CH)_4$, Z = H, is 2-phenylazonaphthalene. [d] In 50% alcoholic 1.2*N* HCl, λ_{max} 348 mμ. [e] In 50% alcoholic 1.2*N* HCl, λ_{max} 367 mμ.

nitrogen) of all types of 4-aminoazobenzene monocations with the spectra of the deaminated analogues in alcohol solution has shown that in all cases the λ_{max} are in the same region. A few examples of this phenomenon are given in Table IV.

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EXPERIMENTAL

Preparation of compounds. Most of the azo dyes were prepared by coupling the appropriate diazotized aromatic amine with the appropriate aromatic amine or phenol. Physical constants, procedures, and references have been given for many of the dyes in previous papers of the series.

Ultraviolet-visible absorption spectra. The absorption spectral data were determined with a Beckman Model DU Quartz spectrophotometer.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE LOS ALAMOS SCIENTIFIC LABORATORY]

Ultraviolet Absorption Spectra of Dinitro Compounds

HERBERT E. UNGNADE AND L. W. KISSINGER

Received April 25, 1957

Ultraviolet absorption spectra have been determined in polar and nonpolar solvents for several representative dinitro compounds. The solvent effects are compared with those in nitromethane.

Few ultraviolet absorption spectra of dinitro and polynitro compounds are recorded in the literature and most of these deal with the anions rather than with the unionized molecules.[1-3] The present study is concerned with solvent effects on dinitro compounds with terminal and nonterminal *gem*-dinitro groups and a comparable 1,2-dinitro compound.

(1) G. Kortüm, *Z. physik. Chem.*, **B43**, 271 (1939); *Z. Elektrochem.*, **47**, 55 (1941).

(2) W. R. Edwards and C. W. Tate, *Anal. Chem.*, **23**, 826 (1951).

(3) J. Reinhart, J. G. Meitner, and R. W. Van Dolah, *J. Am. Chem. Soc.*, **77**, 496 (1955).

EXPERIMENTAL[4]

The required compounds were prepared essentially by literature methods as indicated, and purified by fractional distillation or crystallization. 1,1-Dinitroethane, 1,1-dinitropropane, and 1,1-dinitropentane were obtained from the corresponding 1-halo-1-nitroparaffins by the ter Meer reaction.[5] The experimental details are given only for 1,1-dinitropropane.

1,1-Dinitroethane boiled at 45° (2 mm.); yield 30%, n_D^{25} 1.4320, $\lambda(NO_2)$ 6.34, 7.50μ.

1,1-Dinitropropane. To a flask containing 50 ml. of methanol were added simultaneously, while stirring a solution of

(4) Analyses by M. J. Naranjo.

(5) E. ter Meer, *Ann*, **181**, 1 (1876).

1-chloro-1-nitropropane (123 g., 1 mole) in 200 ml. of methanol and a solution of potassium nitrite (85 g., 1 mole) and potassium hydroxide (56 g., 1 mole) in 300 ml. of 66% aqueous methanol. The rate of addition was regulated so as to maintain gentle refluxing of the alcohol. The mixture was stirred for 1 hr. and allowed to stand overnight. The yellow potassium salt was filtered with suction, washed with methanol and ether, suspended in ether, and treated with hydrogen chloride gas while cooled with ice. The formed potassium chloride was filtered. The blue filtrate gave 68 g. (50%) of green oil which was fractionated from a 1 × 50 cm. packed column. b.p. 45° (1 mm.), yield 55.7 g., n_D^{25} 1.4320, λ(NO_2) 6.35, 7.50μ.

1-Bromo-1-nitropentane. 1-Nitropentane was prepared from 1-bromopentane by the Victor Meyer reaction[6] in 62% yield. The pure compound, b.p. 57° (9 mm.), n_D^{25} 1.4161, λ(NO_2) 6.42 7.25μ, 0.2 mole, was added to a solution of sodium hydroxide in 100 ml. of water at 0° and treated with bromine (0.2 mole) at 0°. The mixture was stirred 0.5 hr. and extracted with chloroform. The extract was washed with sodium bicarbonate, sodium bisulfite, and water, dried over calcium chloride, and fractionated. 1-Bromo-1-nitropentane boiled at 37° (0.5 mm.), n_D^{25} 1.4627, yield 21.1 g. (54%), λ(NO_2) 6.38, 7.41μ.

Anal. Calcd. for $C_5H_{10}BrNO_2$: C, 30.64; H, 5.14; N, 7.14. Found: C, 30.57; H, 4.88; N, 7.69.

1,1-Dinitropentane was obtained from 1-bromo-1-nitropentane (19.6 g., 0.1 mole) as described for the propane derivative. The pale yellow oil (8.0 g., 49%) boiled at 43–44° (0.1 mm.), n_D^{25} 1.4370, λ(NO_2) 6.34, 7.52μ.

Anal. Calcd. for $C_5H_{10}N_2O_4$: C, 37.04; H, 6.21; N, 17.29. Found: C, 36.76; H, 6.14; N, 16.73.

Ultraviolet absorption spectra. Ultraviolet absorption spectra were determined for freshly prepared 1 × 10^{-3} to 1 × 10^{-5} molar solutions in purified solvents with a Beckman Model DR spectrophotometer. Cell corrections, determined with pure solvents, were deducted from the absorbance readings. Duplicate determinations showed the molar absorptivities to be correct to within ±0.5%. The experimental results are given in Table I.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF DINITRO COMPOUNDS

1,1-Dinitro- Solvent	Ethane λmax	Ethane ε	Propane λmax	Propane ε	Pentane λmax	Pentane ε
0.1 Hydrochloric acid	275	45.5	277	48.3	277	59.8
Acetonitrile	276	45.5	277	53.5	277	58.8
Methanol	276	47.2	277	52.0	277	59.2
Ethanol	276	52.6	277	54	278	61.5
Chloroform	280	52.7	280	57.9	280	63.5
Cyclohexane	280.5	54.6	281	61	281	63.7
Dioxan	(280)[a]	115	(280)[a]	117	(280)[a]	120
Benzene	(280)[a]	190	(280)[a]	198	(280)[a]	207

	2,2-Dinitropropane λmax	2,2-Dinitropropane ε	2,3-Di-me-2,3-dinitrobutane λmax	2,3-Di-me-2,3-dinitrobutane ε
Water	276	46.5	279	62.5
0.1*N* Hydrochloric acid	276	47.5	279	61.1
Acetonitrile	278	47.7	280	61.5
Methanol	278	52	280	62.0
Ethanol	278	52	281	61.9
Chloroform	279	54	282	75.4
Cyclohexane	280	55	284	75.7
Dioxan	(280)[a]	105	282	77.8
Benzene	(280)[a]	174	280	87.5

[a] No maximum.

(6) N. Kornblum, B. Taub, and H. E. Ungnade, *J. Am. Chem. Soc.*, 76, 3209 (1954).

DISCUSSION

The ultraviolet absorption spectra of simple nitroparaffins are characterized by a low intensity transition without fine structure at around 280 mμ and a band of greater intensity below 200 mμ.[7]

Solvent effects on these absorption spectra have been examined in detail to date only for a single compound, namely nitromethane.[8] This compound gives "normal" spectra in solvents such as heptane, isoöctane, and petroleum ether; *i.e.*, "inactive" solvents; whereas the molar absorptivities are increased to nearly double in "active" solvents such as benzene. Active solvents, which include carbon tetrachloride, toluene, and dioxan, are believed to exert their specific effects either by complex formation with the solute molecules or by a physical solvent perturbation.[8]

Dinitroparaffins similarly possess a low-intensity absorption band near 280 mμ. The molar absorptivities of these bands, compared with similarly constituted mononitroparaffins, are roughly doubled, regardless of whether the nitro groups are gem or vicinal. The nitro groups therefore absorb inde-

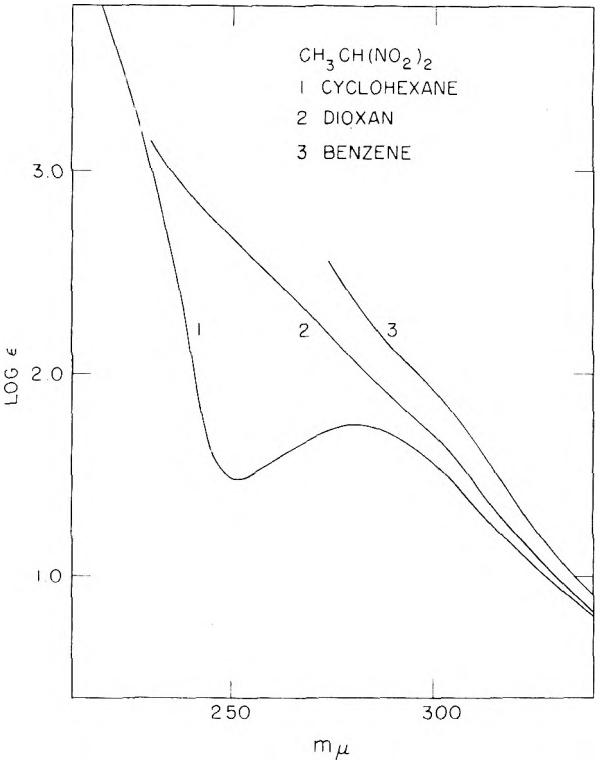

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRUM of 1,1-dinitroethane in (1) Cyclohexane, (2) Dioxan, and (3) Benzene.

(7) R. N. Haszeldine, *J. Chem. Soc.*, 2525 (1953); H. E. Ungnade and R. Smiley, *J. Org. Chem.*, **21**, 993 (1956); A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, Edward Arnold, London, 1954.

(8) N. S. Bayliss and C. J. Brackenridge, *J. Am. Chem. Soc.*, **77**, 3959 (1955).

pendently and there is little or no interaction between them.

Terminal *gem*-dinitro compounds are ionized in alkali, in water aqueous solvents, alcohols, and ordinary acetonitrile. The ions give rise to new, highly intense absorption bands near 380 mμ.[1] In carefully dried acetonitrile the new bands disappear and in dried alcohols the ionization is sufficiently small so that it may be neglected in determining the molar absorptivities of the unionized molecules at 280 mμ.

In inactive solvents the wave lengths as well as the molar absorptivities of the 280 mμ bands in dinitroparaffins decrease with an increase in polarity or dielectric constant; *e.g.*, the blue shift of the maxima (in each case) for cyclohexane → hydrochloric acid is of the order of 4 mμ and the hypochromic shift about 10 units of molar absorptivity. The transition therefore may be classified, as in the case of simple nitroparaffins, as a *blue-shift* band.[9]

Active solvents cause only a slight increase in the molar absorptivities of 2,3-dimethyl-2,3-dinitrobutane but have very pronounced effects in increasing the absorptivities of *gem*-dinitro compounds. In the latter cases the 280 mμ band is completely submerged, possibly because of a simultaneous blue shift of the band (Fig. 1). Regrettably, solvent absorption in the active solvents imposes considerable limitations on measurements in the short wave length region.

In all cases examined, the molar absorptivities of the maxima increase with molecular weight as was observed for the monofunctional compounds.

Los Alamos, N. M.

(9) H. McConnell, *J. Chem. Phys.*, **20**, 700 (1952).

[Contribution from the Research Laboratories of Syntex, S.A.]

Steroids. LXXXVI.[1] Synthesis of Monofunctional 11-Ketones

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Received March 11, 1957

Syntheses of the four monofunctional 11-keto steroids, androstan-11-one (IVa), testan-11-one (IVb), allopregnan-11-one (VIa) and pregnan-11-one (VIb) are described.

In this paper the synthesis of the four monofunctional steroidal 11-ketones—androstan-11-one (IVa), testan-11-one (IVb), allopregnan-11-one (VIa) and pregnan-11-one (VIb)—are described. The first[3] and the last[4] of these have been prepared previously in milligram quantities, whereas the other two are new. This project was undertaken at the request of Dr. Samuel Hall of the U.S. Public Health Service, Bethesda, Md.

For the preparation of androstan-11-one (IVa), we employed allopregnane-17α,21-diol-3,11,20-trione 21-acetate (Ia) as starting material, a substance readily prepared by the hydrogenation of cortisone acetate.[5] Saponification of the acetate Ia produced the diol IIa, which on side-chain degradation by the excellent Rigby-Norymberski sodium bismuthate method[6] smoothly yielded androstane-3,11,17-trione (IIIa). This route to the triketone compares very faborably as regards yield and availability of starting materials with those described previously.[3,7] Finally, reduction of IIIa by the Huang-Minlon modification of the Wolff-Kishner procedure[8] without employing specially dried hydrazine furnished a mixture of androstane and androstan-11-one (IVa), from which the latter was separated in *ca.* 30% yield by chromatography. Although it has been shown that under particular experimental conditions the Huang-Minlon reduction may result in the removal of the 11-keto group,[9] it has generally been assumed that the usual conditions[8] do not affect this function. The structure of the 11-ketone IVa was confirmed by the elemental analysis (one oxygen function) by the infrared spectrum (six-membered ketone) and by the close agreement in melting point with the sample prepared by Steiger and Reichstein[3] from androstane-3,11,17-trione (IIIa) by reduction to androstane-3β,17β-diol-11-one by means of hydro-

(1) Paper LXXV, H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957).

(2) Present address: Department of Organic Chemistry, The Weizmann Institute of Science, Rehovoth, Israel.

(3) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 817 (1937).

(4) A. Ruff and T. Reichstein, *Helv. Chim. Acta*, **34**, 70 (1951).

(5) C. Djerassi, G. Rosenkranz, J. Pataki, and S. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952); E. Wilson and M. Tishler, *J. Am. Chem. Soc.*, **74**, 1609 (1952).

(6) W. Rigby, *J. Chem. Soc.*, 1907 (1950); C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(7) T. Reichstein *et al.*, *Helv. Chim. Acta*, **19**, 402, 979 (1936); **25**, 988 (1942); H. L. Mason and E. J. Kepler, *J. Biol. Chem.*, **161**, 235 (1945); H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger, and O. Jeger, *Helv. Chim. Acta*, **35**, 295 (1952); K. Heusler, H. Heusser, and R. Anliker, *Helv. Chim. Acta*, **36**, 652 (1953).

(8) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(9) R. B. Moffett and J. H. Hunter, *J. Am. Chem. Soc.*, **73**, 1973 (1951); D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

gen and Raney nickel, followed by dehydration *via* the xanthate and hydrogenation. It is interesting to note that this route was chosen, since direct Clemmensen reduction of the triketone IIIa, followed by hydrogenation and reoxidation, had yielded androstan-17-one (in addition to much androstane)[10] instead of androstan-11-one.

For the preparation of testan-11-one (IVb), pregnane-17α,21-diol-3,11,20-trione 21-acetate (Ib), an intermediate in the commercial synthesis of cortisone,[11] was saponified and degraded by the Rigby-Norymberski procedure[6] to testane-3,11,17-trione (IIIb). As in the allo series, this route to the normal triketone is an improvement over those described previously.[12] Huang-Minlon reduction of IIIb then produced testan-11-one (IVb) in *ca.* 65% yield.

11α-Hydroxyprogesterone, readily prepared by the microbiological oxidation of progesterone,[13] served as the starting material for the synthesis of both allopregnan-11-one (VIa) and pregnan-11-one (VIb). While chromic acid oxidation[14] followed by hydrogenation[15] produced allopregnane-3,11,20-trione (Va), the reversal of these two steps, hydrogenation followed by oxidation,[16] yielded pregnane-3,11,20-trione (Vb). The two triketones on being subjected to the Huang-Minlon modification of the Wolff-Kishner reduction[5] furnished the required allopregnan-11-one (VIa) and pregnan-11-one (VIb), respectively. The last mentioned substance agreed well in properties with the compound obtained in somewhat poorer yield from pregnane-3,11,20-trione by desulfurization of the 3,20-dicycloethylenemercaptal.[4]

(10) T. Reichstein, *Helv. Chim. Acta*, **19**, 979 (1936).

(11) *Cf.* G. Rosenkranz and F. Sondheimer, *Progr. Chem. Org. Nat. Prod.*, **10**, 274 (1953); C. Djerassi, *Vitamins and Hormones*, **11**, 205 (1953).

(12) L. H. Sarett, *J. Am. Chem. Soc.*, **68**, 2478 (1946); S. Lieberman, K. Dobriner, B. R. Hill, L. F. Fieser, and C. P. Rhoads, *J. Biol. Chem.*, **172**, 263 (1948); H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 266 (1953); D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub, and L. M. Reineke, *J. Am. Chem. Soc.*, **75**, 412 (1953); M. Finkelstein, J. v. Euw, and T. Reichstein, *Helv. Chim. Acta*, **36**, 1266 (1953).

(13) For references see A. Wettstein, *Experientia*, **11**, 465 (1955).

(14) *Inter al.*, O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **17**, 1066 (1952); D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 5933 (1952).

(15) J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

(16) D. H. Peterson, A. H. Nathan, P. D. Meister, S. H. Eppstein, H. C. Murray, A. Weintraub, L. M. Reineke, and H. M. Leigh, *J. Am. Chem. Soc.*, **75**, 419 (1953); O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953).

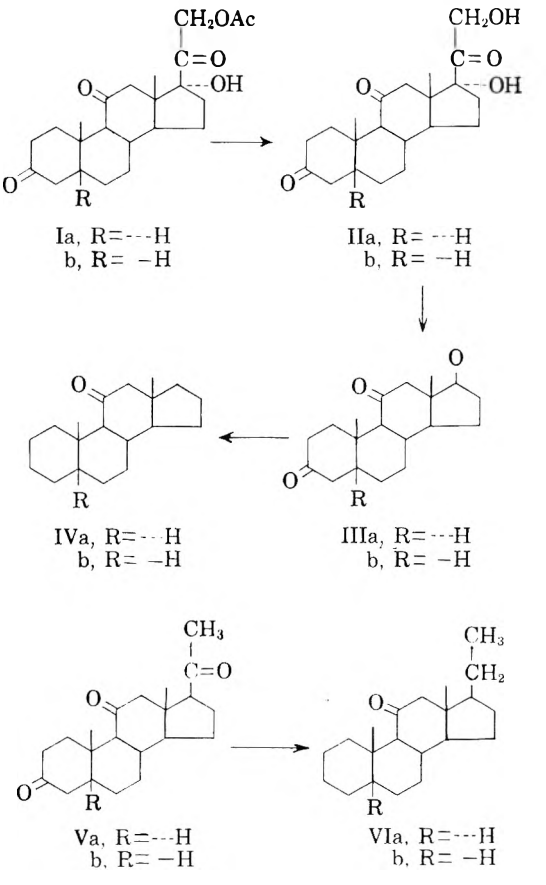
(17) Melting points are uncorrected. Rotations were determined at 20° in chloroform solution. Infrared spectra were also measured in this solvent, on a Perkin-Elmer Model 12 C single beam spectrophotometer with sodium chloride prism. Thanks are due to Miss M. T. Cárdenas for these measurements and to Mrs. A. González for the microanalyses.

EXPERIMENTAL[17]

Androstane-3,11,17-trione (IIIa). A solution of 2.2 g. of potassium hydroxide[18] in 20 cc. of water was added to a suspension of 19 g. of allopregnane-17α,21-diol-3,11,20-trione 21-acetate (Ia)[5] in 1 l. of methanol, the operation being conducted under nitrogen. The mixture was stirred at room temperature for 90 min. (complete solution occurred after *ca.* 30 min.) and 3 cc. of glacial acetic acid were then added. The solution was concentrated to 100 cc. under reduced pressure, 400 cc. of water were added gradually, the mixture was cooled in ice and the resulting precipitate was collected. This procedure furnished 14.64 g. (86%) of allopregnane-17α,21-diol-3,11,20-trione (IIa), m.p. 208–210°, $[\alpha]_D$ + 75°.

Sodium bismuthate (135 g.) was added to a stirred solution of 10 g. of the diol IIa in 340 cc. of glacial acetic acid and 340 cc. of water. The mixture was stirred for a further 30 min. at room temperature, water (1350 cc.) was added, the mixture was cooled to 0° and partially neutralized by the addition of 1400 cc. of 3*N* potassium hydroxide. The product was isolated by extraction with benzene and crystallized from acetone-ether. The resulting androstane-3,11,17-trione (IIIa) (6.23 g.; 75%) showed m.p. 178–180°, $[\alpha]_D$ + 158° (reported for a pure sample:[7] m.p. 180–181°, $[\alpha]_D$ + 155°).

Androstan-11-one (IVa). A mixture containing 6 g. of androstane-3,11,17-trione, 11 cc. of hydrazine hydrate, 7 g. of potassium hydroxide, 7 cc. of water, and 70 cc. of di-



(18) Less than one equivalent of base was sufficient, since the saponification proceeds by ester interchange (*cf.* H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 820 (1956), footnote 11).

ethylene glycol was heated under reflux for 45 min. The open flask was then heated until the temperature of the reaction mixture reached 200°, a reflux condenser was attached and refluxing was continued for a further 2 hrs. The solution was cooled, water was added, and the product was isolated with ether. The oily residue was chromatographed on alumina. Elution with hexane yielded first androstane and then androstan-11-one. The latter was purified most conveniently by pressing between filter paper; it weighed 1.62 g. (30%) and showed m.p. 45–47°, $[\alpha]_D$ + 65°. The analytical sample, obtained by high-vacuum distillation, showed m.p. 49–50°, $[\alpha]_D$ + 65°, ν_{max} 1700 cm.$^{-1}$ (reported:[3] m.p. 50–52°).

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.26; H, 10.85.

Testane-3,11,17-trione (IIIb). The saponification of 10 g. of pregnane-17α,21-diol-3,11,20-trione 21-acetate (Ib) suspended in 400 cc. of methanol was carried out by means of 1 g. of potassium hydroxide[18] in 5 cc. of water, as described above in the allo series. Addition of 1.5 cc. of glacial acetic acid, concentration to 200 cc., addition of 800 cc. of water, and ice-cooling resulted in the precipitation of 7.91 g. (88%) of pregnane-17α,21-diol-3,11,20-trione (IIb), m.p. 231–232° (reported:[19] m.p. 233–235°). This material (7.5 g.), dissolved in 300 cc. of glacial acetic acid and 300 cc. of water, was oxidized with 100 g. of sodium bismuthate as described above. The product was isolated by benzene extraction and the dried solution was evaporated and chromatographed on alumina. Elution with benzene and crystallization from ether furnished 4.73 g. (76%) of testane-3,11,17-trione (IIIb), m.p. 130–132°, $[\alpha]_D$ + 144° (reported:[12] m.p. 132–133°, 135–136°, $[\alpha]_D$ + 143°).

Testan-11-one (IVb). Testane-3,11,17-trione (4 g.) was reduced with 8 cc. of hydrazine hydrate in 50 cc. of diethylene glycol in the presence of 5 g. of potassium hydroxide and 5 cc. of water, as described previously. The product was isolated with ether and chromatographed on alumina. Elution with hexane and crystallization from ether yielded 2.41 g. (66%) of testan-11-one, m.p. 118–121°, $[\alpha]_D$ + 54°. The analytical sample showed m.p. 121–122°, $[\alpha]_D$ + 55°, ν_{max} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.91; H, 10.78.

Allopregnan-11-one (VIa). Allopregnane-3,11,20-trione (Va) (4.5 g.)[15] was reduced with 8 cc. of hydrazine hydrate in 80 cc. of diethylene glycol together with 8 g. of potassium hydroxide in 8 cc. of water, as described above for the preparation of IVa. The cooled reaction mixture was diluted with water, the precipitate was collected, dried, and chromatographed on alumina. Elution with hexane and crystallization from ether-methanol led to 2.44 g. (59%) of allopregnan-11-one with m.p. 101–104°. The analytical sample exhibited m.p. 108–109.5°, $[\alpha]_D$ + 60°, ν_{max} 1700 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.38; H, 11.33. Found: C, 83.74; H, 11.33.

Pregnan-11-one (VIb). Pregnane-3,11,20-trione (Vb) (5 g.)[16] in 100 cc. of diethylene glycol was reduced with 10 cc. of hydrazine hydrate, 10 g. of potassium hydroxide, and 10 cc. of water, as described previously. The product was extracted with ether and chromatographed on alumina. Crystallization of the fractions eluted with hexane from ether-methanol yielded 1.91 g. (42%) of pregnan-11-one, m.p. 106–109°, $[\alpha]_D$ + 52°. A further purified specimen showed m.p. 111–113°, $[\alpha]_D$ + 54°, ν_{max} 1700 cm.$^{-1}$ (reported:[4] m.p. 112–114°, $[\alpha]_D$ + 56°).

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(19) L. H. Sarett, *J. Am. Chem. Soc.*, 70, 1454 (1948).

[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XII.[1] Stereoformulas of Tetrahydro-α-santonins[2]

MASAITI YANAGITA AND HARUO OGURA

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α, β, and γ-Tetrahydro-α-santonins were reassigned the stereoformulas III, VIII, and I on the basis of chemical evidence. Zinc-alcohol hydrogenation of the 5-dehydro-α-santoninic acid (VI, R = H) gave the Δ^1-3,5-diketo acid (VII, R = H), which was converted to santonic acid (XIV) with alkali. This offered strong support for the previously suggested mechanism of santonic acid formation from α-santonin (see ref. 15).

In the paper IV of this series,[3] it was described that α-santonin was catalytically hydrogenated to a mixture of three tetrahydro compounds, α, β, and γ, which are tentatively formulated as I, II, and III, respectively.

In these formulas, the configurations at the 5-, 6-, and 11-positions are the same as those in the α-santonin structure,[3] of which the former two were well established,[4,5] and the latter one remains obscure.[6] The assignment of the configurations at the juncture of two six-membered rings was based on molecular rotation differences, the relative reactivity toward bromine, and the mode of the preparations. However, these reasons for the formulations became questionable and revision of the above formulas seemed necessary on the following grounds.

(1) As shown in the paper VII of this series,[5]

(1) Paper XI, M. Yanagita and K. Yamakawa, *J. Org. Chem.*, 22, 291 (1957).

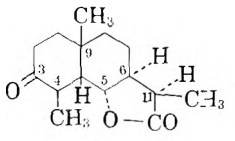
(2) This work was supported in part by the Grant in Aid for Scientific Research from the Ministry of Education of Japan.

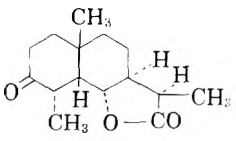
(3) M. Yanagita and A. Tahara, *J. Org. Chem.*, 20, 959 (1955).

(4) For example see R. B. Woodward and P. Yates, *Chemistry & Industry*, 1591 (1954).

(5) A. Tahara, *J. Org. Chem.*, 21, 442 (1956).

(6) Y. Abe, J. Miki, M. Sumi, and T. Toga, *Chemistry & Industry*, 1956, 953.


I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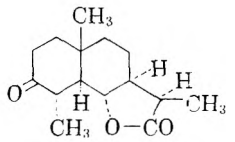
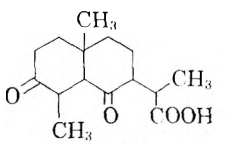
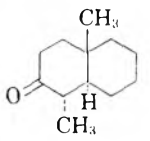
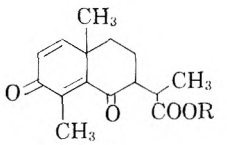

III


IVA,B


V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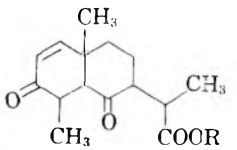
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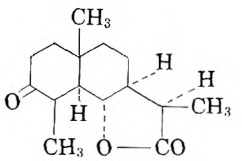
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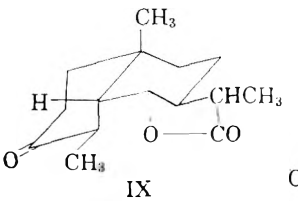
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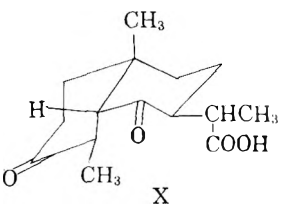
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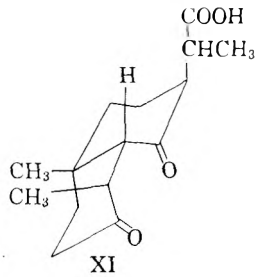
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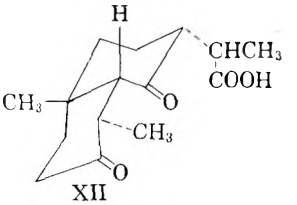
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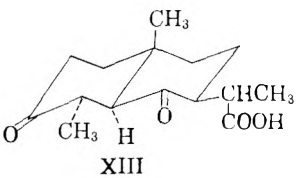
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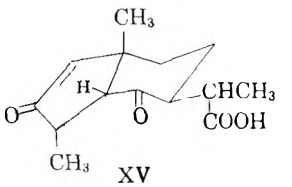
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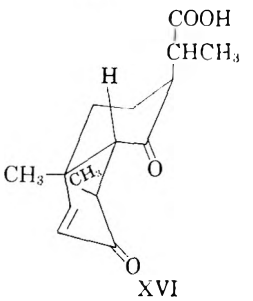
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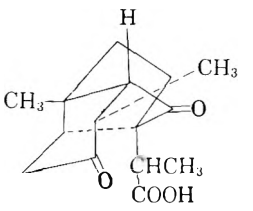
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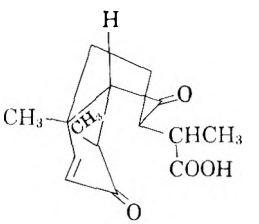
XVII

the α-3,5-diketo acid (IVA), prepared from α-tetrahydro compound (I), was proved to be thermodynamically more stable than the γ-diketo acid (IVB) from III. This relative stability of the two diketo acids is the reverse of that previously assumed.[3]

(2) In paper X[7] it was shown that catalytic hydrogenation of 4,9-dimethyl-Δ^4-3-octalone over palladium-charcoal resulted in a predominant formation of a *trans*-fused decalone (V). This unusual stereospecificity in the course of hydrogenation is difficult to reconcile with the *cis*-juncture of the six-membered rings in the α-tetrahydro compound (I), which is the chief product from α-santonin on similar hydrogenation.[3]

(3) It is known[8] that the 1,4-diketo-2,3-ene system in steroids, where the double bond terminates at the juncture of two six-membered rings, yielded the stable *trans*-fused compound predominantly on zinc–acetic acid hydrogenation, whereas with zinc-alcohol the *cis*-isomer is normally favored.

Matsumura, Iwai, and Ohki[9] reported the ready formation of the methyl ester of the α-diketo acid (IVA) by zinc–acetic acid hydrogenation of methyl 5-dehydro-α-santoninate (VI, R = CH_3), which was prepared from α-santoninic acid by chromium trioxide oxidation followed by esterification. On similar treatment, the free acid (VI, R = H) also was found to give the α-diketo acid but in a lower yield. On the other hand, the free acid (VI, R = H) was reduced with zinc-ethanol to afford a good yield of a monounsaturated acid (VII, R = H). The latter compound, in which the location of the double bond was proved by the ultraviolet absorption spectrum, λ_{max}^{MeOH} 225 mμ (log ϵ 3.84),[10] was readily hydrogenated over palladium-charcoal to the γ-3,5-diketo acid (IVB) quantitatively. Zinc-ethanol hydrogenation of the ester (VI, R = CH_3) to VII (R = CH_3) was less satisfactory than that of the free acid. Obviously, these observations are incompatible with the respective assignments of the *cis*- and *trans*-ring junctures in

(7) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(8) Budziarek and Spring, *J. Chem. Soc.*, **1953**, 956.

(9) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **75**, 1043 (1955).

(10) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, 1949, p. 190.

the α- and γ-diketo acids (IVA and IVB), derived from the tetrahydro formulas I and III, respectively.

Based on the evidences cited above, α-tetrahydrosantonin must be reassigned the formula III and the γ-isomer I, reversing to those proposed previously.[3] Consequently the β-isomer, which differs from the α-isomer only in the configuration of the methyl group at the 4-position, should be formulated as VIII in place of II.[11]

Thus, it is seen that the known correlation between the molecular rotation differences and the juncture configurations of the rings A and B in steroids,[12] which is responsible for the false formulations of I to III, cannot be applied to the tetrahydrosantonins.

It is generally accepted that a simple *cis*-3-decalone might exist in two conformations.[13] The γ-tetrahydrosantonin (I), though it is *cis*-fused, should take up only one conformation IX, since the decalone ring in this compound is fixed by fusion of the *trans*-lactone ring. The γ-3,5-diketo acid (IVB) might be described by the conformations X and XI. In these two, the former possesses the ring substituents at the 4- and 6-positions in equatorial conformation, while in the latter the corresponding groups are axial. It is clear that in the ring conversion equilibrium of these conformations, X is much favored. Since the γ-diketo acid (IVB) contains three labile asymmetric centers α to the keto group, a possibility must be considered that alkali treatment of this acid would give, together with the α-isomer (IVA), the alternative *cis*-isomer (XII), being formed through XI by inversion of its axial ring substituents.

Very recently, Klyne[14] discussed the stability of the cyclohexanones by making allowances for the three kinds of nonbonded interactions, *viz.* 2- and 3-alkylketone effects and the skew-butane interaction. By application of this argument to the present *cis*-diketodecalins (X and XII), the values of nonbonded energy differences for the conformations X and XII are calculated to be approximately 5.1 and 5.2 kcal. mole^{-1}, respectively. With the *trans*-isomer (IVA), the corresponding value for the conformation XIII is almost the same (5.3 kcal. mole^{-1}). These would imply that the three conformations should be of nearly equal stability. In fact, alkali isomerization of the diketo acid (IVA or IVB), as reported previously,[5] gave rise to a mixture of these isomers, in which the *trans*-isomer was predominant. No detection of the alternative isomer of IV was reported in this reaction. The failure in the conversion of X into XII seems not in accordance with Klyne's rule, but this anomaly is corrected by assigning a value <0.8 kcal. mole^{-1} to the 2-alkylketone effect, as in the case of the isomers of 9-methyl-4-decalone, which presented an exception to this rule.

In their brilliant work on elucidation of the structure of santonic acid (XIV), Woodward and his collaborators[15] suggested a possible mechanism for the formation of santonic acid from α-santonin, which proceeds through the hypothetical intermediate possessing the structure (VII, R = H). It may be expected that the compound VII which is now available will afford santonic acid with alkali under analogous conditions. This expectation was confirmed and the yield of santonic acid was comparable to that from α-santonin. For VII, which is *cis*-locked, two conformations XV and XVI, corresponding respectively to X and XI of the γ-diketo acid, would be adopted, in which the former carrying the ring substituents in equatorial position should be much more stable. Conversion of XV into XVI possibly passes through an intermediate XVII, where the ring with double bond is inverted and the other ring assumes a boat form. From the examination of molecular models, it can be seen that transformation of the Δ^1-3,5-diketo acid (VII) into santonic acid proceeds only by way of the conformation XVII, carrying the carbon atoms at the 1- and 6-positions in proximity. It is reasonable to consider that the isomerization of XVII to santonic acid (XIV) under strongly basic conditions involves a bond formation between the above two ring carbons by internal Michael condensation and subsequent inversion of the axial methyl group at the 4-position to an equatorial conformation. Woodward and Yates[4] assigned the same configuration to santonic acid, but in a different expression.

EXPERIMENTAL[16]

All melting points were uncorrected. Rotations were determined in a 0.5-dm. microtube with ethanol as the solvent.

5-Dehydro-α-santoninic acid (VI, R = H). This was prepared from α-santoninic acid with chromium trioxide–pyridine[9] (yield, 62%) or chromium trioxide–acetic acid[7] (yield, 63%) by the procedures previously reported. Recrystallization from ethyl acetate or dilute methanol gave plates, m.p. 135–136°; λ_{max}^{MeOH} 248 mμ (log ε 4.08), $[\alpha]_D^{24}$ −130.4° (c 0.77). Reported, m.p. 134–136°;[9] λ_{max}^{MeOH} 248 mμ (log ε 4.11)[7]; $[\alpha]_D^{15}$ −82.6° (c 2.1, $CHCl_3$)[9] and $[\alpha]_D^{24}$ −120° (*c* 1, EtOH).[17]

The *methyl ester* was prepared with diazomethane as reported previously.[9,17] After chromatographic separation, the petroleum ether elutions gave 76% of the crude ester, m.p. 78°, which was recrystallized from ether–petroleum ether to afford prisms, m.p. 86°; $[\alpha]_D^{24}$ −115.0° (*c* 0.40).

(11) During the later stages of this investigation C. Djerassi kindly informed us that, based on the study of rotatory dispersion curves, the configurations at the juncture of two six-membered rings in α-, β-, and γ-tetrahydrosantonins (I, II, and III) should be revised as described in this paper.

(12) Ref. 10, p. 212.

(13) A. S. Dreiding, *Chemistry & Industry*, 1954, 1419.

(14) W. Klyne, *Experientia*, 12, 119 (1956).

(15) R. B. Woodward, F. J. Brutschy, and H. F. Baer, *J. Am. Chem. Soc.*, 70, 4216 (1948).

(16) Microanalyses were by Miss C. Shibuya, and the ultraviolet measurements by Miss M. Suzuki.

(17) M. Nishikawa, K. Morita, and H. Hagiwara, *J. Pharm. Soc. Japan*, 75, 1199 (1955).

Reported, m.p. 68–69°[9] and m.p. 81°[71]; $[\alpha]_D^{15}$ −62.5° (*c* 2.8, $CHCl_3$)[9] and $[\alpha]_D^{24}$ −112.8° (*c* 1, EtOH).[17]

Zinc-acetic acid reduction of 5-dehydro-α-santoninic acid (VI, R = H). To a solution of 0.50 g. of the above 5-dehydro acid (VI, R = H) in 10 cc. of glacial acetic acid was added 0.75 g. of activated zinc dust (treated with dilute hydrochloric acid). The mixture was heated to reflux for 4 hr. After cooling, the precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The residual viscous oil was dissolved in ether, and the ether solution was washed successively with sodium chloride–saturated water, sodium bicarbonate solution, and water. Evaporation of the dried ether solution gave a neutral oil (0.04 g.), which could not be induced to crystallize even after treatment with pyridine–chromium trioxide in the cold to remove any contaminating alcohol. The bicarbonate solution was acidified and extracted with ether, and the ether solution was dried and evaporated. The residual oil (0.45 g.), which partly solidified, was dissolved in 1 cc. of pyridine, mixed with a solution of chromium trioxide (0.20 g.) in pyridine (4 cc.), and allowed to stand in a refrigerator overnight. After working up as usual, there was obtained 0.22 g. (44%) of an acidic product, which was recrystallized from dilute ethanol to give plates, m.p. 97°.[18] After drying *in vacuo* at 60°, the dehydrated material showed the m.p. 152.5°. It melted at 150.5° on admixture with the α-3,5-diketo acid, m.p. 147–148°, reported previously.[5,19]

In this reduction, use of ethanol–acetic acid in place of acetic acid alone somewhat improved the result. To a refluxing solution of 0.10 g. of the 5-dehydro acid (VII, R = H) in 5 cc. each of acetic acid and ethanol was added 1.5 g. of activated zinc dust in three portions. After the refluxing was continued for 1.5 hr., the reaction mixture was filtered and evaporated under reduced pressure, and the residual oil was extracted with benzene. Evaporation of the dried benzene solution left an oil (0.10 g.), which on treatment with petroleum ether gave 0.06 g. (60%) of a solid (IVA), m.p. 67°. Recrystallization from a mixture of 5% hydrochloric acid and methanol afforded prisms, m.p. 80°, which after drying *in vacuo* at 60° showed the m.p. and mixed m.p. 147–148°.

Zinc-ethanol reduction of 5-dehydro-α-santoninic acid (VI, R = H). To a refluxing solution of 1.0 g. of the 5-dehydro acid (VI, R = H) in 70 cc. of 99% ethanol was added 8 g. of activated zinc dust in four portions. The refluxing was continued for 10 hr. and a yellow color was developed in the early stages of the reaction, which eventually disappeared. The cooled reaction mixture was filtered, the colorless filtrate was evaporated, and a small amount of acetone was added. Filtration and evaporation of the acetone solution gave an oil (0.95 g.), which on treatment with petroleum ether afforded 0.88 g. (88%) of the Δ^1-3,5-diketo acid (VII, R = H), as a microcrystalline solid, m.p. 185°. Recrystallization from benzene by addition with petroleum ether raised the m.p. to 190–191°.

To a solution of this material (0.10 g.) in 2 cc. of acetone was added 10 cc. of 5% hydrochloric acid and the mixture was warmed on a water bath for 30 min. The acetone solution was allowed to stand in a refrigerator under spontaneous evaporation of the solvent and there was obtained 0.08 g. (80%) of plates, m.p. 173°. Recrystallization from ethanol by addition of water raised the m.p. to 178°; λ_{max}^{MeOH} 225 mμ (log ε 3.84); $[\alpha]_D^{24}$ −213.8° (*c* 0.53). It melted at 190° on admixture with the above form, m.p. 190–191°. Probably dimorphism is the cause of the different melting points of these two forms. The substance of the lower melting point was used for analysis.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.60; H, 7.81.

The two forms of this acid quantitatively formed the same *semicarbazone*, which on crystallization from ethanol gave prisms, m.p. 222° (decomp.).

Anal. Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21; N, 13.08. Found: C, 59.59; H, 7.51; N, 12.60.

A solution of 0.14 g. of the acid of the lower melting point in 30 cc. of ether was treated with the ether solution of diazomethane. When the yellow color of the diazomethane did not fade, an excess of the diazomethane was immediately decomposed with acetic acid. The ether solution was washed with sodium bicarbonate solution, dried, and evaporated, leaving a viscous oil (0.12 g.), which was chromatographed on alumina (0.8 × 12 cm.). Elution with benzene gave 0.09 g. (65%) of the *methyl ester* (VII, R = CH_3) as prisms, m.p. 88°. Recrystallization from petroleum ether raised the m.p. to 99°; λ_{max}^{MeOH} 226 mμ (log ε 4.06); $[\alpha]_D^{25}$ −188.6° (*c* 0.23). An analytical sample was dried over phosphorus pentoxide at room temperature for 5 days.

Anal. Calcd. for $C_{16}H_{22}O_4 \cdot H_2O$: C, 64.84; H, 8.16. Found: C, 64.54; H, 8.29.

The methyl ester (VI, R = CH_3) of the 5-dehydro acid was reduced with zinc-ethanol under similar conditions. A mixture of 0.05 g. of the methyl ester and 0.5 g. of zinc dust in 20 cc. of ethanol was refluxed for 3 hr. After addition of another 0.5 g. of zinc dust, the reflux was kept for 3 hr. further. Filtration of zinc and evaporation of the filtrate gave an oily residue, which was dissolved in a small amount of benzene and filtered. The benzene solution was evaporated to give a viscous oil, which could not be crystallized and was chromatographed on alumina (0.8 × 9.5 cm.). Elutions with petroleum ether–benzene gave 0.02 g. (40%) of the Δ^1-3,5-diketo acid methyl ester (VII, R = CH_3), m.p. 69°. Recrystallization from ether–petroleum ether afforded prisms, m.p. 95°, which melted at 97° on admixture with the above sample, m.p. 99°.

Catalytic hydrogenation of the Δ^1-3,5-diketo acid (VII, R = H). The above Δ^1-3,5-diketo acid (VII, R = H) (0.05 g.), m.p. 190–191°, was hydrogenated in acetone (10 cc.) over palladium-charcoal (prepared from 0.1 cc. of 1% palladium chloride solution and 0.01 g. of activated charcoal). One mole of hydrogen (4 cc.) absorbed rapidly. Removal of the catalyst and evaporation of the solvent afforded needles (0.05 g., 100%), m.p. 170°, which on recrystallization from dilute ethanol showed the m.p. 186°, undepressed on admixture with the γ-3,5-diketo acid (IVB), m.p. 186–187°.[5]

The other form, m.p. 178°, was similarly hydrogenated to the same product (IVB).

Conversion of the Δ^1-3,5-diketo acid (VII, R = H) *to santonic acid* (XIV). The above Δ^1-3,5-diketo acid (VII, R = H) was treated with alkali by the procedure previously reported for the conversion of α-santonin to santonic acid (XIV).[15] A solution of 0.10 g. of the Δ^1-diketo acid in potassium hydroxide solution (0.24 g. of KOH in 0.5 cc. of water) was heated to reflux for 1 hr. The solution was acidified and extracted with ether and the dried ether solution was evaporated to leave 0.07 g. (70%) of white crystals, m.p. 163°. Recrystallization from ethanol raised the m.p. to 170°; $[\alpha]_D^{19}$ −75.0° (*c* 0.24). It showed no depression of the melting point on admixture with santonic acid, m.p. 171°, prepared from α-santonin as reported previously.[15] Reported, m.p. 170–172° and $[\alpha]_D^{9}$ −74.1° (EtOH).[20]

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(18) It was 20° higher than the reported m.p. (76–78°),[5] the cause of which was not examined.

(19) H. Matsumura, J. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, 74, 1206 (1954).

(20) J. C. Simonsen and J. H. R. Barton, *The Terpenes*, 2nd Ed., The University Press, Cambridge, 1952, Vol. III, p. 295.

[CONTRIBUTION FROM THE OHARA INSTITUTE FOR AGRICULTURAL BIOLOGY, OKAYAMA UNIVERSITY]

Synthesis of Ring-Substituted *N*-Phenylglycines, Their Nitriles and Amides

AKIRA TAKEDA

Received August 26, 1955

Fourteen new 2,4-di-, 3,4-di- and 2,4,5-trisubstituted *N*-phenylglycines were synthesized *via* the sequence: arylamine, sodium *N*-arylaminomethanesulfonate, *N*-arylglycinonitrile, *N*-arylglycinamide and *N*-arylglycine. Preliminary biological testing of these compounds indicated that all the glycines and the amides were active as plant growth substances.

The high activities of *N*-(2,4-dichlorophenyl) glycine[1] and N-(2,4-dibromophenyl)glycine[2] as well as of N-(3,4-dichlorophenyl)glycine[3] as plant growth regulators, comparable with those of *O*-(2,4-dichlorophenyl)glycolic and α-naphthylacetic acids stimulated the attempt to prepare new

TABLE I

RING-SUBSTITUTED *N*-PHENYLGLYCINES

Substituted[a] Glycine	*p*H[b]	M.P. (Decomposition), °C.	Yield, % Method A[c]	Yield, % Method B[d]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Activity[e] in Pea Test
N-(2,4-Dichlorophenyl)-	5.2–5.4	151–152	72 (33)	87	$C_8H_7Cl_2NO_2$	6.36	6.4	1.90
Diethylamine salt		88–90			$C_{12}H_{18}Cl_2N_2O_2$	9.55	9.5	
N-(3,4-Dichlorophenyl)-	5.2–5.4	128–129	83 (25)	82 (7)	$C_8H_7Cl_2NO_2$	6.36	6.4	0.23
Diethylamine salt		137–138			$C_{12}H_{18}Cl_2N_2O_2$	9.55	9.5	
N-(3-Chloro-4-methylphenyl)-	4.2–4.4	125–126	60 (18)	86 (8)	$C_9H_{10}ClNO_2$	7.01	7.1	6.02
Diethylamine salt		120–121			$C_{13}H_{21}ClN_2O_2$	10.26	10.2	
N-(3-Methyl-4-chlorophenyl)-	4.2–4.4	115–117		69 (6)	$C_9H_{10}ClNO_2$	7.01	6.9	3.22
Diethylamine salt		134–134.5			$C_{13}H_{21}ClN_2O_2$	10.26	10.3	
N-(2-Bromo-4-methylphenyl)-	5.6–5.8	169–170	54 (66)	78 (8)	$C_9H_{10}BrNO_2$	5.74	5.7	6.30
Diethylamine salt		123–124			$C_{13}H_{21}BrN_2O_2$	8.83	8.9	
N-(2-Methyl-4-bromophenyl)-	4.8–5.0	142–145		82 (6)	$C_9H_{10}BrNO_2$	5.74	5.7	10.70
Diethylamine salt		109–111			$C_{13}H_{21}BrN_2O_2$	8.83	8.8	
N-(2-Chloro-4-methylphenyl)-	4.2–4.6	161–164	31 (71)	91	$C_9H_{10}ClNO_2$	7.01	7.2	20.20
Diethylamine salt		110–111			$C_{13}H_{21}ClN_2O_2$	10.26	10.3	
N-(2-Methyl-4-chlorophenyl)-	4.2–4.4	143–144	57 (52)	83 (5)	$C_9H_{10}ClNO_2$	7.01	7.1	7.30
Diethylamine salt		109–110			$C_{13}H_{21}ClN_2O_2$	10.26	10.2	
N-(2-Chloro-4-bromophenyl)-	5.6–5.8	156–157		90 (3)	$C_8H_7BrClNO_2$	5.29	5.4	4.20
Diethylamine salt		107–108			$C_{12}H_{18}BrClN_2O_2$	8.29	8.3	
N-(2-Bromo-4-chlorophenyl)-	5.6–5.8	163–164		87 (6)	$C_8H_7BrClNO_2$	5.29	5.4	5.02
Diethylamine salt		118–118.5			$C_{12}H_{18}BrClN_2O_2$	8.29	8.3	
N-(2,4,5-Trichlorophenyl)-	4.0–4.2	185–186	89 (54)	62 (8)	$C_8H_6Cl_3NO_2$	5.50	5.6	0.35
Diethylamine salt		174–175			$C_{12}H_{17}Cl_3N_2O_2$	8.55	8.6	
N-(2,5-Dichloro-4-methylphenyl)-	4.6–4.8	173–175		83 (4)	$C_9H_9Cl_2NO_2$	5.96	5.9	14.50
Diethylamine salt		141–143			$C_{13}H_{20}Cl_2N_2O_2$	9.11	9.2	
N-(2-Bromo-4-methyl-5-chlorophenyl)-	6.2–6.4	195–196		85 (4)	$C_9H_9BrClNO_2$	5.03	5.1	14.70
Diethylamine salt		170–174			$C_{13}H_{20}BrClN_2O_2$	7.96	8.1	
N-(3-Nitro-4-methylphenyl)-	3.8–4.2	147–149		82 (6)[f]	$C_9H_{10}N_2O_4$	13.32	13.1	4.52
Diethylamine salt		149–150			$C_{13}H_{21}N_3O_4$	14.82	14.8	
N-(3-Nitro-4-chlorophenyl)-	3.8–4.0	174.5–175		67 (17)[f]	$C_8H_7ClN_2O_4$	12.14	12.2	0.79
Diethylamine salt		128–129			$C_{12}H_{18}ClN_3O_4$	13.83	13.9	

[a] These compounds are new with the exception of *N*-(2,4-dichlorophenyl)glycine, whose melting point was recorded as 127° (ref. 6). Since the so-called *N*-(2,4-dichlorophenyl)glycine recorded in the literature, however, has been prepared from *p*-chloronitrobenzene *via* dichloronitrobenzene and dichloroaniline, it is suspected to be *N*-(3,4-dichlorophenyl)glycine. Starting from appropriate dichloroanilines, *N*-(3,4-dichlorophenyl)glycine melting at 128–129° (decomposition) and *N*-(2,4-dichlorophenyl)glycine melting at 151–152° (decomposition) have now been prepared and the surmise mentioned above has been proved correct. Since writing this paper, Dr. Henri Pachéco has kindly sent me his thesis (University of Lyon, 1952) describing the preparation of *N*-(2-methyl-4-bromophenyl)glycine by the method of Schwalbe *et al.*, but there the melting point of this new compound could not be found. [b] Approximate values of *p*H at which glycines were precipitated. They were observed colorimetrically with solutions of methyl red, bromocresol green and bromophenol blue. Enough dilute hydrochloric acid (1:1) was added to bring *p*H of the solution to values lower than these figures by 0.4–0.6. [c] Yields based on the consumed anilines. Parenthesized figures indicate their recoveries. [d] Yields based on the used nitriles. Parenthesized figures are those of accompanying amides. [e] Diethylamine salts of the acids were employed for the experiment. Figures indicate the threshold minimum concentrations to exhibit activity, mg./l. [f] A 2% aqueous solution of sodium hydroxide was used for saponification.

TABLE II

SODIUM *N*-PHENYLAMINOMETHANESULFONATES[a]

Substituted[b] Aminomethanesulfonate	Reaction Time, Min.	Yield,[c,d] %	Formula	Nitrogen, %[e] Calcd.	Found
N-(2,4-Dichlorophenyl)-	120	87[d] (23)	$C_7H_6Cl_2NNaO_3S$	5.03	5.0
N-(3,4-Dichlorophenyl)-	25	94 (0)	$C_7H_6Cl_2NNaO_3S$	5.03	4.8
N-(3-Chloro-4-methylphenyl)-	25	91 (1)	$C_8H_9ClNNaO_3S$	5.43	5.3
N-(3-Methyl-4-chlorophenyl)-	25	90 (0)	$C_8H_9ClNNaO_3S$	5.43	5.3
N-(2-Bromo-4-methylphenyl)-	60	88[d] (7)	$C_8H_9BrNNaO_3S$	4.63	4.4
N-(2-Methyl-4-bromophenyl)-	40	99.5 (0)	$C_8H_9BrNNaO_3S$	4.63	4.5
N-(2-Chloro-4-methylphenyl)-	120	84[d] (8)	$C_8H_9ClNNaO_3S$	5.43	5.2
N-(2-Methyl-4-chlorophenyl)-	120	90[d] (16)	$C_8H_9ClNNaO_3S$	5.43	5.1
N-(2-Chloro-4-bromophenyl)-	120	86[d] (44)	$C_7H_6BrClNNaO_3S$	4.34	4.2
N-(2-Bromo-4-chlorophenyl)-	120	69[d] (51)	$C_7H_6BrClNNaO_3S$	4.34	4.1
N-(2,4,5-Trichlorophenyl)-	180[f]	38[d] (84)	$C_7H_5Cl_3NNaO_3S$	4.48	4.6
N-(2,5-Dichloro-4-methylphenyl)-	180[f]	42[d] (71)	$C_8H_8Cl_2NNaO_3S$	4.79	4.6
N(-2-Bromo-4-methyl-5-chlorophenyl)-	180[f]	82[d] (83)	$C_8H_8BrClNNaO_3S$	4.16	3.9
N-(3-Nitro-4-methylphenyl)-	20	84 (0)	$C_8H_9N_2NaO_5S$	10.44	10.2
N-(3-Nitro-4-chlorophenyl)-	20	87 (0)	$C_7H_6ClN_2NaO_5S$	9.70	9.6

[a] In repeating the *N*-sulfomethylation of monochloro-, mononitro- and monomethylanilines it was experienced that the reaction occurred readily and resulted in almost the theoretical yield except in cases of *o*-nitroaniline and *o*-chloroaniline where 75% and 4%, respectively, of the starting materials were recovered. Sulfomethylation of 2-nitro-4-chloroaniline, 2,4-dichloro-6-bromoaniline, 2,4,6-trichloroaniline, 2-methyl-4,6-dichloroaniline was unsuccessful even with a prolonged heating. [b] These substances appear as glossy white scales which do not melt below 300°. All the compounds listed here are new. The biological tests were all negative. [c] Yield based on the consumed amine. The figures in parentheses indicate the recovery of unchanged amines (%) which had been collected by steam-distillation. [d] Formaldehyde-sodium bisulfite solution was used in great excess (1:2) for the preparation of compounds. [e] Samples were dried for 24 hours at 60–70° after two recrystallizations from water and washing twice with absolute alcohol. [f] Heatings for more than 3 hr. were generally ineffective.

derivatives in the 2,4-di-, 3,4-di- and 2,4,5-trisubstituted *N*-phenylglycine series. This is of interest in order to make clear how the activities of these compounds are changed by the structure modification, since it is not as yet established definitely whether the imino as a linking group in the side chain may be as effective as the oxygen linkage of the ring-substituted *O*-phenylglycolic acids in bringing about the enhanced biological activity.[4]

Fourteen new compounds of the general types mentioned above, along with their intermediates, have been synthesized *via* two routes as formulated in Scheme I, where R_1, R_2 and R_3 are hydrogen, chlorine, bromine, nitro and/or methyl groups, respectively. The properties and yields of the glycines as well as of the intermediates are summarized in Tables I, II, III, and IV, where their responses to the Went pea test[5] are also recorded.

In general, the treatment of arylamines (I) with formaldehyde and potassium cyanide according to the method of Schwalbe *et al.*[6] (Method A) failed to afford satisfactory yields of the desired *N*-arylglycines (V), a large amount of the amine being recovered unchanged as shown in Table I. The glycines herein described were mostly prepared by way of the hydrolysis of the corresponding nitriles (III) synthesized *via* *N*-arylaminomethanesulfonates (II) according to Knoevenagel's method[7] with some modifications which enabled the higher conversion of amines, Method B.

The *N*-sulfomethylation of the amines was carried out by the action of a 3*M* solution of formaldehyde-sodium bisulfite in excess (1:1.5) instead of in an equimolar ratio. This helped to shorten the reaction time without the formation of *N*,*N*-disulfomethylated compound as a by-product. The yield of *N*-sulfomethylation calculated on the starting material, as shown in Table II, varied widely with regard to the position and number of substituents.

These results, with a certain exception, suggest that one *ortho* substituent reduces the reactivity of of the aniline markedly and a second *ortho* substituent reduces the reactivity still further. It must be noted here that the effect of a nitro group is so great that the sulfomethylation of 2-nitro-4-chloroaniline, a mono-*ortho*-substituted compound, also failed. Also Long and Burger[8] reported the failure of the attempt to prepare *N*-(2,4,6-triiodophenyl)glycine according to the method of Schwalbe *et al.*

Sodium *N*-arylaminomethanesulfonates thus pro-

(1) Veldstra and Booij, *Biochim. Biophys. Acta*, **3**, 278 (1949).
(2) Pachéco, *Chem. Abstr.*, **44**, 10993 (1950).
(3) Takeda and Senda, *Rept. Ohara Inst. Agr. Biol.*, **42**, 19 (1954).
(4) Audus, *Plant Growth Substances*, Leonard Hill Ltd., London, 1953, p. 63
(5) Went, *Proc. Kon. Akad. Wet., Amst.*, **37**, 547 (1934).
(6) Schwalbe, Schulz, and Jochheim, *Ber.*, **41**, 3792 (1908).
(7) Knoevenagel, *Ber.*, **37**, 4080 (1904).
(8) Long and Burger, *J. Am. Chem. Soc.*, **63**, 1586 (1941).

TABLE III

N-PHENYLGLYCINONITRILES

Substituted[a] Glycinonitrile	M.P., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
N-(2,4-Dichlorophenyl)-	75–78	87	$C_8H_6Cl_2N_2$	13.92	14.0
N-(3,4-Dichlorophenyl)-	101–102	95	$C_8H_6Cl_2N_2$	13.92	14.0
N-(3-Chloro-4-methylphenyl)-	62–63	91	$C_9H_9ClN_2$	15.50	15.5
N-(3-Methyl-4-chlorophenyl)-	86–87	93	$C_9H_9ClN_2$	15.50	15.6
N-(2-Bromo-4-methylphenyl)-	62–63	89	$C_9H_9BrN_2$	12.44	12.5
N-(2-Methyl-4-bromophenyl)-	104.5–105.5	89	$C_9H_9BrN_2$	12.44	12.5
N-(2-Chloro-4-methylphenyl)-	47–48	83	$C_9H_9ClN_2$	15.50	15.6
N-(2-Methyl-4-chlorophenyl)-	101–101.5	86	$C_9H_9ClN_2$	15.50	15.5
N-(2-Chloro-4-bromophenyl)-	81–82	90	$C_8H_6BrClN_2$	11.40	11.4
N-(2-Bromo-4-chlorophenyl)-	104–105	94	$C_8H_6BrClN_2$	11.40	11.4
N-(2,4,5-Trichlorophenyl)-	122–123	91	$C_8H_5Cl_3N_2$	11.89	11.9
N-(2,5-Dichloro-4-methylphenyl)-	110–112	91	$C_9H_8Cl_2N_2$	12.96	13.0
N-(2-Bromo-4-methyl-5-chlorophenyl)-	121–122	74	$C_9H_8BrClN_2$	10.79	10.8
N-(3-Nitro-4-methylphenyl)-	101–102	99	$C_9H_9N_3O_2$	21.97	21.9
N-(3-Nitro-4-chlorophenyl)-	90.5–91.5	92	$C_8H_6ClN_3O_2$	19.85	20.0

[a] All the compounds listed here are new with the exception of *N*-(2,4-dichlorophenyl)glycinonitrile. Since the contribution of this paper, the author found that this compound had been reported before by Marxer, the reported m.p. 73–75° (uncorrected), *Helv. Chim. Acta*, **37**, 166 (1954); *Chem. Abstr.*, **49**, 13938 (1955).

TABLE IV

N-PHENYLGLYCINAMIDES

Substituted[a] Glycinamide	M.P. (Decomposition) °C.	Yield,[b] %	Formula	Nitrogen, % Calcd.	Found	Activity in Pea Test
N-(2,4-Dichlorophenyl)-	141–142	27 (50)	$C_8H_8Cl_2N_2O$	12.78	12.8	1.36
N-(3,4-Dichlorophenyl)-	139–139.5	49 (37)	$C_8H_8Cl_2N_2O$	12.78	12.8	0.25
N-(3-Chloro-4-methylphenyl)-	152–153	66 (20)	$C_9H_{11}ClN_2O$	14.09	14.1	4.55
N-(3-Methyl-4-chlorophenyl)-	122–123	38 (36)	$C_9H_{11}ClN_2O$	14.09	14.0	6.40
N-(2-Bromo-4-methylphenyl)-	149.5–150.5	38 (45)	$C_9H_{11}BrN_2O$	11.52	11.6	10.80
N-(2-Methyl-4-bromophenyl)-	156–157	40 (39)	$C_9H_{11}BrN_2O$	11.52	11.5	20.20
N-(2-Chloro-4-methylphenyl)-	134–135	18 (55)[c]	$C_9H_{11}ClN_2O$	14.09	14.1	45.25
N-(2-Methyl-4-chlorophenyl)-	152.5–154	37 (48)	$C_9H_{11}ClN_2O$	14.09	14.1	3.86
N-(2-Chloro-4-bromophenyl)-	150–151	46 (45)	$C_8H_8BrClN_2O$	10.62	10.6	4.43
N-(2-Bromo-4-chlorophenyl)-	144–146	44 (51)	$C_8H_8BrClN_2O$	10.62	10.7	2.85
N-(2,4,5-Trichlorophenyl)-	152–153	47 (31)	$C_8H_7Cl_3N_2O$	11.04	11.0	0.27
N-(2,5-Dichloro-4-methylphenyl)-	156–157	55 (24)	$C_9H_{10}Cl_2N_2O$	12.01	11.9	10.10
N-(2-Bromo-4-methyl-5-chlorophenyl)-	167–168	44 (40)	$C_9H_{10}BrClN_2O$	10.09	10.3	—[d]
N-(3-Nitro-4-methylphenyl)-	143.5–144	48 (36)	$C_9H_{11}N_3O_3$	20.07	20.0	5.18
N-(3-Nitro-4-chlorophenyl)-	141–142	48 (33)	$C_8H_8ClN_3O_3$	18.29	18.4	1.05

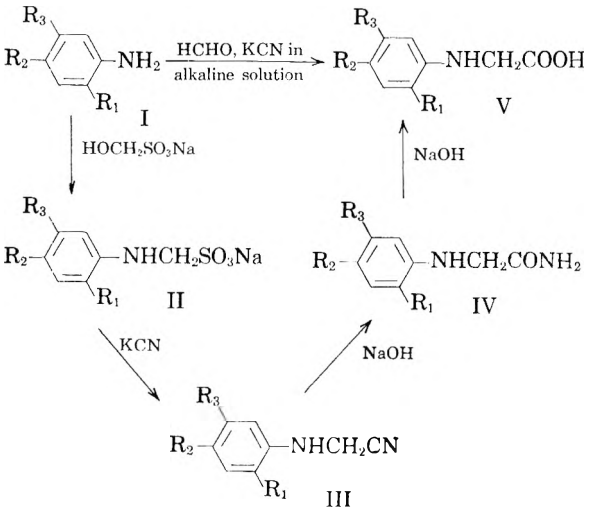
[a] All the compounds listed here are new. [b] The produced amide is partly hydrolyzed to the corresponding glycine. Figures in parentheses are the per cent of nitriles which have been converted to the glycines. [c] Hydrolysis was continued for 1 hr. [d] The biological activity of this compound could not be determined by this method because of its low solubility in water, the saturated aqueous solution containing 15.60 mg. of solute per liter exhibiting no response in the test.

duced were treated with hot potassium cyanide solution to give the corresponding nitriles in about 90% yield (Table III).

Hydrolysis of the nitriles with a 5% sodium hydroxide solution afforded the corresponding glycines together with a small quantity of amides, while saponification of the nitriles with a 1% sodium hydroxide solution gave the amides in better yields as shown in Table IV.

The diethylamine salts of the glycines were prepared. Since these salts are easily soluble both in water and in organic solvents such as ethanol or benzene, they are convenient for use in the biological tests.

The glycines and the amides exhibited reasonable responses in accordance with the nature of the substituted benzene nucleus, whereas the tests of the corresponding nitriles and sodium *N*-arylaminomethanesulfonates were negative.[1] The biological data indicate that neither of the chlorine atoms in *N*-(3,4-dichlorophenyl)glycine which possesses the highest activity in this series can be replaced by a methyl group without the loss of activity, while the chlorine atom in the *ortho* position on *N*-(2,4-dichlorophenyl)glycine can be replaced. *N*-(2,4,5-Trichlorophenyl)glycine is as active as *N*-(3,4-dichlorophenyl)glycine and the replacement of the chlorine atom in the *para*



SCHEME I

position of the former compound is also accompanied by a considerable decrease in the activity. The details of the biological assay which was carried out by Miss Nobuko Yamaji and Mr. Jiro Senda of our laboratory using the Went pea test,[5] the *Avena* cylinder test[9] and the Aduki bean curvature test[3] will be reported elsewhere.

EXPERIMENTAL

Materials. A 3*M* solution of formaldehyde-sodium bisulfite was prepared in the following way. To a solution of 375 g. of sodium bisulfite in 600 ml. of water, 243 g. (3 moles) of commercial formalin (37%) was added gradually with stirring. The mixture was then refluxed for about 10 min. and the filtrate was made up to 1000 ml. by adding water.

2-Bromo-4-methyl-5-chloroaniline. This new compound was prepared *via* the acetanilide as follows: To a stirred solution of 36.6 g. (0.2 mole) of 3-chloro-4-methylacetanilide in 100 ml. of acetic acid, 32 g. (0.2 mole) of bromine was added slowly. During the course of the addition, which required about 10 min., the temperature reached 60°. The mixture was stirred at 50–60° for an additional 40 min. and then poured slowly with efficient stirring into 2000 ml. of cold water containing 6 g. of sodium bisulfite. Needles melting at 139–149° (all m.p. are uncorrected) were separated; yield 47 g. (90% based on 3-chloro-4-methylacetanilide), m.p. 153–154° after two recrystallizations from alcohol.

Anal. Calcd. for $C_9H_9BrClNO$: N, 5.33. Found: N,[10] 5.4.

Saponification of 26 g. of this acetanilide with a 20% sodium hydroxide solution gave 19 g. of the crude amine, m.p. 79–82°. Several recrystallizations from ethyl alcohol gave a pure sample melting at 91–92°.

Anal. Calcd. for C_7H_7BrClN: N, 6.35. Found: N, 6.4.

Deamination of 10.5 g. of this amine[11] yielded 5.5 g. of colorless, non-nitrogenous material, b.p. 116–119°/40 mm. Oxidation of 1.5 g. of this substance with excess potassium permanganate in alkaline solution gave 0.55 g. of 2-chloro-5-bromobenzoic acid (m.p. 157–158°) which did not depress the melting point of an authentic sample.[12]

Sodium N-(3-chloro-4-methylphenyl)aminomethanesulfonate. Since all the compounds given in the accompanying tables were synthesized by essentially the same procedures, only some examples are presented in detail. The following experiments will serve to illustrate the manner in which they were obtained.

A mixture of 28.2 g. of 3-chloro-4-methylaniline (0.2 mole) and 100 ml. of the 3*M* solution of formaldehyde-sodium bisulfite was refluxed in a 300 ml. flask. A clear solution was obtained after about 15 min. and heating was continued for an additional 10 min. The mixture was steam-distilled in order to drive off any unreacted amine. On cooling, the white crystals which precipitated were collected on a filter, washed twice with 50 ml. portions of alcohol, and dried for 24 hr. at 60–70°. The total yield of the crude product, including a small amount obtained from the filtrate after it was concentrated to 80 ml., weighed 47 g. (91% based on the used 3-chloro-4-methylaniline). Further purification was not necessary for use in the next step. For the analysis, it was recrystallized twice from aqueous alcohol, washed twice with alcohol, and dried as above. There were obtained snow-white crystals which did not melt below 300°.

N-(3-Chloro-4-methylphenyl)glycinonitrile. A solution of 7.2 g. (0.11 mole) of potassium cyanide in 20 ml. of water was added to a hot solution of 25.7 g. (0.1 mole) of sodium *N*-(3-chloro-4-methylphenyl)aminomethanesulfonate in 50 ml. of water. The mixed solution was then refluxed for about 40 min. The crude product which separated as an oil at first and solidified on cooling, was filtered off, m.p. 54–58°, yield 16.4 g. (91%) after drying for several days at room temperature *in vacuo* and one day at 40°. Two recrystallizations from alcohol gave pure, fine needles, m.p. 62–63°.

N-(3-Chloro-4-methylphenyl)glycine. Method A. To a vigorously stirred solution of 28.2 g. (0.2 mole) of 3-chloro-4-methylaniline in 40 ml. of alcohol a solution of 13.5 g. (0.2 mole) of potassium cyanide in 35 ml. of water was added together with 1 g. of a 30% aqueous solution of potassium hydroxide. Then 16.2 g. (0.2 mole) of commercial formalin was added to the mixture. After the reaction mixture was refluxed for 6 hr. with stirring, it was steam-distilled until no oil came over. Recovery of 3-chloro-4-methylaniline amounted to 5.1 g. (18% of the used amine). The residual solution was concentrated to 50 ml. on a water bath treated with active carbon and filtered. After cooling, the filtrate was adjusted to a *p*H slightly below 4.0 with dilute hydrochloric acid (1:1) in order to complete the precipitation of the glycine. The oily product solidified on standing for several hours; the crude product, which was freed from moisture with efficient suction and by drying for 12 hr. at 60°, weighed 19.5 g. (60% based on the consumed amine), m.p. 122–123°. Recrystallization from aqueous alcohol afforded white needles melting at 125–126° with decomposition.

Method B. Purified *N*-(3-chloro-4-methylphenyl)glycinonitrile (3.6 g., 0.02 mole) was refluxed with 60 ml. of a 5% aqueous solution of sodium hydroxide for 3 hr. From the alkaline hydrolysate on cooling there separated 0.3 g. of white needles melting at 144–147°; after two recrystallizations from hot water the melting point was 152–153° with decomposition. This substance was shown to be identical with *N*-(3-chloro-4-methylphenyl)glycinamide by analysis and by mixed m.p.

Anal. Calcd. for $C_9H_{11}ClN_2O$: N, 14.09. Found: N, 14.1.

The glycine was precipitated from the filtrate in the manner described in the foregoing experiment. The crude product melted at 124–126°, yield 3.4 g. (86%). Recrystallization from aqueous alcohol gave needles melting at 125–127° (decomposition).

Anal. Calcd. for $C_9H_{10}ClNO_2$: N, 7.01. Found: N, 7.1.

(9) Smith, Wain, and Wightman, *Ann. Applied Biol.*, **39**, 20 (1952).

(10) Takeda and Senda, *Rept. Ohara Inst. Agr. Biol.*, **41**, 109 (1954).

(11) Bigelow, Johnson, and Sandborn, *Org. Syntheses*, Coll. Vol. 1, 133 (1941).

(12) Cohen and Raper, *J. Chem. Soc.*, **85**, 1267 (1904).

N-(3-Chloro-4-methylphenyl)glycinamide. A mixture of 3.6 g. (0.02 mole) of *N*-(3-chloro-4-methylphenyl)glycinonitrile and 60 ml. of a 1% aqueous solution of sodium hydroxide was heated at 94–95° for several minutes under vigorous stirring until ammonia began to be generated as detected by means of litmus paper. Heating was continued for an additional 20 min. The product separated from the cooled reaction mixture was contaminated with the unchanged nitrile. Repeated extraction with 20 ml. of hot water gave 2.6 g. (66%) of white needles melting at 142–145° (decomposition). Two recrystallizations from aqueous alcohol afforded a pure sample, m.p. 152–153° (decomposition). From the filtrate *N*-(3-chloro-4-methylphenyl)glycine was precipitated in the usual manner, yield 0.8 g. (20%).

The diethylamine salts of glycines were prepared by cautious addition of a little excess of the base to a solution of the purified acid in a small amount of alcohol. Products of high purity were obtained in one step. For analysis, they were recrystallized from a mixture of alcohol and diethylamine (1:1).

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KURASIKI, OKAYAMA PREFECTURE, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. VII.[1] Azabicyclo[3.2.0]heptane Derivatives[2]

LEONARD M. RICE[3] AND CHARLES H. GROGAN[4]

March 1, 1957

Series of *N*-alkyl and *N*-dialkylaminoalkyl-3-azabicyclo[3.2.0]heptane-2,4-dione have been prepared from the reaction of the appropriate primary amines and *cis*-1,2-cyclobutane dicarboxylic anhydride and cyclization of the resulting amic acids. The *N*-alkyl and *N*-dialkylaminoalkyl imides thus obtained were reduced to the corresponding *N*-alkyl and *N*-dialkylaminoalkyl-3-azabicyclo[3.2.0]heptanes with lithium aluminum hydride. These bases were characterized as hydrochlorides, mono- and bis-methiodides and picrates. The bis-quaternary salts derived from the 3-azabicyclo[3.2.0]heptane nucleus with a dialkylaminoalkyl side chain possessed hypotensive activity in cannulated dogs. The most favorable structure was one in which the number of methylene carbon atoms between the onium centers was 2 or 3 and the introduced quaternary group was a short chain alkyl group such as methyl or ethyl.

In a study of optimum ganglionic blockage in a series of *alpha, omega* symmetrically substituted bis-trimethylammonium compounds, Paton and Zaimis[5] have shown that for this type of compound the most desirable structure is one that contains 5 to 6 methylene carbon atoms between the positive centers. That this is not necessarily the case when the *alpha, omega* symmetrically substituted polymethylene chain bears bis-quaternary groups, part of which consists of a heterocyclic ring attached at the secondary amine ring nitrogen, has been shown by a comparison of several ring variations of the basic isoindole nucleus.[6] In the case of unsymmetrical bis-quaternary salts containing a large group at one of the quaternary centers and a trimethylammonium group on the other, it has turned out in most cases that a chain of 2 or 3 methylene carbon atoms between the nitrogen atoms gives the most favorable configuration when judged by the criteria of therapeutic index, minimum toxicity, and blood pressure lowering.

In continuation of our work in the synthesis of bis-quaternary salts containing a heterocyclic amine as one of the ammonium centers we have synthesized a series of compounds in which the azabicyclo[3.2.0] heptane nucleus is thus employed. The key starting material in our present investigations was *cis*-1,2-cyclobutane dicarboxylic anhydride. This anhydride was found to be readily accessible through the procedure of Buckman *et al.*[7] The bases prepared in these studise were obtained through the reaction of primary alkyl or dialkylaminoalkyl amines with the anhydride and proceeded through the amic acid, I, and imide, II, to the bases, III, as shown in Figure 1. The only example of any compound of this type previously re-

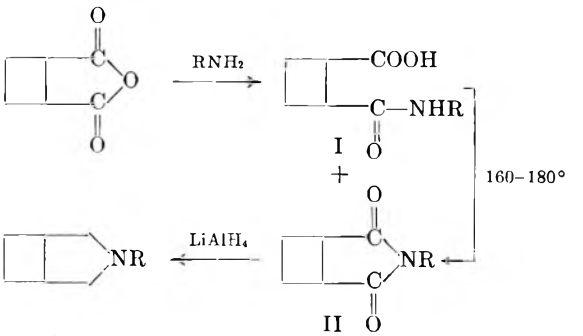

FIG. 1

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(1) Hypotensive Agents. VI. L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 22, 185 (1957).

(2) Supported by a research grant from the Geschickter Fund for Medical Research, Inc.

(3) Present address: Celanese Corp. of America, Summit, N. J.

(4) Present address: National Institutes of Health, Bethesda 14, Md.

(5) W. D. M. Paton and E. J. Zaimis *Brit. J. Pharmacol.* 4, 381 (1949).

(6) L. M. Rice C. H. Grogan and E. E. Reid *J. Am. Chem. Soc.* 77, 616 (1955).

TABLE I

N-ALKYL-3-AZABICYCLO[3.2.0]HEPTANE-2,4-DIONES

N-Substitution	Formula	B.p., °C.	Mm.	n_D^{20}	Analysis					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Methyl	$C_7H_9NO_2$	123–127	14	47.5–48.5[a]	60.42	60.63	6.52	6.75	10.06	9.80
Ethyl	$C_8H_{11}NO_2$	82–84	0.7	46–47[a]	62.73	62.62	7.24	7.23	9.15	9.11
n-Propyl	$C_9H_{13}NO_2$	72–74	0.3	31–31.5[a]	64.65	64.59	7.84	7.75	8.38	8.68
n-Butyl	$C_{10}H_{15}NO_2$	86–92	0.3	1.4878	66.27	66.32	8.34	8.07	7.73	8.02
n-Amyl	$C_{11}H_{17}NO_2$	87–92	0.3	1.4860	67.66	67.85	8.78	8.68	7.17	7.12
n-Hexyl	$C_{12}H_{19}NO_2$	102–108	0.3	1.4844	68.86	68.81	9.15	9.15	6.69	6.79
n-Heptyl	$C_{13}H_{21}NO_2$	100–105	0.1	1.4825	69.92	70.06	9.48	9.65	6.27	6.53
n-Octyl	$C_{14}H_{23}NO_2$	110–113	0.1	1.4814	70.85	70.98	9.77	9.93	5.90	6.10
n-Nonyl	$C_{15}H_{25}NO_2$	118–122	0.2	1.4805	71.67	71.50	10.03	9.89	5.57	5.51
n-Decyl	$C_{16}H_{27}NO_2$	135–139	0.3	1.4807	72.41	72.30	10.25	10.13	5.28	5.14
n-Hexadecyl	$C_{22}H_{39}NO_2$	160–165	0.04	53–54[a]	75.59	75.44	11.25	11.08	4.01	4.18

[a] Melting point.

TABLE II

N-ALKYL-3-AZABICYCLO[3.2.0]HEPTANES

N-Substituent	Formula	B.p., °C.	Mm.	n_D^{20}	Analysis					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
1. Methyl	$C_7H_{13}N$	123–133	760	1.4583	75.61	75.76	11.79	11.69	12.60	12.58
2. Butyl	$C_{10}H_{19}N$	112–115	75	1.4599	78.36	78.38	12.50	12.54	9.14	9.39
3. Hexyl	$C_{12}H_{23}N$	100–105	15	1.4672	79.49	79.70	12.78	12.74	7.73	7.88
4. Decyl	$C_{16}H_{31}N$	117–125	2	1.4648	80.94	80.94	13.16	13.10	5.90	6.15

DERIVATIVES OF ABOVE BASES

	Hydrochloride				Methiodide			
	Formula	M.p., °C.	Analysis Ionic Chloride		Formula	M.p., °C.	Analysis Ionic Iodide	
			Calcd.	Found			Calcd.	Found
1.	$C_7H_{14}ClN$	167–168	24.01	24.19	$C_8H_{16}IN$	197–198	50.14	50.20
2.	$C_{10}H_{20}ClN$	208–209	18.69	18.85	$C_{11}H_{22}IN$	189–190	42.99	43.04
3.	$C_{12}H_{24}ClN$	170–171.5	16.28	16.31	$C_{13}H_{26}IN$	101–102	39.26	39.39
4.	$C_{16}H_{32}ClN$	161–162	12.95	13.10	$C_{17}H_{34}IN$	146–147	33.45	33.63

1. Picrate, m.p. 178–179°: Calcd. for $C_{13}H_{16}N_4O_7$: N, 16.47. Found: N, 16.43.
2. Picrate, m.p. 102–103°: Calcd. for $C_{16}H_{22}N_4O_7$: N, 14.66. Found: N, 14.83.
3. Picrate, m.p. 62–63.5°: Calcd. for $C_{18}H_{26}N_4O_7$: N, 13.65. Found: N, 13.66.
4. Picrate, oil.

ported in the literature is the *N*-phenyl imide of cyclobutane dicarboxylic acid which was prepared by Perkin[8] from aniline and the anhydride.

By reaction of primary alkyl amines with *cis*-1,2-cyclobutane dicarboxylic anhydride we have prepared the corresponding imides from methyl through decyl. The reaction was carried out in all cases in the flask from which the imide was to be distilled by reacting the anhydride with a slight excess of the amine. The mixture of cyclobutane amic acid and imide obtained in all cases, from the exothermic reaction on mixing, was then heated at 160–180° for 2 hr. to complete cyclization of all amic acid to the imide. The *N*-alkyl imides thus obtained, Table I, were isolated by distillation *in vacuo* in a good state of purity and in yields greater than 80% when prepared in quantities of 25 grams or more.

The reduction of representative members of this series of imides by means of lithium aluminum hydride in ether solution proceeded smoothly to yield the corresponding *N*-alkyl-3-azabicyclo[3.2.0] heptane bases in yields of 80% or better when prepared in quantities of 25 grams or more. These bases are all typical tertiary amines and were readily characterized as methiodides, hydrochlorides, and picrates. The methyl, butyl, hexyl, and decyl members of this series, their derivatives, and pertinent characteristics are listed in Table II.

Following the study of the behavior of simple alkyl amines we next employed the dialkylaminoalkylamines and similarly obtained the imides in straightforward manner and in yields of 70% or better on runs of 25 grams or more. Some of the dialkylaminoalkyl imides thus obtained are listed

(7) E. R. Buckman A. O. Reims T. Skei, and M. J. Schlatter, *J. Am. Chem. Soc.*, **64**, 2696 (1942).

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TABLE III

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.0]HEPTANE-2,4-DIONES

N-Substituent	Formula	B.p., °C.	Mm.	n_D^{20}	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1. Dimethylaminoethyl	$C_{10}H_{15}N_2O_2$	86–94	0.08	1.4938	61.20	61.32	8.22	8.24	14.28	14.32
2. Diethylaminoethyl	$C_{12}H_{20}N_2O_2$	93–100	0.2	1.4910	64.25	64.44	8.99	8.83	12.49	12.60
3. Dimethylaminopropyl	$C_{11}H_{18}N_2O_2$	87–97	0.2	1.4942	62.83	62.75	8.63	8.71	13.32	13.22
4. Diethylaminopropyl	$C_{13}H_{22}N_2O_2$	100–103	0.1	1.4918	65.51	65.63	9.31	9.21	11.76	12.01
5. Morpholinopropyl	$C_{13}H_{20}N_2O_3$	150–155	0.3	1.5130	61.88	61.97	7.99	7.84	11.10	11.32

DERIVATIVES OF ABOVE IMIDES

Monohydrochloride: Formula	M.p., °C.	Analysis Ionic Chloride: Calcd.	Found	Monomethiodide: Formula	M.p., °C.	Analysis Ionic Iodide: Calcd.	Found
1. $C_{10}H_{17}ClN_2O_2$	204–205	15.24	15.23	$C_{11}H_{19}IN_2O_2$	259–260	37.53	37.31
2. $C_{12}H_{21}ClN_2O_2$	204–205	13.69	13.60	$C_{13}H_{23}IN_2O_2$	125–126	34.81	34.65
3. $C_{11}H_{19}ClN_2O_2$	238–239	14.37	14.51	$C_{12}H_{21}IN_2O_2$	258–259	36.03	36.10
4. $C_{13}H_{23}ClN_2O_2$	148–149	12.90	13.10	$C_{14}H_{25}IN_2O_2$	184–184.5	33.37	33.43
5. $C_{13}H_{21}ClN_2O_3$	185–186	12.28	12.31	$C_{14}H_{23}IN_2O_3$	239.5–240	32.19	32.12

TABLE IV

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.0]HEPTANE

N-Substituent	Formula	B.P., °C.	Mm.	n_D^{20}	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1. Dimethylaminoethyl	$C_{10}H_{20}N_2$	38–44	0.3	1.4766	71.37	71.64	11.98	11.89	16.65	16.80
2. Diethylaminoethyl	$C_{12}H_{24}N_2$	64–65	0.8	1.4717	73.41	73.23	12.32	12.19	14.27	14.46
3. Dimethylaminopropyl	$C_{11}H_{22}N_2$	53–55	0.3	1.4702	72.47	72.63	12.16	12.27	15.37	15.66
4. Diethylaminopropyl	$C_{13}H_{26}N_2$	75–77	0.7	1.4696	74.22	74.38	12.46	12.35	13.32	13.55
5. Morpholinopropyl	$C_{13}H_{24}N_2O$	84–86	0.2	1.4935	69.59	69.78	10.78	10.63	12.49	12.41

DERIVATIVES OF ABOVE BASES

Dihydrochloride: Formula	M.P., °C.	Analysis Ionic Chloride: Calcd.	Found	Dimethiodide: Formula	M.P., °C.	Analysis Ionic Iodide: Calcd.	Found
1. $C_{10}H_{22}Cl_2N_2$	>305 dec.	29.40	29.30	$C_{12}H_{26}I_2N_2$	219–221	56.14	55.94
2. $C_{12}H_{26}Cl_2N_2$	215–216	26.34	26.10	$C_{16}H_{30}I_2N_2$	230–231	52.86	52.79
3. $C_{11}H_{24}Cl_2N_2$	264–265	27.78	27.53	$C_{13}H_{28}I_2N_2$	242–243	54.45	54.48
4. $C_{13}H_{28}Cl_2N_2$	191–192	25.03	25.20	$C_{15}H_{32}I_2N_2$	189–190	51.36	51.25
5. $C_{13}H_{26}Cl_2N_2O$	271–272	23.85	24.00	$C_{15}H_{30}I_2N_2O$	230–231	49.94	49.45

with derivatives and characteristics in Table III. Reduction of the dialkylaminoalkyl imides with lithium aluminum hydride proceeded in a manner analogous to that of the alkyl imides and yielded the expected bases, Table IV. These bases were also stable to vacuum distillation and were conveniently isolated in this way. Yields in this case were 70% or better on runs of 25 grams or more.

Both the simple alkyl bases and dialkylaminoalkyl bases quaternized readily to form mono- and bis-quaternary salts as was the case in the isoindole series.[9] In the azabicyclooctane series[1] derived from camphoric anhydride, some of the dialkylaminoalkyl bases, particularly those with short methylene side chain between the nitrogen atoms, had to be heated for protracted periods in a bomb tube with excess methyl iodide in methanol to effect bis-quaternization.

In both the *N*-alkyl and *N*-dialkylaminoalkyl series of imides no evidence of cleavage of the cyclobutane ring was observed on reduction of the diones to the bases. All compounds prepared in these series were stable and colorless.

The compounds were screened for hypotensive activity by intravenous injection into dogs prepared for continuous kymographic or intermittent recording of blood pressure by insertion of a cannula into the carotid artery of the animal while under Nembutal anesthesia. When screened by this method the information obtained may be summarized as follows. The dialkylaminoalkyl imide hydrochloride salts were inactive. The dihydrochlorides

of the bicyclic bases were inactive. The bis-quaternary salts of the bicyclic bases were active agents in lowering blood pressure.

The acute toxicities, determined by intraperitoneal injection into rats, showed that the *N*-dimethylaminopropyl bis-methonium salt, one of the most effective in hypotensive properties, had an LD_{50} greater than 1000 mg./kg. With increase in length of the methylene side chain the acute toxicities of the methonium or ethonium salts increased. On keeping a constant side chain length and increasing the length of the dialkyl substituents the toxicity was also increased.

In this series, as in previous series,[1,9] the most active and least toxic compounds were those in which the quaternizing group was methyl or ethyl and the methylene chain between the two positive centers consisted of 2 or 3 carbon atoms.

An interesting observation of the structural relationship of this series of compounds to barbituric acid prompted us to prepare the simple imide, Figure I, II, in which R was hydrogen for testing as a respiratory stimulant and possible anti-barbiturate. These investigations are continuing.

EXPERIMENTAL

The following examples will illustrate the general synthesizing procedures employed.

N-Butyl-3-azabicyclo[3.2.0]heptane-2,4-dione. To 51.2 g. (0.40 mole) of powdered *cis*-1,2-cyclobutane dicarboxylic anhydride, 32.0 g. (10% excess) of *n*-butyl amine was added with cooling and intermittent shaking. The flask was weighed and any *n*-butyl amine lost was replaced. The reaction mixture was then heated slowly in an oil bath to 160–180° and maintained at this temperature for 2 hr. The crude product was allowed to cool and fractionated *in vacuo*. The product distilled at 86–92°/0.3 mm. and weighed 58 g. (80%), n_D^{20} 1.4878.

N-Butyl-3-azabicyclo[3.2.0]heptane. A solution of 18 g. of lithium aluminum hydride was prepared in a 2-liter, 3-necked reaction flask fitted with a dropping funnel, reflux condenser, and Hershberg stirrer. A solution of 36 g. of *n*-butyl-3-azabicyclo[3.2.0]heptane-2,4-dione in 300 ml. of anhydrous ether was added at such a rate so as to just maintain gentle reflux. After all the imide had been added stirring was continued for an additional 2 hr. With vigorous stirring water was added to decompose the mixture, at a rate just sufficient to maintain gentle reflux. An excess of 10 ml. of water was added, stirring continued for an hour, the inorganic material filtered off with rapid suction, the filter cake well pressed, and washed with 3 portions of ether. After drying over sodium sulfate, the ether was stripped off and the residue distilled *in vacuo* to yield 26 g. (85%) of the base, b.p. 112–115°/75 mm., n_D^{20} 1.4599.

The *Hydrochloride* was readily obtained in isopropyl alcohol with alcoholic HCl and precipitated with dry ether. On recrystallization from dry ether-isopropyl alcohol or methanol it melted at 208–209°. The *methiodide* was prepared in isopropyl alcohol with a slight excess of methyl iodide and precipitated with dry ether. Recrystallization from isopropyl alcohol-ether gave a pure white material with m.p. 189–190°. Addition of a saturated solution of picric acid in methanol to the base dissolved in methanol, cooling, and addition of small amounts of water yielded the *picrate* with m.p. 102–103°.

N-Dialkylaminoalkyl-3-azabicyclo[3.2.0]heptane-2,4-diones. These were obtained in a manner analogous to that employed to prepare the *N*-alkyl derivatives. The hydrochlorides and monomethiodides were obtained without difficulty as outlined under the *N*-butyl derivative.

N-Dialkylaminoalkyl-3-azabicyclo[3.2.0]heptanes. These bases were obtained by reduction of the corresponding imides with lithium aluminum hydride in a manner analogous to that outlined for the *N*-butyl base. The hydrochlorides were obtained in the usual manner. The bis-quaternary salts were obtained by refluxing the base in methanol or acetone with a slight excess of alkyl iodide. They were recrystallized from either isopropyl alcohol-ether or methanol-ether.

3-Azabicyclo[3.2.0]heptane-2,4-dione. Thirty-two g. (0.25 mole) of *cis*-1,2-cyclobutane dicarboxylic anhydride were placed in a 125 ml. flask and 45 g. of a 10% aqueous solution ammonia was slowly added with shaking. The anhydride dissolved and the resulting solution was heated to boiling on a hot plate. When all the water had boiled off the temperature was slowly raised to 240°. On cooling the crude product solidified. It was crystallized from methanol, m.p. 130–131.5°. Recrystallization from water yielded a pure product with melting point of 134.5–135°.

Anal. Calcd. for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.78; H, 5.47; N, 11.44.

WASHINGTON, D. C.

(9) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

Notes

A department for short papers of immediate interest.

Derivatives of D-Glucaric Acid[1]

EZRA L. TOTTON AND W. E. REID

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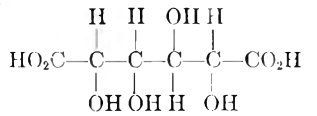
A general reaction of the glycaric acids is the formation of diamides by treatment of these acids with primary aliphatic amines.[2] These diamides are very labile to alkaline hydrolysis. In efforts to find diamides of D-glucaric acid,



less easily hydrolyzed by alkali, some aromatic diamides of D-glucaric acid have been synthesized. These derivatives were less labile to alkali and could be acetylated in good yields without hydrolysis of the amide linkage. This note describes the preparation of *p*-D-glucarotoluidide, 4′,4″-dihydroxy-D-glucaranilide, *p*-D-glucarotoluidide tetraacetate, 4′,4″-diacetoxy-D-glucaranilide tetraacetate.

EXPERIMENTAL[3]

Potassium acid glucarate. There were placed in an evaporating dish of suitable size, 800 g. of starch and 6.4 liters of nitric acid of specific gravity 1.100. The mixture was evaporated over a low flame in a fume hood to a volume of about 2 liters. The cooled solution was filtered and allowed to remain at 0° for 12 hr. Oxalic acid which crystallized out was separated by filtration, and the solution diluted with 2.4 l. of water; the solution was heated to boiling and neutralized to litmus with a saturated solution of potassium carbonate. The dark red solution was acidified to a pH of 4.5 with glacial acetic acid and evaporated to a volume of 1.5 l. The concentrated solution, which contained some crystals, was shaken with 800 ml. of 1:1 acetic acid solution. The precipitated product was collected, washed with several 200-ml. portions of 1:1 acetic acid solution, and purified by crystallization from hot water. The yield was 225 g. When sucrose was used, a yield of 34% based on sucrose was obtained. Analysis by conversion to the silver salt gave a purity of 97%.

Lactone of D-*glucaric acid.* To 460 g. (2 moles) of potassium acid D-glucarate there was added 500 ml. of distilled water containing 122 ml. of concentrated sulfuric acid. The mixture was allowed to stand until solution was complete. The solution was concentrated to a thick sirup under reduced pressure. The sirup was stirred with 4 l. of 95% alcohol, the potassium acid sulfate was separated in a Büchner funnel by filtration, and the solution concentrated as before. More potassium acid sulfate was removed by filtration. The sirup was dissolved in 500 ml. of distilled water and the solution again concentrated under reduced pressure to a sirup. The sirup was heated for 3 hr. on a boiling water bath under reduced pressure. The product was a slightly reddish sirup.

p-D-*Glucarotoluidide* (I). To 348 g. (2 moles) of D-glucaric acid lactone in 2 l. of boiling absolute alcohol in a 5-l. round bottom flask, there was added 500 g. (4.6 moles) of *p*-toluidine dissolved in 500 ml. of boiling absolute alcohol. Precipitation started immediately, and the mixture was stirred rapidly. After the addition of the *p*-toluidine, the mixture was stirred and heated to boiling until the mixture had concentrated to such a point that considerable bumping took place. The time required was 6 hr. The product was collected in a Büchner funnel and the crystals triturated with two successive 500 ml. portions of hot absolute alcohol and filtered. The product weighed 493 g., which represented a yield of 63% based on the lactone of D-glucaric acid. A sample for analysis was purified by crystallization from dioxane. Two recrystallizations gave a pure product which melted at 228°C.

Anal. Calcd. for $C_{20}H_{24}N$: C, 62.10; H, 6.20; N, 7.21. Found: C, 62.00; H, 6.40; N, 7.50.

*4′,4″-Dihydroxy-*D-*glucaranilide* (II). The procedure for the preparation of di-*p*-toluidide of D-glucaric acid was used in the preparation of this compound. The product was purified by recrystallization from hot water. The pure product melted at 290° C.

Anal. Calcd. for $C_{13}H_{20}O_8N_2$: C, 55.09; H, 5.13. Found: C, 55.26; H, 5.07.

p-D-*Glucarotoluidide tetraacetate* (III). There was placed in a 2 liter beaker 393 g. (1.01 moles) of di-*p*-toluidide of D-glucaric acid. To this was added 826 g. of pyridine and 806 g. (8 moles) of acetic anhydride. The mixture became very warm; the *p*-toluidine dissolved. The solution was allowed to remain for 20 hr. at room temperature. The solution was poured slowly into 3 l. of ice cold water with rapid stirring. After the mixture had been stirred for 6 hr., the granular precipitate was collected, dissolved in 2 l. of hot acetone, treated with Norite, filtered, and sufficient distilled water added to precipitate the product. The product weighed 446 g., a yield of 79% based on the di-*p*-toluidide of D-glucaric acid. A pure sample melted at 215° C.

Anal. Calcd. for $C_{28}H_{32}O_{10}N_2$: C, 60.42; H, 5.77; N, 5.03. Found: C, 60.68; H, 5.89; N, 5.27.

4′,4″-Diacetoxy-D-glucaranilide tetraacetate (IV). This compound was prepared from the di-*p*-hydroxyanilide of D-glucaric acid by the procedure described for the acetylation of (I). The product was purified by crystallization from alcohol. It melted at 193–4° C.

Anal. Calcd. for $C_{30}H_{32}O_{14}N_2$: C, 55.58; H, 5.00. Found: C, 55.81; H, 5.14.

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(1) This work was supported by a research grant AF33-(616)-409 from Wright Air Development Center.

(2) Dermer and King, *J. Org. Chem.*, 8, 168 (1943).

(3) (a) All melting points were corrected: They were taken on a Fisher-Johns micro-hot stage.

(b) Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Chlorosulfonylation of 7-Hydroxy-4-methyl-8-acetylcoumarin and Its Methyl Ether

J. R. MERCHANT AND R. C. SHAH

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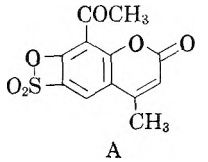
During the course of our investigations on the substitution reactions of benzopyrones, we had oc-

casion to study the chlorosulphonylation of 7-hydroxy-4-methyl-8-acetylcoumarin (I) and its methyl ether. When (I) was heated with one mole of chlorosulfonic acid at 100°, a monosulfonic acid (II) was obtained. Attempts to prove the position of the sulfonic acid group in (II) by bromination, nitration, hydrolysis, and oxidation failed to give definite products. However, the structure 7-hydroxy-4-methyl-8-acetylcoumarin-6-sulfonic acid was given to it by analogy with the sulfonation results of other 7-hydroxycoumarin derivatives.[1,2] Heating (I) with 2.5 moles of chlorosulfonic acid at 100° gave a disulfonic acid (III) and a crystalline neutral substance (IV) containing sulfur but no halogen.

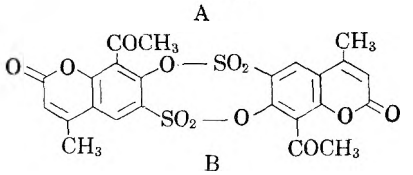
The disulfonic acid (III) was assigned the structure 7-hydroxy-4-methyl-8-acetylcoumarin-3,6-disulfonic acid. The substance (IV) did not give any coloration with alcoholic ferric chloride, whereas the original coumarin (I) gives a violet coloration. Further, the yield of (IV) was found to increase with an increase in the amount of chlorosulfonic acid used in the sulfonation. However, it could not be obtained by direct sulfonation of (II). A study of the properties of (IV) showed that it was quite stable in boiling water and could be crystallized in a pure state from benzene, alcohol, or dilute hydrochloric acid. It was nonacidic acid and did not form a sodium or a barium salt. It dissolved slowly in alkali and was also moderately soluble in sodium bicarbonate without effervescence. This solubility in weak alkalies may be attributed to the hydrolysis of the coumarin ring.

The analytical data ruled out the possibility of a sulfone structure for IV. A reference to literature showed that the other common possibility during sulfonation with chlorosulfonic acid was the formation of cyclic esters of sulfonic acids. These are usually formed in the sulfonation of phenols if there are substituents in the *o*- or *p*-positions in the original phenol.[3]

The analytical results for IV were in close agreement with those required for a cyclic ester. The presence of the ketonic group in the latter was shown by the formation of a 2,4-dinitrophenylhydrazone. The absence of a ferric chloride coloration with IV therefore indicated that the OH group in it was probably involved in an ester formation in one of the following ways:



A



B

A molecular weight determination by the Rast method favored structure B for IV. Such bimolecular compounds containing two ester linkages are termed sulfonylides[3], and accordingly IV was assigned the structure 7-hydroxy-4-methyl-8-acetylcoumarin-6-sulfonic acid sulfonylide.

Sulfonation of I at higher temperatures led to a mixture of sulfonic acids. The methyl ether of I could not be sulfonated completely with one or two moles of chlorosulfonic acid at 60°, whereas at higher temperatures or with excess of the sulfonating agent, the sulfonation was accompanied by complete demethylation.

EXPERIMENTAL[4]

7-Hydroxy-4-methyl-8-acetylcoumarin-6-sulfonic acid (II). A mixture of 2 g. of 7-hydroxy-4-methyl-8-acetylcoumarin (I)[5] and 0.6 ml. (1 mole) of chlorosulfonic acid was protected from moisture and heated on a steam bath for 3 hr. The residue obtained on pouring the reaction mixture over ice weighed 400 mg. and was found to be the unreacted coumarin (I) by a mixed melting point determination. The filtrate after concentration was saturated with sodium chloride, when the sodium salt of (II) separated. The *S* benzylthiuronium derivative prepared from it was crystallized from dilute alcohol in yellowish plates, m.p. 212–214°.

Anal. Calcd. for $C_{20}H_{20}N_2O_7S_2$: N, 6.0. Found: N, 6.4.

The barium salt of (II) was prepared from the sodium salt by the addition of a solution of barium chloride. It was washed free from chloride, crystallized from water and dried at 130°.

Anal. Calcd. for $C_{24}H_{18}BaO_{14}S_2$: Ba, 18.8. Found: Ba, 18.5.

Sulfonation of 7-hydroxy-4-methyl-8-acetylcoumarin (I) *with excess of chlorosulfonic acid.* A mixture of 2 g. of (I) and 3 ml. of chlorosulfonic acid was heated on a steam bath for 2 hr. After cooling, the reaction mixture was poured over ice, when 400 mg. of a solid IV separated. It was washed free from acids and crystallized first from benzene and then from alcohol in colorless needles, m.p. 215–217°.

Anal. Calcd. for $C_{24}H_{16}O_{12}S_2$: C, 51.4; H, 2.85, S, 11.4. Mol. Wt.: 560. Found: C, 51.0, 51.3; H, 2.8, 3.1; S, 11.1. Mol. Wt. 519.

The 2,4-dinitrophenylhydrazone of IV was crystallized from alcohol in orange needles, m.p. 254–255°.

Anal. Calcd. for: $C_{36}H_{24}N_8O_{18}S_2$: N, 12.2. Found: N, 11.8.

The filtrate in the above experiment after removal of IV and concentration was saturated with sodium chloride when the sodium salt of (III) separated. The S-benzylthiuronium derivative from it was crystallized from dilute alcohol, m.p. 216–218°.

Anal. Calcd. for: $C_{28}H_{30}N_4O_{10}S_4$: N, 7.9. Found: N, 8.3.

The barium salt obtained from the sodium salt as before was crystallized from water and dried at 140°.

Anal. Calcd. for: $C_{12}H_{16}BaO_{10}S_2$: Ba, 26.8. Found: Ba, 26.1.

The free sulfonic acid (III) prepared the barium salt after crystallization from concentrated hydrochloric acid had m.p. 212–215° (dec.).

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(1) J. R. Merchant and R. C. Shah, *J. Ind. Chem. Soc.* **34**, 35 (1957).

(2) J. R. Merchant and R. C. Shah, unpublished results.

(3) C. M. Suter, *Organic Chemistry of Sulfur*, John Wiley and Sons, Inc. New York, 1944, p. 230.

(4) All melting points are corrected.

(5) D. B. Limaye, *Ber.*, 65, 375 (1932).

In the above sulfonation, a maximum yield of 800 mg. of (IV) and a very small amount of (III) were obtained by heating 2 g. of (I) with 10 moles of chlorosulfonic acid at 100°.

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Sulfonation of Ethyl γ-Phenylbutyrate with Sulfuric Acid

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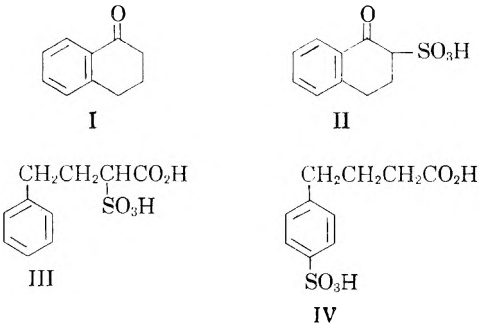
The direct sulfonation of phenylacetic acid with concentrated sulfuric acid,[1] chlorosulfonic acid,[2] and sulfur trioxide,[3] and of β-phenylpropionic acid with fuming sulfuric acid[4] all gave the corresponding ring substituted sulfophenylalkanoic acids.

Sulfonation of γ-phenylbutyric acid however failed to yield γ-(*p*-sulfophenyl)butyric acid (IV).[5,6] Instead, 50% yield of α-tetralone (I) was obtained when the sulfonation reagent was concentrated sulfuric acid,[5] and α-tetralonesulfonic acid (II) (78%) and γ-phenyl-α-sulfobutyric acid (III) (13%) were obtained when dioxane sulfur trioxide was the sulfonation agent.[6]



The present work shows that the action of excess 99% sulfuric acid on ethyl γ-phenylbutyrate at 60–65° gave predominately the ring substituted product, γ-(*p*-sulfophenyl)butyric acid (IV) isolated as its sodium salt. Small amounts of α-tetralone and acetaldehyde-sodium bisulfite adduct were the only by-products isolated.

Since addition of a solution of a simple ester (methyl benzoate) in 100% sulfuric acid to ice water did not result in hydrolysis,[7] it seems likely that the hydrolysis of the present ester took place during sulfonation, although the acid strength in the present case was only 99%. Formation of acetaldehyde can best be explained by oxidation of ethanol which became detached from the ester during sulfonation. Apparently, sulfonation of the benzene ring preceded the hydrolysis, otherwise excessive tetralone formation would ensue as in the case of γ-phenylbutyric acid. The implication is that under the experimental conditions used, ring sulfonation prevented the cyclization of γ-phenylbutyric acid.

EXPERIMENTAL[8]

Ethyl γ-phenylbutyrate. Ethyl γ-phenylbutyrate was prepared from 100 g. (0.58 mole) of γ-phenylbutyric acid[9] and absolute ethanol using the method of Hershberg and Fieser.[10] A standard work-up and distillation produced 94.5 g. (84.5%) of ethyl γ-phenylbutyrate, b.p. 80° (0.5 mm.), n_D^{29} 1.4919.

Sulfonation of ethyl γ-phenylbutyrate. To 45 g. (0.234 mole) of ethyl γ-phenylbutyrate, 236 g. of 99% sulfuric acid was slowly added with stirring. With constant agitation the mixture was heated to and maintained at 60–65° for 4 hr. The mixture was cooled to 33° and 100 ml. of water was added slowly, maintaining the temperature at below 50°. The mixture was then poured into 300 g. of ice and stirred for 1 hr. The resulting turbid mixture was extracted 4 times with 50 ml. portions of benzene, and the extracts were combined.

Identification of α-tetralone (I). The benzene extract was washed 3 times with 25 ml. portions of water and then concentrated to 14 g. by evaporation on a steam bath. The benzene concentrate was refluxed with 100 ml. of 10% sodium hydroxide for 16 hr. Acidification of the aqueous phase gave no precipitation indicating the absence of γ-phenylbutyric acid. The oil phase was dried over anhydrous sodium sulfate and distilled under diminished pressure to yield 5.3 g. (15%) of a colorless oil, b.p. 125–129° (11 mm). I was identified as its semicarbazone, m.p. 216.5–217.5°. A mixed melting point with an authentic sample of the semicarbazone of I, m.p. 217°, showed no depression.

Identification of the acetaldehyde-sodium bisulfite adduct. The mother aqueous acid solution was carefully neutralized with a 50% sodium hydroxide solution, and then evaporated to dryness yielding 353 g. of salt. The salt mixture was stirred with 2.4 l. of boiling 70% alcohol and filtered while hot. On cooling the filtrate gave 5.3 g. of a white crystalline salt which was identified as its *p*-chlorobenzylthiuronium derivative,[11] m.p. 218–219° (dec.). A mixture with the *p*-chlorobenzylthiuronium derivative of an authentic sample of acetaldehyde-sodium bisulfite adduct, m.p. 220–221° (dec.) melted at 218–219° (dec.).

Anal. Calcd. for $C_{18}H_{24}Cl_2N_4O_4S_3$:[12] C, 40.98; H, 4.59; N, 10.62; S, 18.23. Found: C, 40.20; H, 4.65; N, 10.45; S, 17.74.

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(2) Stewart, *J. Chem. Soc.*, **121**, 2555 (1922).
(3) Brust, *Rec. trav. chim.*, **47**, 153 (1928).
(4) Senderens and Aboulenc, *Compt. rend.* **186**, 1497 (1928).
(5) Krollpfeiffer and Schaefer, *Ber.*, **56**, 624 (1923).
(6) Truce and Olson, *J. Am. Chem. Soc.*, **75**, 1651 (1953).
(7) Treffers and Hammett, *J. Am. Chem. Soc.*, **59**, 1711 (1937).

(8) All melting points and boiling points are uncorrected. Elementary analyses were made by Mr. C. W. Nash and his staff, Rohm and Haas Co.
(9) Christian, *J. Am. Chem. Soc.*, **74**, 1591 (1952).
(10) Hershberg and Fieser, *Org. Syntheses*, **Coll. Vol. II**, 196 (1950).
(11) Campaigne and Suter, *J. Am. Chem. Soc.*, **64**, 3040 (1942).
(12) The requirement of two moles of p-chlorobenzylthiuronium chloride for each mole of the acetaldehyde-sodium bisulfite adduct is interesting, but not unanticipated. This means that the hydroxyl group alpha to the sulfonic acid group in the adduct is weakly acidic. The dissociation constant for a similar group in benzaldehyde-sodium bisulfite adduct is 7×10^{-10} (Bayer, Ger. Pat. **464,010** (July 26, 1928).

Identification of (IV). The salt remaining from the hot 70% alcohol extraction was allowed to stand with 2 l. of 70% alcohol at room temperature for two and one-half days. The filtrate was combined with the filtrate from the previous step. On evaporation to dryness 58.6 g. of disodium γ-(*p*-sulfophenyl) butyrate, probably contaminated with a little sodium sulfate, was obtained. It was identified as its *p*-chlorobenzylthiuronium derivative, m.p. 150–152°.

Anal. Calcd. for $C_{18}H_{21}ClN_2O_5S_2$: C, 48.59; H, 4.76; N, 6.30; S, 14.41. Found: C, 49.18; H, 4.57; N, 6.44; S, 14.25.

A 4 g. sample of disodium γ-(*p*-sulfophenyl)butyrate was oxidized with potassium permanganate according to the procedure of Campaigne and Suter.[11] The benzylthiuronium derivative of the resulting *p*-sulfobenzoic acid, m.p. 213–214° (lit. 212–214°),[6] established the position of ring substitution.

Anal. Calcd. for $C_{15}H_{16}N_2O_5S_2$: N, 7.61. Found: N, 7.78.

Continued extractions of the residual salts with 40% alcohol yielded only sodium sulfate.

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6-Amino-2-Hexenoic Acid Lactam[1]

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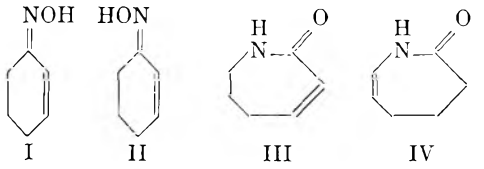
Received November 26, 1956

Although work has been reported concerning the Beckmann rearrangement of various substituted cyclohexenone oximes,[3,4] the rearrangement of 2-cyclohexenone oxime itself has not been reported. This rearrangement has been studied as a route to 6-amino-2-hexenoic acid lactam (III) which was of interest in connection with a projected synthesis of azepine.

2-Cyclohexenone[5] was converted to a mixture of stereoisomeric oximes by the method of Bartlett and Woods.[6] This mixture was separated into the corresponding *syn* (I) and *anti* (II) oximes melting at 97–98° and 87–88°, respectively. These melting points are in substantial agreement with those reported by Montgomery and Dougherty.[3]

A modification of the method of Horning, Stromberg, and Lloyd[4] was used in studying the Beckmann rearrangement. It was not possible to convert the *anti* oxime (II) to any isolable amount of 6-amino-5-hexenoic acid lactam (IV). The *syn* oxime (I), however, yielded 6-amino-2-hexenoic acid lactam (III) which was characterized by analysis, infrared and ultraviolet spectra, and catalytic hydrogenation to ε-caprolactam. The ultraviolet spectrum shows a shoulder in the range 235–245 mμ, ε (average) 2400, corresponding in position to the maxima reported by Montgomery and Dougherty for the lactams of 3,5,5-trimethyl- and 3-methyl-5-phenyl-6-amino-2-hexenoic acid and in position and intensity to those reported by Edwards and Singh[7] for 6-methyl and 1,6-dimethyl-5,6-dihydro-2-pyridone. These results, coupled with the known stereochemisty of the Beckmann rearrangement, confirm the assignment of the *syn* conformation to the high melting oxime.



I II III IV

EXPERIMENTAL

One hundred twenty grams of polyphosphoric acid (prepared by dissolving 35.0 g. of phosphorus pentoxide in 55 ml. of 85% phosphoric acid) was heated to 135°, the heat removed and 4.0 g. of *syn*-2-cyclohexenone oxime added with stirring. The temperature rose to 148° and after 10 min. stirring the reaction mixture was poured into 1500 ml. of an ice and water mixture. The mixture was made alkaline at 0° and adjusted to *p*H 12 by the slow addition of cold 15% sodium hydroxide. The solution was extracted exhaustively with chloroform. The extract was dried with sodium sulfate and concentrated to yield 2.3 g. of a dark brown oil. The crude product was subjected to steam distillation and the residue in the boiler decanted from a small amount of polymeric material and extracted with chloroform. The extract was dried with sodium sulfate, treated with decolorizing carbon, filtered, and concentrated to yield 1.9 g. of a light yellow oil. Distillation of this oil yielded 1.0 g. (25%) of colorless product, b.p. 60–65° at 0.5 mm; n_D^{25} 1.5238; d^{25} 1.092. The infrared spectrum shows peaks at 2.96, 6.02, and 6.20 μ. The ultraviolet spectrum shows a shoulder at 235–245 mμ and ε (average) 2400.

Anal. Calcd. for C_6H_9ON: C, 64.84; H, 8.16; N, 12.6. Found: C, 64.66; H, 8.38; N, 12.4.

Catalytic hydrogenation of the lactam at room temperature using 5% palladium-charcoal yielded ε-caprolactam as determined by infrared spectrum comparison and mixed melting point.

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(1) Abstracted from the M.S. thesis of F. J. Donat, Case Institute of Technology, June 1956.

(2) Present address: Pigments Dept., E. I. du Pont de Nemours & Co., Inc., Newark, N. J.

(3) R. S. Montgomery and Gregg Dougherty, *J. Org. Chem.*, **17**, 823 (1952).

(4) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

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(6) P. D. Bartlett and G. F. Woods, *J. Am. Chem. Soc.* **62**, 2933 (1940).

(7) O. E. Edwards and Tara Singh, *Can. J. Chem.*, **32**, 683 (1954).

Catalytic Reduction of 2-Acylthiophenes

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The removal of sulfur from the thiophene nucleus attached to aromatic compounds has been reported to proceed satisfactorily when the parent substance

TABLE I

PHYSICAL CONSTANTS OF REDUCTION PRODUCTS

Starting Material	Products	Found B.p., °C.	n_D^{15}	d_4^{20}	Literature[a] Values B.P., °C.	n_D^{15}	d_4^{20}
2-Benzylthiophene[5]	1-phenylpentane	200–203	1.4886	.861	205.0	1.4883	.858
2-Acetothienone[6]	*n*-hexane	68–69	1.3752		68.72	1.3750	.659
2-Propiothienone[7]	2-methylhexane	90–92	1.3845	.677	90.10	1.3849	.679
2-Butyrothienone[7]	*n*-octane	125–127	1.3980		125.6	1.3976	.703
2-Benzothienone[8]	1-phenylpentane	204–205	1.4888	.863	205.0	1.4883	.858
	1-phenyl-1-pentene[b]	202–203	1.5154	.874	202	1.5158	.878
2-Octadecanothienone[9]	docosane[9]	45.1° (m.p.)	1.4406		45.7° (m.p.)	1.4400	

(a) M.P. Doss, *Physical Constants of the Principal Hydrocarbons*, The Texas Company, New York, N. Y., 3rd edition, 1942.
(b) This product was obtained when the reaction was stopped after approximately one-half as much hydrogen had been absorbed as when the reaction was allowed to go to completion.

is refluxed with Raney nickel.[1,2] The product of each reaction was an aromatic ring attached to a saturated aliphatic residue. Thus, it seemed that this reduction might be applied to various substituted thiophenes in order to produce hydrocarbons of specific structure that might be difficult to obtain by other means.

However, when the reaction was attempted with various 2-alkylthiophenes very little of the expected hydrocarbons could be isolated. 2-Benzylthiophene did give a 25% yield of 1-phenylpentane by this route.

Since the 2-acylthiophenes are more readily prepared in a pure state than are the 2-alkylthiophenes, it seemed advisable to use these 2-thienyl ketones as starting materials for the study. At this time we secured a Tungsten-Nickel Sulfide Catalyst from Shell Oil Company which was similar to one previously used to hydrogenate and desulfurize 2-alkylthiophenes.[3] Subsequently, the reductions of various 2-acylthiophenes with the Tungsten-Nickel catalyst were carried out in this laboratory in an effort to develop a satisfactory method of synthesizing pure hydrocarbons.

While this work was in progress, Campaigne and Diedrich[4] reported the reduction of 2-acylthiophenes with a cobalt polysulfide catalyst to the corresponding thiophenes (thiocyclopentanes).

In the course of our work we reduced 2-benzo-, 2-accto-, 2-propano-, 2-butyro-, and 2-octadecanothienone. The principal product from all but one of these reductions was a hydrocarbon with the same number of carbon atoms and without rearrangement of the carbon skeleton. However, in the case of the 2-propiothienone, the product was a rearranged one, namely, 2-methylhexane. Appleby and his coworkers[3] noted that isomeric hydrocarbons were obtained when they reduced 2-*tert*-butylthiophene.

The reduction of 2-benzothienone proved to be a very interesting reaction insomuch as a variety of products was obtained, depending upon the conditions of the reaction. Complete reduction of this ketone gave a 46% yield of *n*-amylbenzene. However, when only a partial reduction was carried out, other reduction products were obtained, 2-benzylthiophene and 1-phenyl-1-pentene. We were unable to isolate any of the corresponding alcohol from this reaction, or to obtain a positive alcohol test from the reaction mixture. Although we could not isolate any tetrahydrothiophene derivatives, the reaction mass had a characteristic thiophane odor. Some unreacted ketone was recovered. The 1-phenyl-1-pentene was identified by index of refraction, boiling point, and oxidation to benzoic acid. Our work did not preclude the presence of isomeric 1-phenylpentenes although benzoic acid was obtained in nearly quantitative yield.

The reduction of 2-octadecanoylthiophene gave an excellent yield of docosane. A mass spectrogram of this material showed less than 0.1% of combined tertiary carbon and carbon-to-carbon double bond. This showed that no rearrangement occurred even with this very long chain ketone.

EXPERIMENTAL

Ketones. The ketones were prepared by the action of phosphorus pentoxide and carboxylic acid on thiophene in an inert solvent. The ketones were carefully fractionated before use and their physical data corresponded to those given in the literature.

Reductions. A 1-l., high-pressure, high temperature bomb was charged with the ketone and Tungsten-Nickel sulfide catalyst in a 2-1 weight ratio. Hydrogen was introduced under a pressure of 1500 p.s.i. The bomb was heated to 300°

(1) F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, **70**, 3768 (1948).
(2) E. S. Modest and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **72**, 577 (1950).
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(4) E. Campaigne and J. L. Diedrich, *J. Am. Chem. Soc.*, **73**, 5240 (1951).
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(6) W. Steinkopf and M. Bauermeister, *Ann.*, **403**, 69 (1914).
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(8) J. Volhard, *Ann.*, **267**, 174 (1892).
(9) A. W. Ralston and C. W. Christensen, *Ind. Engineering Chem.*, **29**,194 (1937).

and shaken at constant temperature until no further drop in hydrogen pressure was noted.

The reaction mass was filtered to remove the catalyst and the liquid product was carefully fractionated or recrystallized. (See Table I for the data.) The fractionizations were carried out with a 10-plate, glass helices-packed column. A Corad head was used with the column.

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Analogs of 4-(*p*-Dimethylaminostyryl)-quinoline[1]

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The anti-tumor activity of 4-(*p*-dimethylaminostyryl)quinoline(I)[2-5] and 1-(*p*-dimethylaminostyryl)naphthalene[6] encouraged us to synthesize several analogous compounds in which a nitrogen atom occupies the place of one of the carbons in the ethylene bridge. *N*-(*p*-Dimethylaminophenyl)quinoline-4-aldimine did not produce regression or significant inhibition of the growth of Lymphoma 8 tumors in rats, either when the compound was mixed in the diet or administered by subcutaneous injection of a solution in vegetable oil, although identical concentrations of I brought about prompt regression of similar tumors.[7] The following new compounds have not yet been tested against tumors.

EXPERIMENTAL

N-(*p*-Dimethylaminophenyl)naphthalene-1-aldimine. A mixture of 22 g. of *p*-aminodimethylaniline and 24.8 g. α-naphthaldehyde was heated 5 hr. at 135°. The product was recrystallized from ethyl acetate, from isohexane, and four times from isopropyl ether to yield 7.4 g. (17%) dark yellow crystals, m.p. 77–79°.

Anal.[8] Calcd. for $C_{19}H_{18}N_2$: C, 83.20; H, 6.57. Found: C, 83.08, 82.82; H, 6.57, 6.76.

N-(*p*-Dimethylaminophenyl)pyridine-4-aldimine. A mixture of 8.6 g. of pyridine-4-aldehyde and 10.9 g. of *p*-dimethylaminoaniline was heated 45 min. at 105°. The dirty green crystals were recrystallized twice from isopropyl ether to give 8.5 g. (47%) of light yellow crystals, m.p. 195°.

Anal. Calcd. for $C_{14}H_{15}N_3$: C, 74.68; H, 6.71. Found: C, 74.75; 74.75; H, 6.79, 6.59.

DEPARTMENT OF CHEMISTRY
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4-[4-(*p*-Dimethylaminophenyl)-1,3-butadienyl]quinoline[1]

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The activity of 4-(*p*-dimethylaminostyryl)quinoline[2,3] and 4-(*p*-dimethylaminostyryl)quinoline methiodide[4] in causing regression of Lymphoma 8[5] tumors in rats encouraged the authors to synthesize the corresponding compounds in which the ethylene bridge is replaced by a butadiene bridge. The antitumor activity of the compounds has been investigated at the Wistar Institute of Anatomy and Biology through the cooperation of Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Aubrey L. Bates, with the assitance of a grant from the National Cancer Institute. 4-[4-(*p*-Dimethylaminophenyl)-1,3-butadienyl]quinoline did not seem exceptionally toxic but had little or no effect on Lymphoma 8 when fed at a concentration of 0.03% in the diet. The methiodide, however, seemed more toxic than 4-(*p*-dimethylaminostyryl)quinoline methiodide.

EXPERIMENTAL

4-[4-(p-Dimethylaminophenyl)-1,3-butadienyl]quinoline. A mixture of 10.3 g. (0.059 mole) of *p*-dimethylaminocinnamaldehyde,[6] 8.5 g (0.059 mole) of lepidine, and 2.1 g. (0.03 mole) of anhydrous zinc chloride was heated 8 hr. at 120°. The resulting tar was washed thoroughly with concentrated ammonium hydroxide and crystallized from ethanol. The 7 g. of crude product was recrystallized twice from ethyl acetate to obtain 1.3 g. of brown crystals, 7%, m.p. 165–166°.

Anal.[7] Calcd. for $C_{21}H_{20}N_2$: C, 83.95; H, 6.77. Found: C, 83.74, 83.82; H, 6.59, 6.51.

4-[4-(p-Dimethylaminophenyl)-1,3-butadienyl]quinoline methiodide. A mixture of 15 g. (0.080 mole) of *p*-dimethylamino cinnamaldehyde and 22.5 g. (0.079 mole) of lepidine methiodide was poured into 500 ml. of boiling acetic an-

(1) The research was aided by a grant from the American Cancer Society.

(2) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

(3) M. R. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946).

(4) M. R. Lewis, B. Hughes, C. T. Bahner, and A. L. Bates, *Growth*, **19**, 1 (1955); M. R. Lewis, B. Hughes, *Growth*, **19**, 323 (1955).

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(6) A. Haddow, R. J. C. Harris, G. A. R. Kon, and E. M. F. Roe, *Phil. Trans. Royal. Soc. London*, **241**, 147 (1948).

(7) We are indebted to Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Mr. Aubrey L. Bates for testing the compounds at the Wistar Institute of Anatomy and Biology, with the aid of a grant from the National Cancer Institute.

(8) Analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(1) This project was aided by a grant from the American Cancer Society.

(2) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

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(6) W. König, W. Schramek, and G. Rösch, *Ber.* **61B**, 2074 (1928).

(7) Analyses were carried out by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

hydride. The mixture was refluxed 30 min., cooled, and filtered after standing. The crystals were recrystallized repeatedly from methanol; m.p. 256°. They were slightly soluble in water, more soluble in alcohol. The water solution was cherry red. The alcohol solution was deep blue. The absorption spectra of these and other compounds are to be presented in a separate paper. Even though the analytical sample was dried 1 hr. at 95° at 0.05 mm. the analysis indicated that the compound was a monohydrate.

Anal. Calcd. for $C_{22}H_{25}IN_2O$: C, 57.39; H, 5.47; I, 27.57. Found: C, 57.06; H, 5.10; I, 27.43, 27.30. (Other samples: C, 57.45, 56.99, 57.68, 57.93; H, 4.96, 5.69, 5.48, 5.74.)

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Quaternary Salts Similar to 4-(*p*-Dimethylaminostyryl)quinoline Methiodide[1]

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Although 4-(*p*-dimethylaminostyryl)quinoline[2,3] was more potent than 4-(*p*-dimethylaminostyryl)-quinoline methiodide[4] in causing regression of Lymphoma 8 tumors in rats,[5] the latter was less toxic. For this reason a number of similar quaternary salts have been prepared for testing against this and other tumors.

Preliminary tests by Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Aubrey L. Bates at the Wistar Institute of Anatomy and Biology[6] indicate that 4-(*p*-dimethylaminostyryl)quinoline propiodide shares the activity of the methiodide and ethiodide in producing regression of Lymphoma 8 tumors in rats, and that 2-(*p*-fluorostyryl)quinoline methiodide is inactive under the same conditions. Tests on the other compounds are not yet complete.

EXPERIMENTAL

Most of the compounds were prepared by adding a mixture of equimolar amounts of the *p*-aminobenzaldehyde and the lepidine methiodide (or propiodide) to boiling acetic anhydride and refluxing 30 min. (Method A). After cooling, the crystals were recovered and recrystallized from methanol. A few of the preparations were carried out by refluxing the reactants 4 hr. in methanol with piperidine catalyst (Method B). The dialkylamino compounds were purple-black, except the brown-black 4-(*p*-dimethylaminostyryl)-3-methylquinoline. The 4-(*p*-acetamidostyryl)quinoline methiodide was orange and the *p*-fluorostyryl compounds were tan. The compounds melted with decomposition. The melting points were determined by rapid heating.

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TABLE I
Quaternary Salts

Compound	Method	Yield, %	M.P., °C.	Analyses[a] Calcd. C	Calcd. H	Found C	Found H
Methiodides							
4-(*p*-Dimethylaminostyryl)-6-iodoquinoline[b]	A	21	307–308			[c]	
4-(*p*-Dimethylaminostyryl)-3-methylquinoline	A	72	284–285	58.61	5.39	58.75, 58.85	5.25, 5.23
4-(*p*-Dimethylaminostyryl)-8-methylquinoline	A	68	272	58.61	5.39	58.62, 58.36	5.36, 5.28
4-(*p*-Dimethylaminostyryl)-8-phenylquinoline	A	15	231–232	63.42	5.12	63.44, 63.28	5.05, 5.21
4-(*p*-Dimethylaminostyryl)-5,6-benzoquinoline[d,e]	B	36	241	59.51[f]	5.20	59.38, 59.55	4.97, 5.07
2-(*p*-Dimethylaminostyryl)-5,6-benzoquinoline[d]	A	39	253	59.51	5.20	59.33, 59.14	5.01, 4.90
4-(*p*-Acetamidostyryl)quinoline[g]	B	45	320	55.82	4.45[h]	55.70, 55.81	4.55, 4.53
4-(*p*-Nitrostyryl)quinoline	B	79	260	51.69	3.62	51.76, 51.55	4.18, 4.12
4-(*p*-Fluorostyryl)quinoline	B	4	237			[i]	
2-(*p*-Fluorostyryl)quinoline	B	50	249	55.25	3.84	55.16, 54.98	4.00, 3.98
2-(*p*-Dimethylaminostyryl)-5-methylpyrazine[j]	B		237–238	50.40	5.29[k]	50.25, 50.43	5.44, 5.22
Propiodide							
4-(*p*-Dimethylaminostyryl)quinoline	A		226			[l]	

[a] Carbon, hydrogen, and nitrogen analyses were carried out by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Iodine was determined by the Volhard Method. [b] Recrystallized from 50% methanol. [c] Calcd.: I, 46.82; Found: (Carius Method) I, 46.95, 46.78. [d] Monohydrate. [e] Recrystallized from methanol and from isopropyl alcohol. [f] Calcd.: I, 26.20; Found; I, 26.01, 26.28. [g] Crude product was dissolved in hot 8*N* acetic acid and precipitated by neutralizing with ammonia. Recrystallized from methanol. [h] Calcd.: N, 6.51; Found: N, 6.54. [i] Calcd.: I, 32.44; Found: I, 32.50. [j] Recrystallized from methanol and from isopropyl alcohol. 2,5-Dimethylpyrazine was donated by Wyandotte Chemicals Corp., Wyandotte, Mich. [k] Calcd.: N, 11.02; Found: N, 10.59. [l] Calcd.: I, 28.56; Found: I, 28.7, 28.9.

(1) Aided by grants from the Research Corporation, the Medical Research Foundation, and the American Cancer Society.

(2) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, 67, 342 (1945).

(3) M. A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, 68, 1332 (1946).

(4) C. T. Bahner, E. S. Pace, and R. Prevost, *J. Am. Chem. Soc.*, 73, 3407 (1951).

(5) B. Hughes, A. L. Bates, C. T. Bahner, and M. R. Lewis, *Proc. Soc. Exptl. Biol. Med.*, 88, 230 (1955); M. R. Lewis, B. Hughes, C. T. Bahner, and A. L. Bates, *Growth*, 19, 1 (1955); M. R. Lewis, B. Hughes, and A. L. Bates, *Growth*, 19, 323 (1955); C. T. Bahner, *Cancer Research*, 15, 588 (1955).

(6) Assisted by a grant from the National Cancer Institute.

A New Approach to Synthesis of Dihalogenated 8-Quinolinol Derivatives

A. Das[1] and S. L. Mukherji

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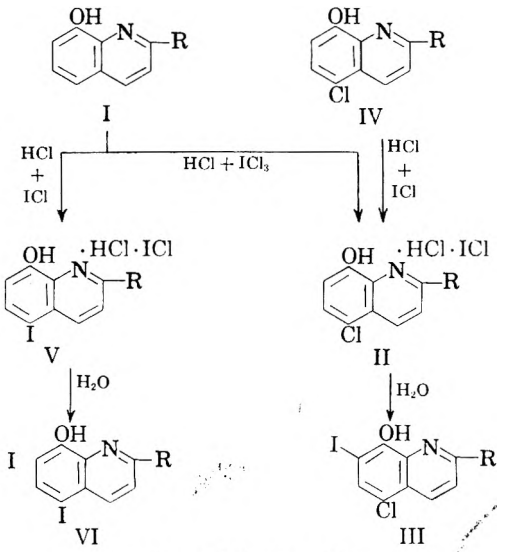
Of the halogenated 8-quinolinols, 5-chloro-7-iodo (IIIa) and 5,7-diiodo-8-quinolinols (VIa), commonly known as Vioform and Diodoquin respectively, have proved very useful in the treatment of intestinal amoebiasis. Among the recently prepared amoebicidal compounds containing the quinoline group, 5-chloro-7-diethylaminomethyl-8-quinolinol showed considerable promise in laboratory animals according to the preliminary results reported by Burckhalter and Edgerton.[2]



a, R = H; b, R = CH_3

Various methods of preparing IIIa from 5-chloro-8-quinolinol have been reported.[3–5] Certain patents[6,7] claim its preparation from 8-quinolinol (Ia) and iodine trichloride; however, the product isolated by Lasker and Ghosh[8] by a similar reaction was VIa. The authors prepared IIIa and VIa[9] most conveniently by the treatment of Ia in hydrochloric acid with iodine trichloride and iodine monochloride to give the respective iodine chloride-addition compounds; these were then decomposed with water to give IIIa and VIa. By the action of iodine monochloride in 15% hydrochloric acid, Papesch and Burtner[10] obtained VIa directly but in a less pure state as is evident from the low melting point. This compound has also been reported by Zeifman[11] using iodine and potassium iodate as the iodinating agent.

The preparation of dihalogenated 8-quinolinols described in this paper has resulted from our study of the reactions of iodine trichloride and iodine monochloride on Ia in a variety of media. In view of the recent report that 5,7-dichloro-2-methyl-8-quinolinol possesses stronger bactericidal properties than the di-halogenated 8-quinolinols,[12] the authors also prepared the Vioform and Diodoquin analogs of 2-methyl-8-quinolinol (Ib) by similar reactions for pharmacological studies against amoebiasis.

We have observed that the reaction of iodine trichloride or iodine monochloride with Ia in hydrochloric acid, IIIa or VIa is not formed directly, but through the respective iodine chloride-addition compounds. Probably iodine trichloride, as a strong chlorinating agent, chlorinates the 5-position of Ia liberating one molecule of iodine monochloride *in situ* which, instead of iodinating the 7-position directly, immediately forms an iodine chloride-addition compound of 5-chloro-8-quinolinol hydrochloride (IIa). This compound on treatment with water or very dilute acetic acid effects iodination of the 7-position. The formation of IIIa through IIa has been confirmed by its synthesis from 5-chloro-8-quinolinol (IVa) as shown in the experimental section. Similarly, VIa is not formed directly but through the iodine chloride-addition compound of 5-iodo-8-quinolinol hydrochloride (Va), which on subsequent decomposition with water yields VIa. This mechanism is supported by the fact that under similar conditions, by using one molecular equivalent of iodine monochloride or less, Va has always been obtained[13] instead of the expected mono-iodo derivative.[14] Similar addition compounds have not been observed when the reactions were conducted in glacial acetic acid and other solvents, *e.g.*, chloroform and ethanol. The direct formation of VIa by the action of iodine monochloride on Ia in ethanol is described in the Experimental part.

(1) To whom enquiries concerning reprints are to be made. Present address: Research Section, Emsons Pharmaceutical Works, 124C, Vivekananda Road, Calcutta 6, India.

(2) J. H. Burckhalter and W. H. Edgerton, *J. Am. Chem. Soc.*, **73**, 4837 (1951).

(3) Basler, German Patent **117767**.

(4) M. K. Vose, *J. Indian Chem. Soc.*, **22**, 169 (1945).

(5) R. Sengupta, *J. Indian Chem. Soc.*, **22**, 171 (1945).

(6) F. Boedecker and L. Cassel, German Patent **697,731** (1940); *Chem. Abstr.* **35**, 6603 (1941).

(7) S. L. Mukherji, Indian Patent, **34380** (1948).

(8) S. L. Lasker and T. N. Ghosh, *Science and Culture (India)*, **10**, 58 (1944).

(9) Albert David Limited, Indian Patent **43579** (1951).

(10) V. Papesch and R. Burtner, *J. Am. Chem. Soc.*, **58**, 1314 (1936).

(11) V. Zeifman, *Trans. Inst. Pure Chem. Reagents (U.S.S.R.)*, No. 16, 80–2 (1939); *Chem. Abstr.*, **34**, 3745 (1940).

(12) Emil Senn, Switzerland, U.S. Patent, **2,411,670** (1946); *Chem. Abstr.*, **41**, 6024 (1947).

(13) Unreacted 8-quinolinol has been recovered from the filtrate after neutralization.

(14) K. Glue and W. Jageman, *J. prakt. Chem.*, **145**, 257–264 (1936).

The preparation of the Vioform and Diodoquin analogs of Ib through their iodine chloride compounds is described, and their structures have been assigned by analogy to the related derivatives of 8-quinolinol.

EXPERIMENTAL[15]

Iodine chloride addition compound of 5-chloro-8-quinolinol hydrochloride (IIa).[16]

A. To a solution of Ia[17] (30 g.) in concd. hydrochloric acid (150 ml.) was gradually added a solution of iodine trichloride (48 g.) in 300 ml. of concd. hydrochloric acid with stirring; a deep yellow crystalline solid precipitated out instantaneously. Stirring was continued for 0.5 hr. after the last addition of iodine trichloride. The addition compound was then filtered under suction, washed with glacial acetic acid followed by dry ether to give 74 g. (95%) of the product, m.p. 144–145° after desiccation over night. Repeated recrystallization from glacial acetic acid gave yellow prismatic crystals, m.p. 148–149°.

Anal. Calcd. for $C_9H_7ONICl_3$: N, 3.69; total halogen, 61.69. Found: N, 3.46; total halogen, 60.82.

B. To A solution of iodine monochloride (17 g.) in 150 ml. of concd. hydrochloric acid was added with stirring 15 g. of 5-chloro-8-quinolinol hydrochloride[18] suspended in 150 ml. of concd. hydrochloric acid. After standing for 0.5 hr., the deep yellow crystalline compound was collected on a filter and sucked dry to yield 21 g. (80%) of dry product. Recrystallized from glacial acetic acid, it melted at 149–150°. Its admixture with IIa, A did not depress the melting point.

Anal. Calcd. for $C_9H_7ONICl_3$: N, 3.69. Found: N, 3.81.

5-Chloro-7-iodo-8-quinolinol (IIIa). The crude addition compound, 38 g. (IIa,A) was decomposed by being added to water with vigorous mechanical stirring. The precipitate was filtered, washed with water, and then with 2% sodium bisulfite solution to give a brownish white powder, 28.1 g. (90%), m.p. 178°. On recrystallization from glacial acetic acid it yielded long brownish silky needles, m.p. 181°. Admixture with an authentic sample,[4] m.p. 178–179°, gave no depression of melting point.

Anal. Calcd. for C_9H_5ONICl: Cl, 11.62; I, 41.57. Found: Cl, 11.45; I, 41.03.

IIa,B was similarly decomposed and the precipitate recrystallized from glacial acetic acid, m.p. 180–181°. The iodine and the chlorine values agreed with those of IIIa, and it showed no depression of melting point on admixture with IIIa.

Iodine chloride addition compound of 2-methyl-5-chloro-8-quinolinol hydrochloride (IIb). *A.* A solution of iodine trichloride (5 g.) in concd. hydrochloric acid (40 ml.) was gradually added to a solution of Ib[19] (3.3 g.) in 2 ml. of concd. hydrochloric acid with stirring. The crystalline yellow compound was filtered and dried to give 6.3 g. (80%) of product which on recrystallization from glacial acetic acid melted at 146°.

Anal. Calcd. for $C_{10}H_9ONICl_3$: N, 3.56; total halogen, 59.49. Found: N, 3.60; total halogen, 60.02.

B. To a suspension of 2-methyl-5-chloro-8-quinolinol hydrochloride[20] (17 g.) in 100 ml. of concd. hydrochloric acid was gradually added a solution of iodine monochloride (17 g.) in concd. hydrochloric acid (100 ml.) with constant stirring. The crystalline yellow compound was filtered on a Buchner funnel and dried. The desiccated addition compound, 22.3 g. (77%) on recrystallization from glacial acetic acid melted at 148°.

Anal. Calcd. for $C_{10}H_9ONICl_3$: N, 3.56; total halogen, 59.49; Found: N, 3.35; total halogen, 58.92.

Admixture with IIb, A gave no depression of melting point.

2-Methyl-5-chloro-7-iodo-8-quinolinol (IIIb). The decomposition of 6.1 g. of crude iodine chloride addition compound (IIb, A) was carried out as for IIIa and IIIb. The product was collected as a brownish white powder, 3.5 g. (70%) which on repeated recrystallization from ethanol yielded light brown needles, m.p. 125–126°.

Anal. Calcd. for $C_{10}H_7ONICl$: Cl, 11.11; I, 39.74. Found: Cl, 10.82; I, 39.90.

The addition compound (IIb, B) was decomposed by stirring into water. The compound obtained after repeated recrystallization from ethanol, m.p. 124–125°, was identified as IIIb by analyses and mixed melting point.

Iodine chloride addition compound of 5-iodo-8-quinolinol hydrochloride (Va). Ia (20.4 g.) in 100 ml. of concd. hydrochloric acid reacted with a solution of iodine monochloride (47 g.) in 50 ml. of concd. hydrochloric acid under constant stirring to give a yellow crystalline mass. The solid mass was filtered under suction, washed, and dried as usual to give 62.7 g. (95%) of the product. On repeated recrystallization from glacial acetic acid, it melted at 172°.

Anal. Calcd. for $C_9H_7ONI_2Cl_2$: N, 2.97; total halogen, 69.14. Found: N, 2.72; total halogen, 70.05.

5,7-Diiodo-8-quinolinol (VIa). *A.* The crude Va (65 g.) was decomposed in water and the product collected as a yellowish brown powder, 52.1 g. (94%), m.p. 207–208°. Recrystallization from benzene gave pale yellow microcrystals, m.p. 213–214° (m.p. reported[11] 208–210°). Admixture with an authentic sample did not depress the melting point.

Anal. Calcd. for $C_9H_5ONI_2$: I, 63.97. Found: I, 64.00.

B. A solution of iodine monochloride, prepared by carefully adding 32.5 g. to 50 ml. of ice cold ethanol, was added to a solution of Ia (14.5 g.) in 100 ml. ethanol with stirring. There was an immediate separation of light brown crystalline needles which were collected under suction and washed with ethanol until the washings were colorless. The washings combined with the mother liquor afforded further crystalline material. The light brown microcrystalline needles, 35.7 g. (90%) melted at 211–212°. Recrystallization from benzene caused no elevation of the melting point, and there was no depression of melting point upon admixture with the above specimen.

Anal. Calcd. for $C_9H_5ONI_2$: I, 63.97. Found: I, 63.5.

Iodine chloride addition compound of 2-methyl-5-iodo-8-quinolinol hydrochloride (Vb). A solution of iodine monochloride (7 g.) in 10 ml. of concd. hydrochloric acid was stirred into a solution of Ib (3.2 g.) in 30 ml. of concd. hydrochloric acid. After some time the yellow crystalline mass was filtered and washed as usual to give 7.3 g. (76%) of the product. A sample crystallized from glacial acetic acid melted at 140–142°.

Anal. Calcd. for $C_{10}H_9ONI_2Cl_2$: N, 2.89; total halogen, 67.14. Found: N, 2.64; total halogen, 67.30.

5,7-Diiodo-2-methyl-8-quinolinol (VIb). Vb (5.1 g.) was decomposed in water under vigorous mechanical stirring. The diiodo-derivative was obtained as 2.8 g. (64%) of a brown powder. Repeated recrystallization from ethanol gave the pure compound, m.p. 147–148°.

Anal. Calcd. for $C_{10}H_7ONI_2$: I, 61.80. Found: I, 62.53.

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(15) All melting points are uncorrected.

(16) All the addition compounds were made using hydrochloric acid of sp. gr. 1.07 and 1.15.

(17) A. Das and S. L. Mukherji, *Science and Culture (India)*, 16, 477–478 (1951).

(18) T. N. Ghosh, *et al.*, *J. Indian Chem. Soc.*, 21, 354 (1944).

(19) O. Doebner and W. v. Miller, *Ber.*, 14, 2812 (1881).

(20) Prepared by the general procedure of the Doebner and Miller reaction.

Bromination of α-Methylstyrene with *N*-Bromosuccinimide. Synthesis of 2-Phenyl-1,5-hexadiene

HERMAN PINES, HUSNI ALUL, AND MARJAN KOLOBIELSKI

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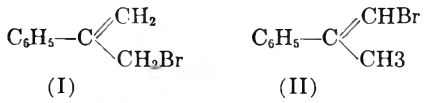
During the bromination of α-methylstyrene by means of *N*-bromosuccinimide[1] it was observed that the bromides obtained from this reaction consisted of a mixture of two compounds: the expected 2-phenylallyl bromide (I) and 1-methyl-1-phenylvinyl bromide (II).



(I) (II)

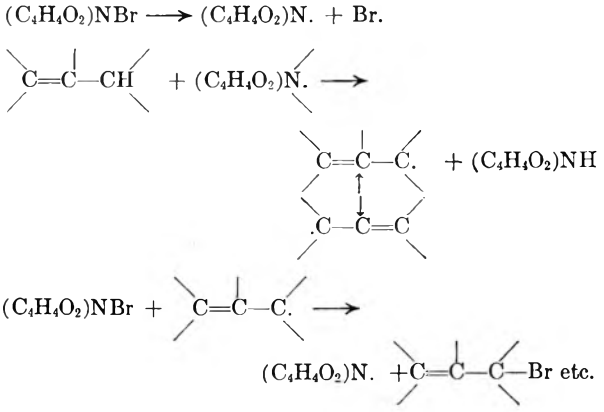
The presence of II was first suspected when the crude bromide failed to react quantitatively with an alkyl Grignard reagent.

Bromides I and II were separated in pure form chromatographically at room temperature, using activated silica as adsorbent and absolute ethanol as desorbant. During chromatography the allylic isomer I underwent partial polymerization and attempts to carry out the separation at 3–5° did not result in any appreciable improvement. The two isomers have distinct different infrared and ultraviolet spectra.

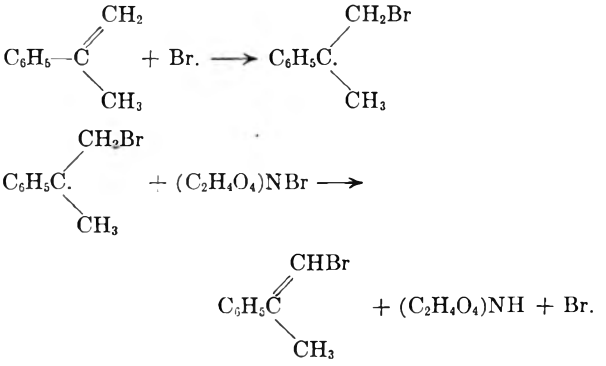
The bromination of α-methylstyrene by means of *N*-bromosuccinimide yields on the average, according to infrared spectroscopy, 65–75% of isomer I and 25–35% of isomer II. The allylic bromide is a strong lachrymator, reacts readily with aqueous silver nitrate solution in the cold and it clouds on standing at room temperature. The vinylic bromide, II, does not possess the lachrymatory properties and is stable toward alcoholic silver nitrate solution even at reflux temperature.

Ozonolysis of II yielded acetophenone while the ozonolysis of I formed a compound which was a very strong lachrymator, presumably bromoacetophenone. Compound I reacted with allyl magnesium bromide to form the expected 2-phenyl-1,5-hexadiene, which on ozonolysis yielded β-benzoylpropionic acid.

The bromination with *N*-bromosuccinimide and related compounds[2] is assumed to proceed *via* a free radical mechanism[3] which involves the homolytic dissociation of *N*-bromosuccinimide.



In the case of α-methylstyrene however, owing to the resonance-stabilizing effect of the phenyl group, it appears to be possible for the bromine atom to add to the olefinic double bond, followed by the elimination of a hydrogen atom:



A similar type of abnormal bromination was observed by Roberts and coworkers in the case of camphene which formed 8-bromocamphene[4] and norbornylene which formed 3-bromonortricyclene.[5]

EXPERIMENTAL

Bromination of α-methylstyrene. One hundred grams of *N*-bromosuccinimide, 250 ml. of α-methylstyrene, and 40 ml. of carbon tetrachloride were heated just to boiling, and the flask was then quickly immersed in an ice bath. One hundred ml. of pentane was added to the flask and the solid succinimide was separated by filtration. The unreacted α-methylstyrene was then removed from the filtrate by means of vacuum distillation. An additional 100 ml. of pentane was added to the residue of the flask in order to precipitate the remaining succinimide, and the solid was then separate by filtration. The filtrate on distillation yielded 64 g. of bromides boiling at 105–110° at 15 mm.; yield 64%, based on *N*-bromosuccinimide.

Forty two grams of the bromides dissolved in 30 ml. of n-pentane were chromatographed using activated silica gel[6] as the adsorbent and absolute ethanol as the desorbant.

(1) K. Ziegler, A. Spaeth, E. Schaaf, W. Schumann, and E. Winkelman [*Ann.*, **551**, 80 (1942)] reacted α-methylstyrene with *N*-bromosuccinimide and in connection with it they stated the following: "Die etwa 1 Stunde dauernde Reaktion soll in anderem Zusammenhang publiziert werden." According to our knowledge further report of this reaction was not published.

(2) For the general review of the Wohl-Ziegler reaction see C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(3) G. F. Bloomfield, *J. Chem. Soc.*, **1944**, 114.

(4) J. D. Roberts and E. R. Trumbull, *J. Am. Chem. Soc.*, **71**, 1630 (1949).

(5) J. D. Roberts, E. R. Trumbull Jr., W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **73**, 3116 (1950).

(6) Davison Chemical Co., Baltimore, Md.

The first fractions were composed of pure 1-methyl-1-phenylvinyl bromide (II), while the end fractions were composed of 2-phenylallyl bromide (I); about 24% of I underwent polymerization during separation. From the infrared spectra of the pure I and II isomer it was calculated that the crude bromides were composed of 73% of I and 27% of II.

Compound I: b. p. 104–105° at 10 mm., n_D^{20} 1.5925, d_4^{20} 1.3729. MR_D: found 48.39; calcd. 47.46 $\lambda_{max.}$ 242 mμ.: ε 8,700 (in isooctane).

Anal. Calcd. for C_9H_9Br: C, 54.82; H, 4.57. Found: C, 54.90; H, 4.49.

Compound II: b.p. 98° at 10 mm., n_D^{20} 1.5891, d_4^{20} 1.3716. MR_D: found 48.39, calcd. 47.46. $\lambda_{max.}$ 247 mμ (in isooctane) ε 13,240 (in isooctane) Literature[7] b.p. 105–106° at 9 mm., d_4^{0} 1.366.

Anal. Calcd. for C_9H_9Br: C, 54.82; H, 4.57, Found: C, 54 78; H, 4.44.

Ozonolysis of II. Compound II, 2.35 g., dissolved in 25 ml. of methylene chloride was ozonized at −78°. The ozonide was decomposed by the usual method with hot water. Acetophenone, 1.23 g., (89%) was obtained which formed 2,4-dinitrophenylhydrazone, m.p. 243°. It did not depress the melting point of an authentic sample.

Synthesis of 2-phenyl-1,5-hexadiene. Phenylallyl bromide, I, 31 g. was reacted with 15% excess of allylmagnesium bromide. A 78% yield of 2-phenyl-1,5-hexadiene was obtained, which distilled at 104° at 10 mm, n_D^{20} 1.5314.

Anal. Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.75; H, 8.75.

Ozonolysis of 2-phenyl-1,5-hexadiene. Two grams of the hydrocarbon dissolved in 25 ml. of methylene chloride was ozonized at −78° and decomposed oxidatively,[8] except that no sulfuric acid was added. The benzoylpropionic acid which was obtained melted, after recrystallization from water, at 116–117° (literature[9]) m.p. 116.5°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5 62. Found: C, 67.11; H, 5.95.

Acknowledgment. The authors express their thanks to Miss Hildegard Beck for the elementary analyses.

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(7) M. Tiffeneau, *Compt. rend.*, **135**, 1346(1902).

(8) A. L. Henne and P. Hill, *J. Am. Chem. Soc.*, **65**, 752 (1943).

(9) E. P. Kohler and H. Engelbrecht, *J. Am. Chem. Soc.*, **41**, 764 (1919).

Effect of Substituents on the Rates of Pyrophosphate Hydrolysis[1]

FRED H. BROCK

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In a recent paper,[2] Heath has summarized (from earlier work of Ketelaar and Blaksma,[3] and of Toy[4,5]) the neutral hydrolysis rate constants of the pyrophosphates listed below. Since Heath has concluded that the transmission of electronic effects along the P-O-P bond is small,[6] the observed rate constant will be the sum of the rate constants for the groups attached to each phosphorus atom. Individual rate constants were obtained based upon the symmetrical pyrophosphates. Using these constants to calculate the expected rate for the unsymmetrical pyrophosphates, agreement was observed only in the cases when R_1 = Et, R_2 = Pr, and R_1 = Et, R_2 = *n*-Bu. Consequently, Heath concluded that steric effects are very much more important than inductive effects in this series.

TABLE I

RATE CONSTANTS FOR HYDROLYSIS OF PYROPHOSPHATES, $(R_1O)_2P(O)—O—P(O)(OR_2)_2$

No.	R_1	R_2	$k \times 10^3$ min^{-1}	$\Sigma\sigma^*$
1	Me	Me	25	0.000
2	Me	Et	7.0	−0.200
3	Me	Pr	5.6	−0.230
4	Et	Et	1.6	−0.400
5	Me	iPr	1.1	−0.380
6	Et	rPr	1.0	−0.430
7	Et	rBu	0.95	−0.460
8	nPr	rPr	0.65	−0.460
9	Et	iPr	0.28	−0.580
10	nPr	iPr	0.20	−0.610
11	nBu	iPr	0.20	−0.640
12	iPr	iPr	0.09	−0.760

The hydrolysis data have been reexamined in an attempt to establish a quantitative correlation of these reaction rates with structure.

All of the above data are correlated successfully by means of Taft's linear free energy-polar energy equation.[7]

$$\log k/k_0 = \rho^*\Sigma\sigma^*$$

where ρ^* = reaction rate constant, $\Sigma\sigma^*$ = sum of polar substituent constants (aliphatic series), k = observed rate constant, k_0 = observed rate constant for tetramethyl pyrophosphate. The accompanying figure gives the plot of log k/k_0-vs. $\Sigma\sigma^*$, the line being that calculated using the method of least squares. The following constants were obtained: ρ^* = 3.38 ± 0.08, intercept = 0.0561 ± 0.0376, correlation coefficient = 0.994.

Unfortunately, the range of σ^* values is small. Consequently, if the above correlation is confirmed for the reaction with groups of greater σ^* values, then the following conclusions, based on this limited data, will follow.

1. The fact that the total polar effect of all groups is operative, as given by $\Sigma\sigma^*$, indicates a

(1) The work herein reported was carried out on Project NR055-328 between the Office of Naval Research and The Pennsylvania State University. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) D. F. Heath, *J. Chem. Soc.*, 1956, 3804.

(3) J. A. A. Ketelaar and A. H. Blaksma, *Rec. trav. chim.*, **67**, 665 (1948).

(4) A. D. F. Toy, *J. Am. Chem. Soc.*, **70**, 3882 (1948).

(5) A. D. F. Toy, *J. Am. Chem. Soc.*, **72**, 2065 (1950).

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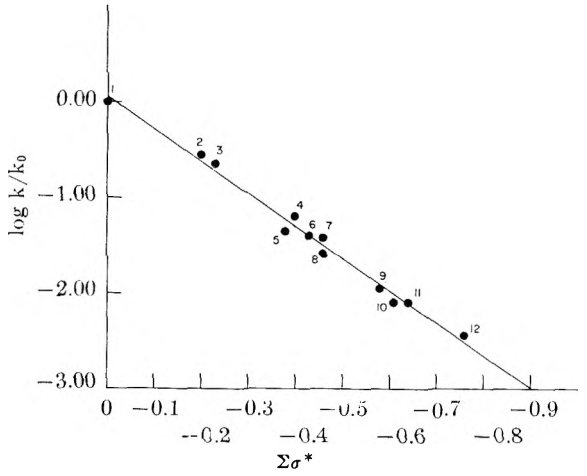
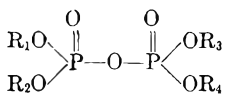


FIG. 1. PLOT OF LOG k/k_0 *vs.* $\Sigma\sigma^*$. Numbers refer to pyrophosphates in Table I.

symmetrical transition state for the P-O-P structure. Possibly the rate-determining step involves an attack on the central oxygen atom, followed by a rapid scission of one of the P-O-P bonds. This postulate is in contrast to the proposed P-O bond scission in phosphate ester hydrolysis as the rate-determining step.[8] A mechanism involving two independent attacks by water molecules on each phosphorus atom, as suggested by Heath[2] is ruled out. The fact that the observed rate constants almost agree in the two cases cited above with the sum of two rate constants calculated from the symmetrical pyrophosphates is purely fortuitous.

2. These reactions are influenced chiefly by polar effects, and very little, if at all, by steric effects, as is strikingly demonstrated by the high value of the correlation coefficient and by the agreement of the rate constant for tetraisopropyl pyrophosphate which obeys the above relationship. This conclusion is in conflict with those of Toy[6] and Heath.[2]

3. In the data available, all pyrophosphates of general structure



have either $R_1{=}R_2{=}R_3{=}R_4$ or $R_1{=}R_2$ and $R_3{=}R_4$. Due to the fact that the correlation depends on $\Sigma\sigma^*$, it is expected that it will also hold when $R_1{=}R_3$, $R_2{=}R_4$ and when $R_1 \neq R_2 \neq R_3 \neq R_4$.

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Preparation of 2-Hydroxydiethyl Sulfoxide[1]

KERMIT GROVES AND R. R. LEGAULT

Received February 4, 1957

Many procedures for the preparation of sulfoxides are based on the controlled oxidation of the corresponding sulfides. Difficulties are sometimes encountered with these methods when sulfones are formed, resulting in purification complications, and when other portions of the molecule are attacked by the oxidation process. Both of these difficulties were encountered in attempts to prepare 2-hydroxydiethyl sulfoxide from 2-hydroxydiethyl sulfide by conventional methods.

Patein[2] has shown that the reaction

$$R_2S + Br_2 \longrightarrow R_2SBr_2 \xrightarrow{H_2O} R_2SO + 2HBr$$

quantitatively forms the sulfoxide and hydrobromic acid. This reaction has since been used as a basis for the determination of sulfides[3-5] and by Harnish and Tarbell[5] for the preparation of benzyl phenyl sulfoxide. It has been used on occasion by a few other workers for sulfoxide preparation.[6]

Pure 2-hydroxydiethyl sulfide reacts stochiometrically with bromine when determined by the method of Siggia.[4] It was impractical to separate the sulfoxide from this analytical reaction mixture, and the preparative reaction was carried out by adding pure bromine to the acidified aqueous solution of 2-hydroxydiethyl sulfide. The equivalence point could be observed precisely by the appearance of the yellow bromine color when a slight excess bromine was added. The final reaction mixture contained the sulfoxide, water, hydrobromic acid, and a little hydrochloric acid. 2-Hydroxydiethyl sulfide is soluble in about five parts of water and the sulfoxide is very soluble. The extraction of the sulfoxide from the neutralized and salted reaction mixture with ether was very inefficient because of the unfavorable partitioning. However, it was found that an anion-exchange column (Amberlite IR-4B) retained the acids completely with excellent recovery of the product in dilute aqueous neutral solution. Concentration and distillation gave pure 2-hydroxydiethyl sulfoxide.

(1) This investigation was supported in part by funds provided for biological and medical research by the State of Washington Initiative Measure No. 171. Scientific Paper No. 1576, Washington Agricultural Experiment Stations. Work conducted under Project No. 1229.

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(3) J. R. Sampey, K. H. Slagle, and E. E. Reid, *J. Am. Chem. Soc.*, 54, 3401 (1932).

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(6) "Methoden der Organischen Chemie," Houben-Weyl, Band IX, Georg Thieme Verlag, Stuttgart, 1955.

EXPERIMENTAL

2-Hydroxydiethyl sulfoxide. 2-Hydroxydiethyl sulfide (74.3 g., 0.70 mole) was placed in an 800 ml. beaker containing 225 ml. water and 10 ml. concentrated hydrochloric acid. Bromine was added to the well stirred mixture from a buret having a long capillary tip that extended below the surface of the solution. The rate of addition was regulated so that the bromine reacted as fast as it was added. Water was added at intervals to reduce the hydrobromic acid concentration, until the final volume of the mixture was about 500 ml. Near the equivalence point (indicated by slight persistence of color) the rate of addition of bromine was reduced and the final additions were made dropwise until one drop colored the mixture yellow.

The mixture was diluted to 2000 ml. and passed in two 1000 ml. portions through a column containing about 400 g. moist IR-4B resin. The column was washed with water until a total of 3000 ml. neutral solution had been collected.

The sulfoxide solution was concentrated in a flash vacuum evaporator and the remaining water removed at 60° C. under 10 mm. pressure. The product was finally distilled in a molecular still at 54° C. A yield of 70% was obtained with much of the loss mechanical. Analysis by a modified method of Barnard[7-9] for sulfoxide indicated 100.4 ± 0.7% sulfoxide.

Calcd. for $C_4H_{10}OS$: S, 26.26. Found: S, 26.47.

The product had a density of 1.1685 25°/4°, and a refractive index, n_D^{25} 1.5019. The vapor pressure at 54° C. was estimated from molecular distillation data at about 3 microns.

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(7) D. Barnard and K. R. Hargrave, *Anal. Chim. Acta*, 5, 476 (1951).

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Nitric Acid Oxidation of 5,14-Octadecanedione

CHARLES M. SELWITZ AND A. C. WHITAKER

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To study the effect of the nitric acid oxidation of a long paraffin chain containing two distantly placed carbonyl groups, 5,14-octadecanedione was oxidized with 50% nitric acid at 55°. The diketone was prepared in 50% yield by a modification of Cason's[1] method for preparing keto esters, whereby sebacyl chloride was added to di-*n*-butyl cadmium. Random attack on either side of the carbonyl groups of the diketone should have given 25% sebacic, 50% azelaic, and 25% suberic acid, and the theoretical amounts of the eight and ten carbon dibasic acids were found (Table I). However, far less than the theoretical yield of azelaic acid resulted, and smaller quantities of the four to seven carbon acids were also found.

(1) J. Cason and F. S. Prout, *Org. Syntheses*, **Coll. Vol. III**, 601 (1955).

TABLE I

MOLAR YIELD OF DIBASIC ACIDS

Acid	Yield: %
Sebacic	25.8
Azelaic	14.6
Suberic	24.2
Pimelic	8.7
Adipic	7.0
Glutaric	8.2
Succinic	5.3
	93.8

Apparently azelaic acid was degraded to the smaller acids. This tendency of higher molecular weight dicarboxylic acids having an odd number of carbon atoms to break down more readily into shorter chain dicarboxylic acids than those having an even number of carbon atoms has been noted by others.[2]

EXPERIMENTAL

Preparation of Diketone. To 24.3 g. (1.0 mole) of magnesium covered with 150 ml. of dry ether was added 137 g. (1.0 mole) of *n*-butyl bromide in 350 ml. of ether over a period of 1.5 hr. The reaction mixture was refluxed for 15 min. and cooled, and to it was added 100 g. (0.54 moles) of anhydrous cadmium chloride. After the mixture was refluxed with stirring for 1 hr., the ether was stripped, 350 ml. of benzene was added, and, after the removal of 100 ml. of benzene by distillation, an additional 350 ml. of benzene was added. The mixture was stirred and refluxed for a few minutes to disperse solids, the heat was removed, the mixture was cooled with an ice bath, and 100 g. (0.40 moles) of sebacyl chloride, dissolved in 150 ml. of benzene, was added to the vigorously stirred solution over a 0.5 hr. period. The heat of reaction caused the mixture to reflux, although the flask was immersed in an ice bath. After the addition was complete, stirring and refluxing were continued for 2 hr., during which time it was necessary to apply heat.

To the product was added 600 ml. of ice water and then a large excess of 20% sulfuric acid. After the further addition of benzene and the separation into two phases, the undissolved solids were removed from each layer by filtration. The benzene solution was extracted successively with 200 ml. of water, 200 ml. of 5% sodium carbonate, 200 ml. of water, and 100 ml. of saturated sodium chloride solution and then passed through a column of anhydrous sodium sulfate. The aqueous phase was extracted with three 150 ml. portions of benzene, which were added to 200 ml. of a hot benzene solution of the gum in the original flask. This was washed and dried as above and added to the initial solution. After stripping the benzene the diketone was obtained by distillation as 56 g. (0.20 moles; 50%) of a colorless, hard, waxy solid boiling at 191° at 6.7 mm., and melting, after two recrystallizations from hexane, at 75.6–76.0°.

Anal. calcd. for $C_{18}H_{34}O_2$: C, 76.50; H, 12.08; mol. wt., 282. Found: C, 75.87; H, 11.87; mol. wt., 270.

Oxidation of Diketone. To 100 ml. of 50% nitric acid and 0.1 g. vanadium pentoxide in a 500 ml. 3-neck flask equipped with stirrer and vented reflux condenser was added 5.64 g. (0.05 moles) of 5,14-octadecanedione in small increments over a 4 hr. period while the temperature was maintained at 54.8–55.3°. The oxidation was marked by the evolution of brown nitrogen oxide fumes. Heating was maintained for another 2.5 hr.

(2) R. L. Logan, U. S. Patent 2,662,908 (December 15, 1953).

The oxidation product was neutralized with 20% NaOH at 0°, and water was carefully evaporated from aliquot portions. The dry salts were acidified with minimum quantities of concentrated hydrochloric acid, and then extracted with four 10-ml. portions of ether. The residues after the evaporation of ether and monobasic acids were analyzed for dibasic acids by liquid partition chromatography.[3]

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(3) T. Higuchi, N. C. Hill, and G. B. Corcoran, *Anal. Chem.*, **24**, 491 (1952).

Reaction of *Exo*-norbornylene Oxide with Hydrogen Bromide[1,2]

H. M. WALBORSKY AND D. F. LONCRINI

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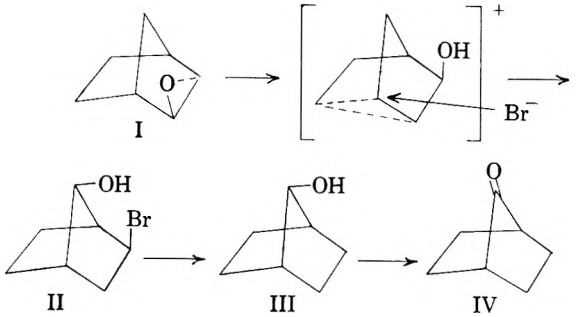
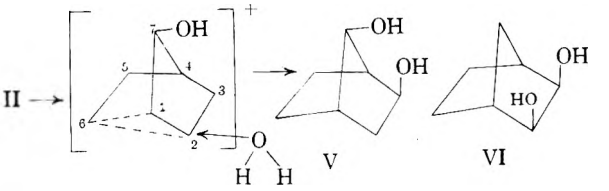
It has previously been demonstrated[3] that the reaction of norbornylene with peracetic acid yields the *exo*-norbornylene oxide (I). Treatment of I with hydrogen bromide produced a bromohydrin (II) as the main product.[2] The structure of II has been tentatively assigned as 2-*exo*-bromo-7-*syn*-hydroxy-norbornane based on analogy to the product formed by the hydrolysis[3] of I.



That the hydroxyl group is located at the 7-position was established by treating II with hydrogen and palladium to yield the known 7-hydroxynorbornane (III).[4] Oxidation of III yielded ketone IV which was isolated as the 2,4-dinitrophenylhydrazone.



Hydrolysis of II did not produce the rearranged product (VI) but yielded V.[2] Apparently the hydroxyl group at C-7 shields C-1 from attack by solvent so that reaction occurs at C-2. A similar observation has been made by Roberts[5] who obtained 2-*exo*-hydroxy-*syn*-7-chloronorbornane from the basic hydrolysis of *exo-syn*-2,7-dichloronorbornane.

EXPERIMENTAL[6]

2-exo-Bromo-7-syn-hydroxy-norbornylene (II). To 36 ml. of 48 per cent hydrobromic acid, cooled to 10°, was slowly added 20 g. (0.18 mole) of *exo*-norornylene oxide. The temperature was not allowed to rise above 15° during the addition. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with aqueous sodium carbonate, dried over anhydrous sodium sulfate, and stripped. The residual oil was distilled to yield 13.5 g. (39%) of product, b.p. 98–100° (5 mm.), m.p. 75.5–76° from ether-pentane. An oil was also isolated but not identified.

Anal. calcd. for $C_7H_{11}BrO$: C, 43.94; H, 5.80; Br, 41.82. Found: C, 43.97; H, 6.00; Br, 41.78.

7-Hydroxynorbornane (III). Five grams (0.026 mole) of II dissolved in ethanol was hydrogenated using one gram of 10% palladium on charcoal catalyst. The reaction mixture was filtered, solvent stripped *in vacuo*, and the residue taken up in pentane. The pentane solution was dried over Drierite and stripped to yield 2.7 g. (92%) of III, m.p. 149–150° (Lit.[4] m.p. 149–150°).

The phenylurethan derivative melted at 138–139° from acetonitrile.

Anal. calcd. for $C_{14}H_7O_2N$: C, 72.72; H, 7.31; N, 6.66. Found: C, 72.78; H, 7.38; N, 6.69.

Norbornone-7. To a solution of 1 g. (0.008 mole) of III in 4 ml. of glacial acetic acid was slowly added a solution of 0.54 g. (0.0054 mole) of chromium trioxide in 10 ml. of acetic acid. The mixture was stirred for several hours at room temperature and extracted with pentane. Removal of the solvent yielded 0.2 g. (20%) of an oil with a strong camphoraceous odor. The oil was converted to the 2,4-dinitrophenylhydrazone which melted at 133–134° (Lit.[4] 133–134°).

exo-syn-2,7-Dihydroxynorbornane (V). To an aqueous solution of lithium carbonate was added 2 g. (0.001 mole) of II. The mixture was refluxed for several hours and then continuously extracted with ether. The ether extract was dried over anhydrous sodium sulfate and stripped to yield 1.1 g. (91%) of V, m.p. and mixed m.p. 180–181°. The diphenylurethan derivative m.p. and mixed m.p. 221–222°.

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(1) This paper is based on a portion of the thesis submitted by D. F. L. in 1956 to the Florida State University in partial fulfillment of the requirements for the Ph.D. degree in chemistry.

(2) During the preparation of this manuscript a communication appeared describing this reaction (Winstein and Stafford, *J. Am. Chem. Soc.*, **79**, 505 (1957)).

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

(4) Dissertations by P. Wilder, Jr. (1950) and R. E. Vanelli (1950) at Harvard University. S. Winstein, M. Shatovsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955); S. Winstein and M. Shatovsky, **78**, 592 (1956).

(5) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *J. Am. Chem. Soc.*, **76**, 5692 (1954).

(6) All melting points and boiling points are uncorrected.

Oxidation of Trialkyl Phosphites by Epoxides

CARLETON B. SCOTT

Received February 18, 1957

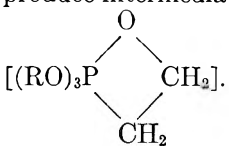
Much interest has been focused recently upon the oxidation reactions of trivalent phosphorus compounds. Particularly prominent have been the reactions of trialkyl phosphites with carbonyl compounds,[1] and of trisubstituted phosphines with oxidizing agents.[2,3] This note reports some preliminary data on another new reaction[4,5] of phosphites.

Triethyl phosphite was oxidized very smoothly to triethyl phosphate by ethylene oxide and propylene oxide at 150–175°. The epoxides were reduced to the corresponding olefins.

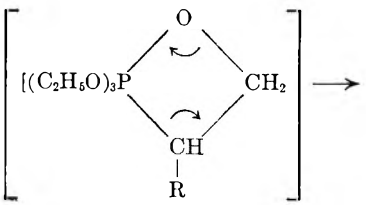
$$(C_2H_5O)_3P + RCH\underset{\diagdown O \diagup}{CH_2} \longrightarrow (C_2H_5O)_3PO + RCH{=}CH_2$$

There are indications that the reaction is applicable to other phosphites and epoxides. It is hoped that this additional work will be published in more detail at a later date.

Although the phosphite might attack the epoxide oxygen directly, recent mechanism discussions[1,6–8] suggest a nucleophilic attack on carbon to produce intermediates like $[(RO)_3\overset{+}{P}\text{–}CH_2CH_2\text{–}\overset{-}{O}]$ or



then the following rearrangement could account for the observed products.



$$(C_2H_5O)_3PO + RCH{=}CH_2$$

EXPERIMENTAL

Reaction of triethyl phosphite with ethylene oxide. A mixture of 133 g. (0.8 mole) triethyl phosphite and 35.2 g. (0.8 mole) ethylene oxide was placed under 50 p.s.i.g. of dry nitrogen in a 300-ml. stainless steel bomb. The bomb was rocked and heated slowly to 174° over a period of 3 hr. The pressure rose steadily to 275 p.s.i.g. at 154°, then rapidly to 400 p.s.i.g. at 174°. These conditions were held for 1 hr., then heat was removed and the bomb allowed to cool overnight. The gas which formed consisted of 92.3 mole per cent ethylene, 3.5% ethylene oxide, 2.1% nitrogen, and minor quantities of other contaminants.

Distillation of the liquid product gave three fractions:

(1) 22 g., b.p. 62–80° C. (24 mm.), was mostly triethyl phosphite with some triethyl phosphate.

Anal. Calcd. for $C_6H_{15}PO_3$: P, 18.7. Found: P, 18.1.

(2) 87 g., (60%) b.p. 80–113° (mostly 110°) (24 mm.), was triethyl phosphate.

Anal. Calcd. for $C_6H_{15}PO_4$: P, 17.0. Found: P, 16.7.

(3) 16 g., residue, was essentially all phosphate.

Anal. Found: P, 16.4.

Reaction of triethyl phosphite with propylene oxide. A mixture of 133 g. (0.8 mole) triethyl phosphite and 46 g. (0.8 mole) propylene oxide was rocked in a bomb for 23 hr. The temperature was 150° and the pressure rose to 350 p.s.i.g. The gas was 95.9 mole per cent propylene.

Distillation of the 155.5 g. of liquid product gave four fractions:

(1) 3.1 g., b.p. 33–34°, was mostly propylene oxide.

(2) 30.4 g., b.p. 54–58° (20 mm.), was essentially all triethyl phosphite.

Anal. Found: P, 18.2.

(3) 86 g. (59.5%), b.p. 58–108° (mostly 97–108°) (20 mm.), was nearly all phosphate.

Anal. Found: P, 17.2.

(4) 14.7 g., residue, was mostly phosphate with some unidentified higher boiling material.

Anal. Found: P, 14.9.

Identification of products. The gas samples were analyzed by mass spectrometry. The phosphorus compounds were identified by boiling point differences, elemental analyses, and infrared spectra. The spectra were particularly helpful because the elemental analyses occasionally were erratic due to the formation of solid masses that resisted combustion.

Triethyl phosphate has a very characteristic, strong absorption peak at 7.86–7.95 μ which is attributed to the P=O stretching motion.[9] In addition, there is a very strong absorption at 10.30 μ. This latter absorption is subject to some discussion,[9–11] but apparently it is due to the P—O stretching in the P—O—C structure of trialkyl phosphates.

The phosphites, of course, do not have the P=O absorption at 7.86–7.95μ. In triethyl phosphite the peak at 10.30μ is absent also, but there is a comparable, very strong absorption at 10.84μ. Although little is known about this peak, it seems reasonable to believe that it is caused by the P—O stretching in P—O—C structures of phosphites.

The large peaks in the 10.00- to 10.84-μ range are particularly helpful in analyzing mixtures of phosphites and phosphates. They are of essentially equal intensity, so the relative sizes shown in the spectrum of a mixture are a good indication of the composition of that mixture.

Known, redistilled samples of phosphite and phosphate were used as standards in the spectral work.

Acknowledgment. The author is grateful to the Union Oil Co. of California for permission to publish this work, to Messrs. D. O. Alford and A. Menefee for the spectral studies, and to Mr. S. V. Vande-

(1) I. S. Bengelsdorf, *J. Org. Chem.*, **21**, 475 (1956), and references therein cited.

(2) M. A. Greenbaum, D. B. Denney, and A. K. Hoffman, *J. Am. Chem. Soc.*, **78**, 2563 (1956).

(3) L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, No. 15, 473 (1956), and references therein cited.

(4) F. W. Hoffmann, T. B. Moore, and B. Kagan, *J. Am. Chem. Soc.*, **78**, 6413 (1956).

(5) F. W. Hoffmann, R. J. Ess, T. C. Simmons, and R. S. Hanzel, *J. Am. Chem. Soc.*, **78**, 6414 (1956).

(6) J. F. Allen and O. H. Johnson, *J. Am. Chem. Soc.*, **77**, 2871 (1955).

(7) G. Wittig, *Angew. Chem.*, **68**, 505 (1956).

(8) G. Wittig, *Experentia*, **12**, 41 (1956).

(9) L. J. Bellamy, *Infrared Spectra of Complex Molecules*, p. 257, John Wiley and Sons, New York, N. Y., 1954.

(10) P. E. Carbridge and E. J. Lowe, *J. Chem. Soc.*, **1954**, 4555.

(11) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, **1952**, 475.

grift for capable assistance with the experimental sections.

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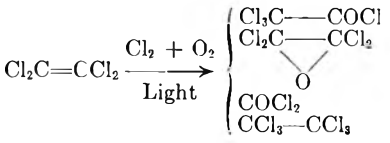
Preparation and Properties of Tetrachloroethylene Oxide

DONALD M. FRANKEL, CLAUDE E. JOHNSON, AND HAROLD M. PITT

Received February 18, 1957

The photochemical oxidation of tetrachloroethylene has been studied by several previous investigators.[1-8] The primary object of these workers was the preparation of trichloroacetyl chloride, with only one making reference to tetrachloroethylene oxide as a byproduct.[5,6]

In the present study, tetrachloroethylene, kept saturated with oxygen and with an excess of chlorine added, was exposed to sunlight at 36–40°. Under these conditions the following products were obtained: trichloroacetyl chloride, tetrachloroethylene oxide, phosgene, and hexachloroethane.

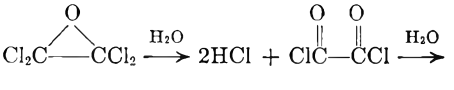


After most of the phosgene was removed, under vacuum, at room temperature, analysis of the liquor was 40 mole per cent trichloroacetyl chloride, 9 mole per cent tetrachloroethylene oxide, 8 mole per cent hexachloroethane, and 43 mole per cent tetrachloroethylene.

Vacuum distillation through a helices-packed, five-foot, distillation column gave a solution whose analysis showed it to contain 40 mole per cent trichloroacetyl chloride, 54 mole per cent tetrachloroethylene oxide, and 6 mole per cent tetrachloroethylene. Trichloroacetyl chloride was removed from this solution by washing with dilute alkali. The tetrachloroethylene was converted, by addition of chlorine, to hexachloroethane, then the solution vacuum distilled through a short, center rod column. A trace of trichloroacetyl chloride was removed with a dilute alkali wash, then the purified tetrachloroethylene oxide dried with calcium chloride. The infrared spectrum (Fig. 1) shows that the material is free from trichloroacetyl chloride, tetrachloroethylene, and hexachloroethane. The photochemical oxidation was repeated at −3–0°, 60–75°, and at 80°. The highest yield of tetrachloroethylene oxide was obtained at 60–75°.

Tetrachloroethylene oxide rearranges to trichloroacetyl chloride upon heating. The specific reaction rates for this conversion at 65°, 80°, and 100° are 6×10^{-7}, 8.9×10^{-6}, and 1.2×10^{-4} sec.$^{-1}$, respectively. The energy of activation is approximately 31.4 kcal./mole.

Tetrachloroethylene oxide reacts readily with methanol in the presence of mercuric chloride, evolving hydrogen chloride and forming methyl trichloroacetate. It reacts rapidly with *N* potassium hydroxide in methanol to give potassium oxalate as the major product. When stirred with either dilute basic or acidic aqueous solutions, the epoxide very slowly partially rearranges to its isomer and partially decomposes to give carbon monoxide, carbon dioxide, and hydrogen chloride. The latter reaction probably forms oxalyl chloride as an intermediate, which then hydrolyses to carbon monoxide, carbon dioxide, and hydrogen chloride.[9] In concentrated



sulfuric acid, however, tetrachloroethylene oxide undergoes rapid and exothermic rearrangement to trichloroacetyl chloride.

EXPERIMENTAL[10]

Photochemical oxidation of tetrachloroethylene. The reactor was made from two sections of borosilicate glass pipe, 2 ft. long by 3 in. diameter, joined together at both ends by 3 in. pipe. The lower section contained a cold finger, while a plane-parabolic mirror of 8 sq. ft. was focused on the upper section. The reactor was charged with 3 gal. of commercial grade (Stauffer) tetrachloroethylene, excess oxygen and chlorine were added, and the solution was agitated and exposed to sunlight for 12 hr. The temperature was controlled at 36–40°. Phosgene was removed by aspiration. Infrared analysis of the solution showed: 40% CCl_3COCl, 9% $(CCl_2)_2O$, 43% C_2Cl_4, 8% C_2Cl_6 (mole %).

Separation of tetrachloroethylene oxide. The solution was distilled through a 5-ft., vacuum-jacketed distilling column of 1-in. diameter, packed with 1/8 inch borosilicate glass helices. Using a reflux/take-off ratio of 30/1, 310 ml., boiling 32–36.3° (45 mm.–38 mm.), was collected in 23 hr. Infrared analysis of the distillate showed: 40% CCl_3COCl, 54% $(CCl_2)_2O$, 6% C_2Cl_4 (mole %).

Trichloroacetyl chloride was removed by washing with dilute aqueous alkali. Tetrachloroethylene was chlorinated

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(10) Infrared analyses were made on a Perkin-Elmer Model 21 Spectrophotometer.

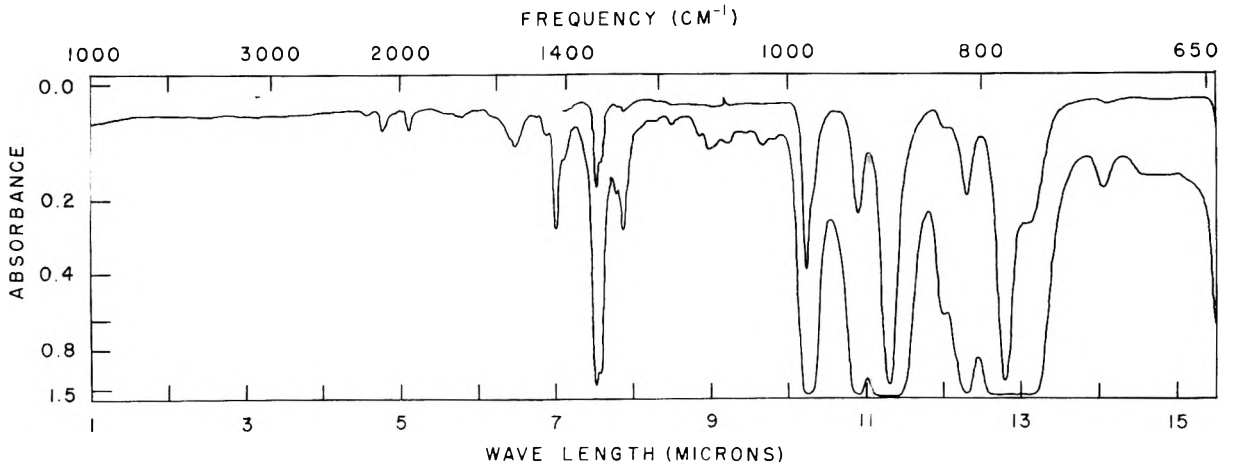

FIG. 1. INFRARED SPECTRA OF TETRACHLOROETHYLENE OXIDE; Determined on the pure liquid in a 0.0273 mm. cell; and a 2.5% carbon disulfide solution in a 0.109 mm. cell (10–14 microns).

to hexachloroethane by addition of chlorine and exposure to sunlight. This solution was distilled through an 18-in., modified center-rod column at 40° (65 mm.). A trace of trichloroacetyl chloride was removed with a caustic-water wash and the material was dried with calcium chloride. One hundred ml. of purified tetrachloroethylene oxide was recovered, n_D^{25} 1.4588, d_4^{25} 1.63, b.p. *ca.* 110° (1 atm.), f.p. −58° to −59° (corr.). Molecular weight, by freezing point depression of benzene, was 189 (theoretical 182). Boiling point data are in Table I.

Anal. Calcd. for C_2Cl_4O: Cl, 78.0%. Found 77.5%.

TABLE I

BOILING POINT DATA OF TETRACHLOROETHYLENE OXIDE

Pressure, Mm.	Temperature, ° C.
50	35.2
100	50.8
150	60.3
200	68.5
250	74.5
760 (Extrapolated)	109

Oxidation of tetrachloroethylene at various temperatures. Chlorine and oxygen were continuously passed through 35–40 ml. tetrachloroethylene in a 50–60 ml. glass bulb with the solution exposed to sunlight. Temperature was controlled externally. The results are given in Table II.

TABLE II

OXIDATION OF TETRACHLOROETHYLENE AT VARIOUS TEMPERATURES

Temperature, ° C.	Reaction Time (Min.)	$(CCl_2)_2O$, Vol. %	CCl_3COCl, Vol. %
−3–0	30	Trace	7
60–75	30	5	16
80	25	6[a]	20[a]

(a) Results are analyses of filtrate after the solution was cooled and filtered to remove excess hexachloroethane. Filtrate contained 21% C_2Cl_6.

Thermal rearrangement. Tubes containing the epoxide were immersed in boiling baths of methanol (65°), benzene (80°), and water (100°). The solutions were analyzed by infrared at 1-hr. intervals.

Reactions. A. Tetrachloroethylene oxide (9×10^{-3} mole) was stirred with 1*N* sodium hydroxide solution. A gas slowly evolved (5×10^{-4} mole) which was identified by infrared analysis to be carbon monoxide. The solution was extracted with carbon disulfide and tests for chloride and trichloroacetate on the extract were positive.[11]

B. Tetrachloroethylene oxide (9×10^{-3} mole) was stirred with 12*N* sulfuric acid, evolving a gas (3.5×10^{-3} mole) whose infrared analysis showed it to contain carbon monoxide and carbon dioxide. The acid solution contained 1.45×10^{-2} equivalent of chloride.

C. Tetrachloroethylene oxide, stirred with 96% H_2SO_4, reacted rapidly (exothermic) without evolution of gas. Infrared analysis of the acid-insoluble layer showed it to be trichloroacetyl chloride.

D. Tetrachloroethylene oxide (2.2×10^{-3} mole) was dissolved in 1*N* potassium hydroxide-methanol solution. The solution was acidified with hydrochloric acid, then boiled to remove the methanol and excess hydrogen chloride. Saturated barium chloride solution was added and a precipitate (0.37 g.) was collected. This product was undoubtedly barium oxalate, and corresponded to 1.65×10^{-3} mole of the latter.

E. With methanol containing a small amount of mercuric chloride, tetrachloroethylene oxide undergoes a rapid exothermic reaction after an induction period of a few minutes. The infrared spectrum of the reaction product is almost identical to that of methyl trichloroacetate.

Acknowledgment. The authors express thanks to Dr. Norman Kharasch, University of Southern California, for helpful discussions and criticisms.

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(11) $AgNO_3$ was used for chloride test; cuprous chloride and ammonia for trichloroacetate test.

A Crystalline Monoprocaine Salt of Pyridoxal Phosphate

ANDREW N. WILSON

Received February 18, 1957

Pyridoxal phosphate is a coenzyme involved in transamination processes, in amino acid decar-

boxylation, in thioether cleavage, and in other enzymatic reactions. Crystalline sodium[1,2] and acridine[3] salts have been reported. We should like to describe here the preparation of a crystalline monoprocaine salt of the coenzyme.

Pyridoxamine dihydrochloride was phosphorylated with a mixture of phosphoric acid and phosphorus pentoxide,[4] and the product was isolated in crystalline form[5] by means of ion-exchange chromatography on Amberlite resin IRC-50. The pyridoxamine phosphate was oxidized to pyridoxal phosphate by manganese dioxide in aqueous solution at *p*H 6. The coenzyme was separated from inorganic compounds and was obtained as a bright yellow solid[2] by drying its aqueous solution in the frozen state.

The procaine salt was prepared by dissolving pyridoxal phosphate in water and adding to the solution an ethanolic solution of one equivalent of procaine. The procaine salt of pyridoxal phosphate crystallized in the form of orange needles.

Bioassay of the crystalline monoprocaine salt of pyridoxal phosphate by Dr. W. W. Umbreit of the Merck Institute for Therapeutic Research using a tyrosine-decarboxylase system indicated that the theoretical amount of coenzyme was present.

The procaine salt of pyridoxal phosphate is more stable than the calcium salt. The calcium salt, kept in a desiccator in the dark for $4^1/_2$ years, lost 60% of its codecarboxylase activity; the procaine salt, stored under similar conditions for $1^1/_2$ years, retained full codecarboxylase activity.

EXPERIMENTAL

Pyridoxal phosphate. One g. of pyridoxamine phosphate was dissolved in 84 ml. of 0.1*N* sulfuric acid. Manganese dioxide (0.4 g.) was added, and the mixture was stirred and heated at 65–75° for 1 hr. The reaction mixture was cooled and filtered. The filtrate was passed through a column of Amberlite resin IR-120 (H^+ cycle), and the column was washed with water. The eluate was treated with enough barium hydroxide to neutralize the sulfuric acid, and the precipitate of barium sulfate was removed. The filtrate was concentrated to about 100 ml. at reduced pressure and at a temperature below 40°. The concentrate was filtered through Super-Cel and was dried in the frozen state, giving 0.75 g. of pyridoxal phosphate.

Pyridoxal phosphate procaine salt. One hundred mg. of pyridoxal phosphate was dissolved in 3 ml. of water. To this solution was added 96 mg. (1 equivalent) of procaine, dissolved in 3 ml. of ethanol. The reaction mixture was chilled for several days in the refrigerator, and 120 mg. (60%) of the procaine salt of pyridoxal phosphate separated. Two recrystallizations from 50% water-ethanol (85% recovery) provided a sample of m.p. 150° (dec.), $\lambda_{max}^{0.1N\ NaOH}$ 275 mμ (ε16,000) and 390 mμ (ε6800). The sample was dried at 25°/0.1 mm. for analysis.

Anal. Calcd. for $C_{21}H_{30}N_3O_8P$: C, 52.17; H, 6.26, N, 8.69; P, 6.41. Found: C, 51.72; H, 6.32; N, 8.81; P, 6.24.

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Direct Preparation of Aryllithium Compounds from Aryl Fluorides

HENRY GILMAN AND THEODORE S. SODDY

Received February 21, 1957

The investigation of Wittig and coworkers, which was concerned with the preparation of organolithium derivatives from aryl fluorides, was confined to the metalation of fluoroaromatics with phenyllithium.[1–4] More recently, some success in the preparation of fluoroaryllithium derivatives from the halogen-metal interconversion reaction has been reported from this laboratory.[5] The attempts, however, to prepare the aryllithium compound directly from an aryl fluoride and lithium met with some success. By refluxing lithium ribbon and fluorobenzene in diethyl ether for 24 hours, 0.7% of benzoic acid was obtained on carbonation.[6] Benzoic acid was obtained in 0.5% yield when fluorobenzene and lithium dispersion were refluxed in diethyl ether for 5 hours and then carbonated.[6]

The first attempt to prepare aryllithium compounds from aryl fluorides and lithium in tetrahydrofuran under reflux conditions was unsuccessful.[6] Recently, it was reported that benzoic acid was obtained in a yield of 54% from chlorobenzene and lithium in tetrahydrofuran on carbonation.[7] The preparation of α-naphthyllithium from α-fluoronaphthalene and lithium wire in tetrahydrofuran illustrated the importance of solvent and temperature control in these reactions. On carbonation of α-naphthyllithium, 23% of crude α-naphthoic acid was obtained. Although the initiation of this reaction did not require a catalyst, the reaction which involved fluorobenzene and *p*-fluorotoluene would not commence until their respective bromo analogs were added. The yields of phenyl- and *p*-tolyllith-

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ium, which were based on the crude acids that were obtained on carbonation, averaged 50%, and one preparation of *p*-tolyllithium was 80%. In this particular run the higher yield may have been due to a better initiation of the reaction.

Since other experiments were run which gave little or no acid, the authors are led to believe that the conditions which are presented in the experimental should be followed carefully in order to insure successful preparation of the aryllithium compounds from aryl fluorides.

EXPERIMENTAL[8]

α-Fluoronaphthalene and lithium in tetrahydrofuran. Method A. Into a 500-ml., 3-necked, round-bottomed flask were placed 100 ml. of anhydrous tetrahydrofuran[9] and 0.22 g.-atom of lithium wire. This suspension was cooled by means of an ice bath to 2°, and 14.5 g. (0.1 mole) of α-fluoronaphthalene in 50 ml. of tetrahydrofuran was added dropwise. After the addition of 10 ml. no reaction occurred. A few drops of bromobenzene were added as a catalyst. When the reaction still failed to begin, the reaction mixture was warmed to room temperature, 3 more drops of bromobenzene and the remainder of the α-fluoronaphthalene were added, but no indication of a reaction was discernible. The reaction mixture was warmed to 45°. The color turned yellow, green, and then black. The lithium wire became bright, and the reaction flask had to be cooled with an ice bath to prevent the reaction from becoming too violent. When the vigorous reaction had ceased, the reaction mixture was carbonated by pouring it jetwise onto a Dry-Ice–ether slurry. The basic extract on acidification yielded no acid. The neutral layer was concentrated, and the residue was sublimed under reduced pressure. Naphthalene was obtained in a yield of 1.5 g. (10%). A mixture melting point with an authentic speciman was undepressed.

Method B. Into a 500-ml. flask were placed 50 ml. of tetrahydrofuran, 0.22 g.-atom of lithium wire and 4 g. of α-fluoronaphthalene. After 5 min. the color became light green. The temperature of the reaction mixture rose from 24° to 28° over a period of 10 min. The color became darker green and a small amount of black particles separated. The reaction mixture was cooled to −10° as the remaining 10 ml. of α-fluoronaphthalene, which had been diluted with 10 ml. of tetrahydrofuran, were added. The color became black, and the lithium wire coated. After the addition was completed, the reaction mixture was stirred for about 25 min. at the same temperature and then carbonated. The basic extract on acidification yielded 4 g. (23%) of crude α-naphthoic acid which melted between 120–140°. The pure acid on recrystallization from an ethanol-water pair melted at 158–159°. (lit. value 159–160°). The yield was 1 g. (6%).

Fluorobenzene and lithium in tetrahydrofuran. Method A. Into a flask, which contained 50 ml. of tetrahydrofuran and 0.22 g.-atom of lithium wire at 24°, was placed 4 g. of fluorobenzene. A few drops of bromobenzene were added as a catalyst, and after being stirred for 15 min., a noticeable increase was observed in the temperature of the reaction mixture. When the temperature had risen to 28°, a Dry-Ice–acetone bath was employed to lower the temperature to −10°. The color of the reaction mixture became red as the remaining 6 g. (6 ml.) of fluorobenzene was added dropwise over a 5-min. period. The temperature was kept between 0 and −10°. When the reaction was completed, the reaction mixture was so viscous that 50 ml. of tetrahydrofuran was added to insure sufficient fluidity for carbonation purposes. The carbonation was carried out in the usual manner. On acidification of the basic extract, the crude benzoic acid was obtained in a yield of 6 g. (50%). The melting point was 115–117°. The pure acid on crystallization from water melted at 119–120°, and the yield was 4 g. (33.3%). A mixed melting point with an authentic sample of benzoic acid was undepressed.

Method B. The reaction was repeated again under the same conditions as that described above except that, after the reaction was initiated, the remaining 6 g. of fluorobenzene was diluted to twice its volume with the solvent, prior to addition. The yield of crude acid was only 29%.

p-Fluorotoluene and lithium in tetrahydrofuran. This reaction was run in the same manner as described in Method A for fluorobenzene. The yield of crude acid was 10.8 g. (80%) and melted between 171–174°. The pure acid melted at 176–177°, and the yield was 9.1 g. (70%). A triple melting point with an authentic sample of *p*-toluic acid was undepressed. This reaction was repeated under the same conditions, but the yield in this case was only 50%. In another run, the conditions that were used were identical with those employed in Method B for fluorobenzene. The yield of crude acid was 50%.

This work was supported by the United States Atomic Energy Commission under contract No. AT(11-1)-59, and the reactions were used in connection with organic liquid solution scintillators to be evaluated by Dr. Wright Langham and coworkers at Los Alamos.

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(8) All melting points are uncorrected, and all reactions were carried out in an atmosphere of dry, oxygen-free nitrogen.

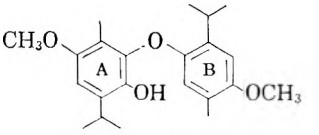
(9) The tetrahydrofuran was dried and purified by first shaking with sodium hydroxide pellets, refluxing over sodium metal for several hours, and finally distilling, immediately before use, from lithium aluminum hydride.

Extractive Components from Incense Cedar Heartwood. V. (*Libocedrus decurrens* Torrey.) Synthesis of Libocedrol

EUGENE ZAVARIN AND ARTHUR B. ANDERSON

Received February 22, 1957

In determining the structure of libocedrol,[1] 2-hydroxy-4′,5-dimethoxy-5′,6-dimethyl-2′,3-di-*iso*-propyldiphenyl ether (I), the question of which one of the two hydroxy groups was methylated was resolved by assuming that libocedrol was formed by oxidative coupling of two parent phenolic units. Since this takes place *ortho* or *para* to hydroxyl, the libocedrol molecule was held to be composed of two *p*-methoxythymol units *i.e.*, the 2- hydroxy group was assumed to be methylated. It was felt desirable to substantiate the above deduction by synthesis.



I

(1) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, 20, 788 (1955).

It has long been known that alkaline ferricyanide solutions bring about the oxidation of phenolic compounds.[2,3] When *p*-methoxythymol was submitted to the ferricyanide reaction, a 49% yield of libocedrol was obtained with 20% recovery of the starting material. The identity of the synthetic material with the naturally occurring compound was established by examination of the infrared absorption spectra and by the mixed melting points of the compounds themselves as well as their *p*-methoxythymol addition complexes, *p*-nitrobenzoates, and benzoates.

It has been stated frequently that oxidative coupling of phenolic substances plays an important role in biosynthesis. Thus, it has been established that several lignans can be obtained by ferric chloride,[4–6] ammonium persulfate,[6] or enzymatic coupling[7,8] of the parent phenolic units, and it has been suggested that the lignans may be formed in a similar manner in wood.[9–11] It also has been demonstrated that the same reaction is very likely responsible for the formation of lignin in plants.[12] The formation of thyroxine[13] and of dehydrodigallic acid[14] was ascribed to similar biosynthetic paths.

Cousin and Herissey, working with mushroom dehydrogenase, established that carvacrol and thymol are able to undergo oxidation under these conditions. Dehydrodithymol was isolated from the reaction mixture in the second case.[15,16] However, so far as we are aware, no coupling product of phenolic compounds with *p*-cymene carbon skeleton has been isolated from a natural source. The structure of libocedrol suggests it is the first member of a new group of naturally occurring compounds that, as far as their biosynthesis is concerned, can be regarded as the products of the oxidative coupling of the *p*-cymene type phenols in the same way that lignans are regarded as derived from *n*-propylbenzene-type phenols. The occurrence of the mixed-type compounds represents another probability.

EXPERIMENTAL[17]

p-Methoxythymol.[18] Hydrothymoquinone (96.0 g., m.p. 142–143°C.) was added to a solution of 3.5 g. of sodium hydrosulfite in 400 ml. of 10% sodium hydroxide in a separatory funnel filled with nitrogen and equipped with a stirrer. To this mixture was added 90 g. of commercial dimethyl sulfate in 10 portions. The formation of the dimethylation product was minimized by extracting the monomethylated hydrothymoquinone from the reaction mixture. Thus, after addition of each portion, the mixture was stirred for 5 min., then 100 ml. of chloroform was added, stirred, and the organic phase removed. Hydrothymoquinone itself is not extractable under these conditions. After all of the dimethyl sulfate was added, the aqueous portion was acidified and extracted with 100 ml. of chloroform. The extracts were filtered from the unreacted hydrothymoquinone that separated at this point. The latter weighed 5 g. and melted at 144–145° C. All of the chloroform extracts were combined, dried over sodium sulfate, and filtered. The solvent was removed by evaporation. The residue was dissolved in 300 ml. of petroleum ether and extracted 6 times with 100 ml. portions of 10% sodium hydroxide. The organic phase was dried, the solvent removed by evaporation, and the residue distilled. The main fraction was collected between 70 and 90° C. at 0.03 mm. It weighed 11.1 g., n_D^{24} 1.5119, and was composed mainly of dimethylhydrothymoquinone.[19]

The sodium hydroxide extract was acidified and extracted with ethyl ether in several portions. The ether extract was dried, the solvent evaporated, and the residue crystallized from 400 ml. of petroleum ether at −5° C. to give 26.4 g. of *p*-methoxycarvacrol, m.p. 63–64° C. The filtrate was evaporated to dryness and the residue was benzoylated in the usual manner. Crystallization of the benzoate mixture from 250 ml. of methanol at −5° C. gave 37.4 g. of *p*-methoxythymol benzoate, m.p. 85–86° C. The filtrate was hydrolyzed by adding 7.0 g. of sodium hydroxide and refluxing for 1 hr. on a steam bath. The resulting mixture was cooled and neutralized with gaseous CO_2. The methanol was evaporated, the residue was dissolved in 150 ml. of water, and extracted with petroleum ether in several portions. The petroleum ether extract was dried over sodium sulfate, filtered, and upon evaporation of the solvent, the residue was crystallized from 125 ml. of petroleum ether at −5° C. to give an additional 9.5 g. of *p*-methoxycarvacrol, m.p. 65–66° C. Repetition of the benzoylation procedure gave an additional crop of 8.3 g. of *p*-methoxythymol benzoate, m.p. 84–85° C. Residue from benzoylation, weighed after removal of the solvent, was 19.0 g.; further separation was not attempted. Thus, there were obtained: 5 g. of unreacted hydrothymoquinone benzoate (5%), 35.9 g. *p*-methoxycarvacrol (34.5%), 45.7 g. *p*-methoxythymol benzoate (28%), 11.1 g. of dimethylhydrothymoquinone (10%), and 19.0 g. of unseparated monobenzoates (11.5%). To obtain *p*-methoxythymol, its benzoate was hydrolyzed with alcoholic alkali as described.[18]

Libocedrol. *p*-Methoxythymol (2.107 g., n_D^{24} 1.5228) was dissolved in 50 ml. of 8% sodium hydroxide solution. To the resulting liquid was added 50 ml. of carbon tetrachloride and the mixture was vigorously stirred. A solution of 5.0 g. of potassium ferricyanide in 100 ml. of water was then added dropwise to the point at which the aqueous phase assumed a yellowish color and no white emulsion formed around the drops of ferricyanide solution. The addition took about 1 hr. at the rate of 20 drops per min. The mixture was then trans-

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ferred into a separatory funnel, acidified with hydrochloric acid, and shaken. The slightly yellow organic phase was separated, the aqueous solution was washed with 60 ml. of chloroform, and the chloroform was combined with the carbon tetrachloride solution. The resulting liquid was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from petroleum ether at −5° C. to give 1.273 g. of white crystals, m.p. 88–89° C. Further crystallization raised the melting point to 90–91° C. The melting point was undepressed upon admixture with libocedrol *p*-methoxythymol adduct. The material was separated using the previously described procedure[1] into libocedrol, m.p. 86–87° C., and *p*-methoxythymol characterized as its *p*-nitrobenzoate, m.p. 126–127° C.; both melting points were undepressed on admixture with authentic samples.

The filtrate was diluted to 30 ml. with petroleum ether and extracted with 150 ml. of 5% sodium hydroxide in 3 portions. The petroleum ether solution was dried and evaporated to dryness. The residue was heated on a steam bath with 1.0 g. of *p*-nitrobenzoyl chloride in 5 ml. of pyridine, cooled, and treated with 25 ml. of 10% bicarbonate solution and 50 ml. of ethyl ether. The ethyl ether solution was washed with 50 ml. of 10% sodium carbonate and 50 ml. of 10% hydrochloric acid, dried, and evaporated to dryness. The residue was crystallized from methanol to give 244 mg. of libocedrol *p*-nitrobenzoate, m.p. 165–170° C. (8%). Further crystallization from isooctane followed by crystallization from methanol raised the melting point to 174–175° C., undepressed on admixture with an authentic sample.

The sodium hydroxide extracts were combined, acidified with hydrochloric acid, and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate, filtered, evaporated to dryness, and *p*-nitrobenzoylated in the usual manner to give a very small amount of material of indefinite melting point which was not further investigated.

Thus, the reaction gave 1.020 g. (49%) of libocedrol and 0.425 g. (20%) of the original material.

Comparison of the infrared spectra of the synthetic libocedrol and the naturally occurring material revealed that they were identical. Also the benzoylation of the synthetic libocedrol[11] gave a benzoate, m.p. 137–138° C., which did not depress the melting point of the naturally occurring libocedrol benzoate.

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Bromination Rates of Some Norcamphor Derivatives[1]

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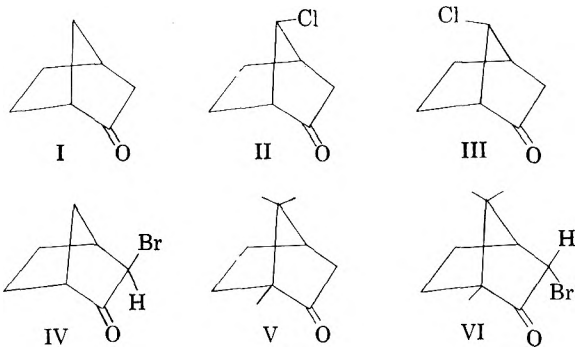
In continuation of earlier work on the effect of structure on reactivity in the norbornyl system,[3] a study has been made of the sodium acetate-catalyzed rates of bromination of norcamphor (I), *syn*- and *anti*-7-chloronorcamphor (II and III), *exo*-3-bromonorcamphor (IV), *d*-camphor (V) and *endo*-3-bromo-*d*-camphor (VI).

Ketones I, II, and III were prepared from the corresponding *exo*-norborneols by chromic acid oxidation, a method found to be superior to nitric acid oxidation.[4] I–III were purified by regeneration from their pure semicarbazones by steam distillation from oxalic acid solution. *d*-Camphor (V) was brominated under acid-catalyzed conditions[5] to give



VI, whose structure has been unequivocally established by an x-ray crystal structure determination.[6,7] *exo*-3-Bromonorcamphor (IV) was prepared by a similar method. In addition to the kinetic argument given below, the *exo*-configuration assigned to the bromine atom of IV was consistent with a comparison of its ultraviolet absorption with those of VI and its *exo*-isomer (Table I).

TABLE I

ULTRAVIOLET SPECTRAL DATA[a]

Ketone	Solvent	λ_{max} Mμ	ε
d-Camphor(V)	95% EtOH	289.5[b]	32
	cyclo-C_6H_{12}	292[b]	23
exo-3-Bromo-*d*-camphor	*cyclo*-C_6H_{12}	312[b]	89
endo-3-Bromo-*d*-camphor(VI)	95% EtOH	306[b]	100
	cyclo-C_6H_{12}	307.5[b]	95.5
Norcamphor(I)	95% EtOH	287	30.9
exo-3-Bromo-norcamphor(IV)	95% EtOH	312	84.4
	cyclo-C_6H_{12}	317	73.2

[a] Determined with a Cary Model 11M recording spectrophotometer using 1-cm. quartz cells. [b] R. C. Cookson, *J. Chem. Soc.*, 1954, 282 and references cited therein.

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(3) (a) J. D. Roberts, W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3329 (1950). (b) J. D. Roberts and W. Bennett, *J. Am. Chem. Soc.*, **76**, 4623 (1954). (c) W. G. Woods, R. A. Carboni, and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 5653 (1956).

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(5) F. S. Kipping and W. J. Pope, *J. Chem. Soc.*, **63**, 576 (1893).

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(7) E. H. Wiebenga and C. J. Krom, *Rec. trav. chim.*, **65**, 663 (1946).

Kinetic measurements. The kinetics of the ketone brominations were measured using the methods of Evans and coworkers.[8,9] Pseudo-first order rates of bromination were determined at 35° in 75% aqueous acetic acid containing 0.238*M* sodium acetate, prepared by diluting 750 ml. of purified acetic acid to 1000 ml. with conductivity water, all at 35°. The low reactivities of the ketones necessitated a correction for the bromine-solvent reaction. The rate of disappearance of bromine in the absence of ketone was cleanly first order and a least-squares fit of the data gave $2.656 \pm 0.056 \times 10^{-7}$ sec.$^{-1}$ for the rate constant at 35°.

Since the rate of the bromine-solvent reaction was of the same order of magnitude as the ketone bromination rates, the rate data were treated in the following semiempirical manner.

Let: [B] = concentration of bromine at time t.
[B_0] = initial concentration of bromine.
[K] = concentration of ketone at time t.
[K_0] = initial concentration of ketone.
k' = rate constant for the bromine-solvent reaction.
k = rate constant for the ketone bromination.

The total rate of disappearance of bromine is given by Equation 1 and that of ketone by Equation 2. Integration of Equation 2 yields Equation 3 for the concentration of ketone at time t. It was

$$\frac{d[B]}{dt} = -k'[B] - k[K] \quad (1)$$

$$\frac{d[K]}{dt} = -k[K] \quad (2)$$

$$[K] = e^{(\ln[K_0] - kt)} \quad (3)$$

found that plots of log ([K_0] − [B_0] + [B]) *vs.* times were strictly linear, except for a minor curvature in the early stages of the reaction. This linearity is expressed by Equation 4 which yields Equation 5 on integration.

$$\frac{d \ln ([K_0] - [B_0] + [B])}{dt} = -c \quad (4)$$

$$\ln \frac{[K_0] - [B_0] + [B]}{[K_0]} = -ct \quad (5)$$

Rearrangement and differentiation of Equation 5 gives Equation 6 for the slope at any time t. Substituting Equation 3 and Equation 6 into Equation 1 gives Equation 7, which allows the evaluation of k

$$\frac{d[B]}{dt} = -[K_0]ce^{-ct} \quad (6)$$

$$ke^{(\ln[K_0] - kt)} = [K_0]ce^{-ct} - k'[B] \quad (7)$$

for various pairs of [B] and t values, since [K_0] c and k' are known. A typical set of data is given in Table II.

TABLE II

ANALYSIS OF KINETIC DATA FOR THE BROMINATION OF NORCAMPHOR AT 35° IN 75% ACETIC ACID (0.238*M* IN SODIUM ACETATE)

10^5t, sec.	10^2[B], mol. l.$^{-1}$	10^9d[B]/dt, mol. l.$^{-1}$ sec.$^{-1}$	10^7k, sec.$^{-1}$
0.000	(1.1066)[a]	−5.619	0.98
0.012	1.1055	...	...
0.037	1.0995	...	...
0.133	1.0935	−5.611	0.99
1.800	1.0025	−5.413	1.03
3.586	0.9095	−5.219	1.07
5.301	0.8314	−5.038	1.10
6.971	0.7384	−4.868	1.15

[a] Evaluated by least squares, $c = 2.058 \times 10^{-7}$ sec.$^{-1}$.

As expected from the results of other workers,[9] the k values are found to increase slowly with time, presumably due to further bromination. However, the rate constants could be evaluated with assurance at zero time and are reported in Table III for ketones I–VI.

It has been well established[10] that the rate-determining step in the base-catalyzed bromination of ketones is the removal of the α-hydrogen by the base to give an enolate ion. This enolate ion then rapidly reacts with bromine to give the α-bromoketone. The results in Table III appear to reflect the

TABLE III

PSEUDO-FIRST ORDER BROMINATION RATE CONSTANTS AT 35° IN 75% ACETIC ACID CONTAINING 0.238*M* SODIUM ACETATE

Ketone	K_0, *M*	10^8k, sec.$^{-1}$	Rel. *l*
Norcamphor(I)	0.0273	9.8 ± 0.7	1.00
syn-7-Chloro-norcamphor(II)	0.0173	3.2 ± 0.5	0.3
anti-7-Chloro-norcamphor(III)	0.0174	11.5 ± 0.6	1.2
exo-3-Bromo-norcamphor(IV)	0.0181	2.7 ± 0.4	0.3
d-Camphor(V)	0.0217	<0.28[a]	0.03
endo-3-Bromo-*d*-camphor(VI)	0.0161	5.2 ± 0.7	0.5

[a] Upper limit of experimental error.

importance of steric effects in determining the reactivity of the α-hydrogen atoms of norcamphor derivatives towards acetate ion.

The *exo*-α-hydrogens are apparently attacked faster than the *endo*-α-hydrogens since II is substantially less reactive than either I or III. If the *endo*-α-hydrogens were attacked initially, I, II, and

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(9) T. G. Bonner, D. P. Evans, and H. B. Watson, *J. Chem. Soc.*, 1939, 1353.

(10) C. K. Ingold, "*Structure and Mechanism in Organic Chemistry*," Cornell University Press, Ithaca, N. Y., 1953, pp. 570-71.

III would be expected, in the absence of polar effects, to react at about the same rate. The slightly increased rate of III relative to I is consistent with a small polar effect of the remote *anti*-7-chlorine atom. The threefold decrease in the rate of II relative to I is most simply interpreted as the result of steric shielding of the *exo*-3-hydrogen atom by the *syn*-7-chlorine atom. Partial substantiation of this interpretation is given by the extremely low relative rate of V, presumably due to steric inhibition of *exo*-attack by the *syn*-7-methyl group and the combined inductive (+I) effect of all three methyl groups.

The very high rate of VI relative to V is in agreement with the observation[11] that the introduction of one α-bromine atom generally greatly increases the base-catalyzed rate of bromination of aliphatic ketones. However, IV is found to be less reactive than I, which indicates that steric interference has overcome the accelerating effect expected from the α-bromine atom. Taken with the previous discussion, this result leads to the conclusion that IV is, indeed, *exo*-3-bromonorcamphor.

Although one might find it difficult to predict *a priori* that the *exo*-hydrogens should be more easily removed by base than *endo*-hydrogens, it is of interest to note that the additions of chlorine, hypochlorous acid and bromine[4,12] to norbornene are initiated by *exo* attack on the double bond. A similar *exo* attack of bromine on the enol of I accounts for the formation IV as the acid-catalyzed bromination product of norcamphor (see Experimental).

In an effort to evaluate the relative reactivities of *exo*- and *endo*-hydrogens to attack by base, an attempt was made to prepare *endo*-3-bromonorcamphor(VII). Brief boiling of an ethanolic solution of IV with a catalytic amount of sodium ethoxide[13,14] gave a solution whose ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 307.4 mμ, ϵ 70–79 was different from that of IV and suggested (See Table I) that isomerization to VII had occurred. However, experiments on a preparative scale yielded only impure material of unknown composition.

Preliminary measurements were made of the rates of bromination of I and IV in aqueous sodium hypobromite solution.[11,15] The second order rate constant of I was found to drift upward as the reaction progressed while that of IV decreased with time. Although the kinetic data were of little value in evaluating relative reactivities, infinity titers showed that I ultimately consumed three moles of bromine per mole of ketone and IV consumed two moles of bromine. A preparative scale experiment with I afforded a liquid acidic compound which formed an amide containing bromine but was not investigated further.

EXPERIMENTAL

Norcamphor (I). To an ice-cooled, stirred solution of 99.5 g. (0.338 mole) of potassium dichromate, 136 g. of concentrated sulfuric acid and 600 ml. of glacial acetic acid in 1500 ml. of water, was added 115 g. (1.025 mole) of *endo*-norborneol.[16] The mixture was stirred for 6 hr. and then allowed to stand at room temperature overnight. A cold solution of 500 g. of technical grade sodium hydroxide in 800 ml. of water was added slowly with cooling and the resultant green slurry was steam distilled. A total of 1500 ml. of steam distillate was collected, saturated with sodium chloride, and extracted with three 500-ml. portions of ether. The combined extracts were dried over magnesium sulfate and calcium sulfate, filtered, and the ether removed. The residue was distilled through a Vigreux column to give 84.5 g. (0.744 mole) of ketone, b.p. 89–119° (60–70 mm.). The semicarbazone had m.p. 195.7–196.7° (lit.,[17] m.p. 196–196.5°) and a mixture of 18.7 g. (0.112 mole) of the purified substance with a solution of 14.5 g. (0.115 mole) of oxalic acid dihydrate in 200 ml. of water was steam distilled until 350 ml. of distillate was collected. Sodium chloride was added and the milky suspension extracted with three 75-ml. portions of ether. The combined extracts were dried over magnesium sulfate and again over calcium sulfate. Most of the ether was removed on the steam bath and the residue was sublimed to give 10.4 g. (0.0945 mole, 84%) of waxy sublimate, m.p. 95.5–96.5° (lit., m.p. 91–92°;[18] 95°[19]).

syn-7-Chloronorcamphor (II). Prepared by the chromic acid oxidation of *syn*-7-chloro-*exo*-norborneol[4] as described above for norcamphor in 59% yield. Regeneration from its semicarbazone gave the pure ketone in 76% yield, m.p. 69–70°.

anti-7-Chloronorcamphor(III). Prepared as above from *anti*-7-chloro-*exo*-norborneol[4] in 43.5 to 65% yield. Regeneration from its semicarbazone gave the pure ketone in 73% yield, m.p. 68–70.5°.

exo-3-Bromonorcamphor(IV). The method of Kipping and Pope[5] was employed. Addition of 7.3 g. (0.0455 mole) of bromine to 5.0 g. (0.0455 mole) of norcamphor heated on the steam bath resulted in the evolution of copious quantities of hydrogen bromide. The reaction mixture was swirled and heated for 20 min. and then allowed to stand at room temperature for 30 min. The resulting yellow oil was taken up in 75 ml. of ether and the ethereal solution was washed with water, saturated sodium bicarbonate solution and then dried over magnesium sulfate. The ether was removed on the steam bath and the residue distilled through a semimicro column[20] to give a forerun of solid norcamphor, 0.4 g., b.p. 110° (53 mm.) followed by two intermediate liquid fractions, 0.80 g., b.p. 100–126.2° (23 mm.). The product was collected as 2.75 g. (38%) of liquid, b.p. 126.2–128.5° (23 mm.), n_D^{25} 1.5219, m.p. 30°.

Anal. Calcd. for C_7H_9OBr: C, 44.47; H, 4.80; Br, 42.27. Found: C, 44.27; H, 4.70; Br, 42.17.

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21-Methoxyprogesterone. Improved Synthesis

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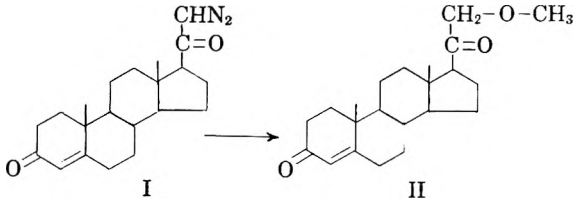
In connection with a current interest in preparing derivatives of adrenocortical hormones which might, possibly, have a modified physiological activity, we became interested, as a first consideration, in securing a quantity of the previously described 21-methoxyprogesterone (II) (21-methyl ether of 11-deoxycorticosterone), prepared by two different routes.[3] The first of these, by Meystre and Wettstein,[3a] was accomplished in eleven steps starting with 3β-hydroxy-Δ⁵-cholenic acid and involved methoxylation at C(21) of 3β-acetoxy-5-chloro-21-bromo-24,24-diphenyl-Δ^{20,23}-choladiene as the key step in the synthesis. The other, a considerably simpler procedure, described by Heusser, *et al.*,[3b] was effected in eight steps starting with 3β-hydroxy-Δ⁵-etiocholenic acid and involved treatment of 21-diazo-Δ⁵-pregnen-3β-ol-20-one in boiling methanol with cupric oxide to give the corresponding 21-methoxy derivative which, on subsequent oxidation, gave 21-methoxyprogesterone (II) in 34% yield.

The method which we wish to describe proceeds *via* 21-diazoprogesterone (I), which may be conveniently prepared from 3β-hydroxy-Δ⁵-etiocholenic acid in five steps.[4] The conversion of I to 21-methoxyprogesterone (II) provides for an extension to



I II

steroid compounds of a reaction described by Newman and Beal,[5] whereby α-diazoketones may be converted directly to α-alkoxyketones in good yield, using boron trifluoride as a catalyst. This reaction, in our case, proved to be virtually quantitative and should apply equally satisfactorily in the case of other steroid 21,20-diazoketones.

EXPERIMENTAL

All melts were performed on the Kofler hot-stage.

21-Methoxyprogesterone (II). To a solution of 34 mg. of 21-diazoprogesterone (I) (m.p. 178–182°) in 2 ml. of anhydrous methanol at 55°, was added 0.1 ml. of boron trifluoride etherate. The reaction was complete in 5 min. as evidenced by cessation of nitrogen evolution. The solution was taken up in ether and extracted first with water, then with dilute sodium bicarbonate. The dried extract was evaporated *in vacuo*, leaving 34 mg. of a white, crystalline residue (m.p. 145–159°). One crystallization from methanol gave pure II, m.p. 159–164° (recrystallization did not improve the melting point), which did not depress the melting point of an authentic specimen.[3a] $[\alpha]_D^{20}$ + 189° ± 4° (*c*, 1.25 $CHCl_3$), λ_{max}^{alc} 240 (4.22).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.34, 76.19; H, 9.69, 9.49.

Bis(2,4-dinitrophenylhydrazone) of II. The method for the preparation of this compound was essentially the same as one previously described.[6] To a solution of 11 mg. of 21-methoxyprogesterone (II) in 1 ml. of absolute ethanol was added a solution of 25 mg. of 2,4-dinitrophenylhydrazine in 3 ml. of the same solvent containing 6 drops of hydrochloric acid. After standing at room temperature overnight, 4 ml. of Benedict's reagent was added, followed by 4 ml. of water. The resulting suspension was heated on a water bath for 10 min. and extracted twice with chloroform. The extract in turn was washed with water, dried, and evaporated, leaving a colored residue which was chromatographed on 3 g. of alumina. Benzene-chloroform (4-1) yielded the desired product. One fraction (8 mg.), selected for its relative purity, was recrystallized twice from chloroform-ethanol, giving 4 mg. of pure 21-methoxyprogesterone bis(2,4-dinitrophenylhydrazone), m.p. 251–253.5°.

Anal. Calcd. for $C_{34}H_{40}O_9N_8$: N, 15.90. Found: N, 14.89.

Acknowledgment. The authors are grateful to Dr. A. Wettstein for having his laboratory carry out the mixed melting point. They wish also to thank Dr. E. B. Hershberg of the Schering Corp. for generously supplying the 3β-hydroxy-Δ⁵-etiocholenic acid, and Dr R. E. Peterson, NIAMD, National Institutes of Health, for the ultraviolet analysis and for having the microchemical laboratory, NIAMD, perform the elemental analyses.

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Steroids. LXXXVII.[1] Preparation of Some Estrone-Ethers

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During an investigation of the effect of substitution on physiological activity it became of interest to prepare some substituted estrone and estradiol ethers of glycol and glycolic acid. This communication describes some of the derivatives made.

Condensation of estrone sodium salt with halogenated alcohols[2] in ethanol at elevated temperature

(1) Paper LXXXVI, F. Sondheimer, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, 22, 1090 (1957).

(2) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949) have described the preparation of estrone and estradiol glyceryl ethers.

led to the corresponding glycol (I) but in poor yields. Considerably better yields were obtained by refluxing with a higher boiling glycol or by using 2-bromoethyl acetate, preferably in the presence of equimolar quantities of sodium iodide, which afforded the corresponding glycol acetate (II).

The desired carboxylic function was introduced by reacting estrone sodium salt and monochloroacetic acid in aqueous medium,[3] giving in good yields the glycolic acid ether (III) which afforded on esterification the corresponding methyl and ethyl esters (IV and V). Lithium aluminum hydride reduction of the ester led to the corresponding diol (VI).

The glycolic acid ether (III), in the mouse uterine weight increase assay (subcutaneous administration),[4] showed an unexpectedly low estrogenic activity of *ca.* 0.002 that of estrone.[5]

EXPERIMENTAL[6]

Estrone glycol ether acetate (II). Estrone (1.35 g.) was added to a solution of sodium ethoxide (prepared from 0.12 g. of sodium), the excess of alcohol was removed by distillation *in vacuo*, and the resulting sodium salt was well dried in a vacuum desiccator over sulfuric acid.

The dry sodium salt was suspended in 30 ml. of dry toluene, 900 mg. of sodium iodide was added, and the suspension was refluxed with 0.75 ml. of 2-bromoethylacetate added dropwise during the first 2 hr. After 20 hr. refluxing the toluene was removed by distillation under reduced pressure and the solids were suspended in absolute methanol. Acidification of the reaction mixture, removal of the insoluble material, and chromatography of the total crudes on alumina yielded, in the first benzene fractions, 170 mg. of crystalline material, m.p. 118–132°. Crystallization from acetone-ether furnished the pure compound as stout needles, m.p. 135–136°, $[\alpha]_D$ + 126° (methanol), λ_{max} 277 and 286 mμ (log ε 3.28 and 3.25, respectively).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.12; H, 7.92; —$COCH_3$, 12.05. Found: C, 74.27; H, 7.90; —$COCH_3$, 12.32.

Estrone glycol ether (I). (a) *By saponification of the acetate.* The acetate, 80 mg. dissolved in 20 ml. of methanol, was treated with 160 mg. of potassium hydrogen carbonate dissolved in 15 ml. of water and kept at room temperature under nitrogen for 22 hr. Usual isolation procedure and crystallization from hexane-ether produced the free compound as a microcrystalline powder, m.p. 117–118°, $[\alpha]_D$ + 131°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.36; H, 8.36; —$COCH_3$, 0.0.

(b) *By reaction with 2-bromoethanol.* The dry sodium salt of estrone (made from 10.0 g. of estrone) was suspended in 75 ml. of freshly distilled ethylene glycol and heated to 140° for 4 hr. with 6.6 ml. of 2-bromoethanol added dropwise during the first 2 hr. The mixture was cooled, diluted with 300 ml. of ice water and made acidic with dilute hydrochloric acid. The resulting gummy material was extracted with ethyl acetate, the extract was washed with aqueous sodium hydrogen carbonate and water, and the oily material obtained after removal of the solvent was chromatographed on alumina. Elution of the column with benzene ether (2:1), followed by crystallization from acetone-ether furnished 2.9 g. of crystalline material, m.p. 112–114°. The identity of this compound with the glycol ether already described was established by mixture melting point and infrared comparison.

Estrone glycolic acid ether (III). Estrone, 1.0 g., suspended in 3.5 ml. of 33% aqueous sodium hydroxide solution, was brought into solution by the addition of 1 ml. of methanol. Two and one-half ml. of 50% aqueous monochloroacetic acid was added and the solution was heated on the steam bath for 0.5 hr. Heating was then continued for 2 hr. while alternate portions of monochloroacetic acid (1 ml.) and sodium hydroxide solution (1.5 ml.) were added at 20 min. intervals. The crude solid product, obtained after acidification of the cold reaction mixture, was purified by extracting the acidic material (76% yield) from an organic phase with aqueous sodium hydrogen carbonate. Crystallization from ethanol produced the analytical sample as needles, m.p. 213–214°, $[\alpha]_D$ + 132°, λ_{max} 277 and 286 mμ (log ε 3.34 and 3.33, respectively).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37; M/NE, 328. Found: C, 73.10; H, 7.32; M, 322; NE, 309.

The *methyl ester* (IV) was obtained by esterification of the above compound with absolute methanol and dry hydrogen chloride in almost quantitative yield; crystallization from methanol gave needles, m.p. 128–129°, $[\alpha]_D$ + 117°.

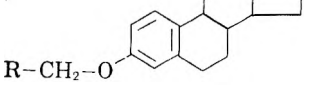
Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.09; H, 7.65.

The *ethyl ester* (V) was obtained in similar manner and crystallized from ether in stout prisms, m.p. 100–102°, $[\alpha]_D$ + 126°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.14; H, 7.92. Found: C, 74.00; H, 7.75.

Estradiol 3-glycol ether (VI). The ethyl ester, 1.0 g., was reduced with lithium aluminum hydride by the Soxhlet technique in tetrahydrofuran by refluxing for 1 hr. The resulting oily material, obtained after removal of the solvent, was triturated with ether to produce the desired estradiol glycol ether, 520 mg., as needles, m.p. 142–148°. The analytical sample crystallized from ether-acetone, m.p. 155–156°, $[\alpha]_D$ + 74°, + 65° (methanol).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 9.13. Found: C, 75.91; H, 8.92.



I. R = —CH_2OH, R′ = =O
II. R = —CH_2OAc, R′ = =O
III. R = —COOH, R′ = =O
IV. R = —COOMe, R′ = =O
V. R = —COOEt, R′ = =O
VI. R = —CH_2OH, R′ = —OH

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(3) C. F. Koelsch, *J. Am. Chem. Soc.*, **53**, 304 (1931).

(4) We wish to thank Dr. Ralph I. Dorfman, The Worcester Foundation for Experimental Biology for bioassay determination.

(5) R. Courrier, L. Velluz, J. J. Alloiteau, and G. Rousseau, *Compt. rend. Soc. biol.*, **139**, 128 (1945) reported only slightly lower activity for estrone 3-ethyl ether as compared to the parent compound.

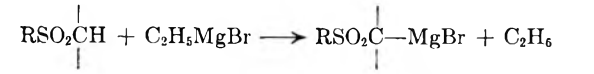
(6) All melting points were taken on the Kofler block; rotations were measured in chloroform unless otherwise stated. The ultraviolet absorption spectra were measured in 96% ethanol with a Beckmann Model DU spectrophotometer. We wish to thank Mr. E. Avila for the physical measurements. Thanks are also due to Miss J. Lisci for able technical assistance.

Grignard Reagents of Sulfones. V. Preparation of Methyl and Ethyl Aryl Sulfones[1]

LAMAR FIELD AND R. DONALD CLARK

Received March 15, 1957

A Grignard reagent of a sulfone may be prepared by metalating a sulfone which contains an alkyl group having a hydrogen atom adjacent to the sulfone group. Such Grignard reagents are useful intermediates for preparing sulfones containing a variety of functional groups.[2] Since interest in the products afforded by these Grignard reagents frequently would be centered either about the sulfone group or the functional group introduced, simple starting materials often would suffice, such as methyl phenyl sulfone (I) or methyl *p*-tolyl sulfone (II). The synthetic utility of Grignard reagents of sulfones therefore frequently being a function of the ready availability of I or II, development of the best possible means for preparing I and II in quantity became desirable. Of the various preparations of methyl aryl sulfones,[3] that involving alkylation of an arenesulfinate provided the best compromise of economy, convenience, and adaptability to large scale.



Oxley and coworkers prepared II by reducing *p*-toluenesulfonyl chloride with sodium sulfite to sodium *p*-toluenesulfinate and alkylating this product with methyl iodide.[4] Methyl iodide has the disadvantage, however, of expense, high volatility, and susceptibility to a side reaction which yields iodine and a thiol. Baldwin and Robinson, on the other hand, having prepared sodium benzenesulfinate in essentially the same way, isolated the sulfinic acid and then converted it to I by alkylation with methyl sulfate in the presence of aqueous sodium hydroxide.[5]

The procedures of this paper, based mainly on that of Baldwin and Robinson,[5] involve reduction of the sulfonyl chloride with sodium sulfite by a somewhat simplified process, followed by alkylation of the sulfinate salt using methyl sulfate, water, and sodium bicarbonate under vigorous conditions. Differences from the earlier procedure[5] require brief comment: (a) Only technical grades of organic reagents are specified. (b) The scale is increased eleven fold; one advantage of the present method is its presumed adaptability to further increase by minor modification. (c) The salt rather than the free sulfinic acid is used, thus eliminating the extra step of acidification and the copious evolution of sulfur dioxide (from excess sulfite) associated with it, as well as the necessity for alkylating the reduction product soon after its formation (the acid differs from the salt in being unstable). (d) A feature of more general interest and applicability is that the vigorous conditions of the present procedure seem to have caused methyl sodium sulfate to function as an alkylating agent, in contrast to the usual situation in alkylations where it is simply an inert by-product resulting after alkylation by methyl sulfate; thus, under vigorous conditions, the amount of methyl sulfate specified[5] for preparation of a given weight of sulfone could be reduced by more than one half. (e) A more concentrated solution was used for the alkylation to increase the temperature and rate of reaction. (f) Sodium bicarbonate was substituted for sodium hydroxide to prevent etching of glassware. (g) The sulfone was extracted from the reaction mixture with benzene, a modification which permits effective drying of the sulfone when it is to be used for organometallic reactions (recrystallization of the product from water[5] was unnecessary).

In preliminary work, essentially the procedure of Baldwin and Robinson was used (but with a molar ratio of methyl sulfate to benzenesulfinic acid of 1.7:1). Periods of reflux of 1–9 hr. during the alkylation gave I in yields of 53–59%. A study of the hydrolysis of methyl sulfate[6] strongly suggested that little or none of the sulfate would survive the 9-hr. period of reflux. On the other hand, since methyl potassium sulfate reportedly methylates sulfinates under vigorous conditions,[7] the possibility referred to in (d) above became attractive, *i.e.*, that the by-product, methyl sodium sulfate, could still be induced to effect alkylation. The fact that a reflux period of 18 hr. did result in an increase in the yield of I to 73% lends support to this viewpoint (since the yield increased only to 76% after a 36-hr. period, a 20-hr. period seemed optimum and was used in the modified procedure cited in the Experimental).

Alkylation with methyl sulfate in organic solvents was examined as a matter of interest connected with the general preparation of methyl aryl sulfones, but proved rather unpromising.

The preparation reported in the Experimental for methyl phenyl sulfone (I) gave even better results when extended to methyl *p*-tolyl sulfone (II). Efforts to extend the alkylation step to the prep-

(1) Work supported by the Office of Ordnance Research, U. S. Army. Abstracted from the M.A. thesis of R.D.C., December, 1956.

(2) See Paper IV of this series and leading references there: L. Field, J. E. Lawson, and J. W. McFarland, *J. Am. Chem. Soc.*, **78**, 4389 (1956).

(3) C. M. Suter, *The Organic Chemistry of Sulfur*, p. 660 ff., John Wiley and Sons, Inc., New York, N. Y., 1944.

(4) P. Oxley, M. W. Partridge, T. D. Robson, and W. F. Short, *J. Chem. Soc.*, **1946**, 763.

(5) W. A. Baldwin and R. Robinson, *J. Chem. Soc.*, **1932**, 1445.

(6) H. F. Lewis, O'Neal Mason, and R. Morgan, *Ind. Eng. Chem.*, **16**, 811 (1924).

(7) R. Otto, *Ann.*, **284**, 300 (1895).

aration of the analogous ethyl aryl sulfones by substitution of ethyl sulfate, however, were less well rewarded. Despite a number of variations in the alkylation of sodium benzenesulfinate by ethyl sulfate, the yields could not be increased beyond about 34–48%; sodium *p*-toluenesulfinate gave ethyl *p*-tolyl sulfone in 45% yield. The route of choice for ethyl aryl sulfones, therefore, probably is ethylation of the sulfinate with an ethyl halide.

EXPERIMENTAL[3]

Methyl phenyl sulfone (I). The reduction was based on that of Oxley *et al.*[4] A mixture of 600 g. of anhydrous sodium sulfite, 420 g. of sodium bicarbonate, and 2.4 l. of water was heated on a hot plate at 70–80°. This temperature was maintained by switching off the hot plate occasionally, while 447 g. (325 ml.) of benzenesulfonyl chloride[9] was added with stirring during 3 hr. Heating and stirring were then continued until the volume did not exceed 2.4 l. (but at least for 1 hr.). The mixture was then allowed to stand overnight at room temperature, and the solid was collected by filtration. The filter cake was then used without further treatment in the alkylation step; moisture in the cake is unimportant, and salts other than the sulfinate probably have a desirable effect in reducing the rate of hydrolysis of methyl sulfate.[6]

In the alkylation procedure, suggested by that of Baldwin and Robinson,[5] the filter cake was mixed with 400 g. of sodium bicarbonate and 490 g. (370 ml.) of methyl sulfate[9,10] in a 3-necked flask provided with a stirrer, condenser, and dropping funnel containing 925 ml. of water. Enough of the water was added to permit stirring (*ca.* 100 ml.), and the remainder then added during 3 hr. with stirring. The mixture was then heated under reflux with stirring for 20 hr. It was then cooled to about 75°, and 200 ml. of benzene was added and the mixture was stirred briefly. All liquid was then decanted from solid into a separatory funnel. The aqueous layer was separated, extracted with 200 ml. more of benzene, and returned to the funnel. Solid remaining in the flask was washed into the separatory funnel with *ca.* 2 l. of water, after which the mixture was shaken with 200-ml. portions of benzene until all solid had been dissolved (three portions usually sufficed).

After the combined benzene extracts had been dried over calcium chloride, the benzene was removed by distillation under reduced pressure. (If the temperature was kept below 50°, well formed crystals were obtained.) The yield of colorless nicely crystalline I was 260 g. (66%), m.p. and mixture[11] m.p. 86–88°. Use of 134 g. of benzenesulfonyl chloride gave I in 69% yield, m.p. 86.5–87°.

The procedure of Baldwin and Robinson,[5] and our own experience on a small scale, suggests that if the I is not to be used in organometallic reactions, where the advantage of thorough drying of the extract is important, it can be isolated simply by allowing it to crystallize from the reaction mixture and washing with water. Carbon tetrachloride and 1:3 ethanol-water are convenient for recrystallization (or water[5] on a small scale), if this should be desired. The only limiting factor toward considerable increases in scale seems to be the extraction.

In exploring alkylation under other conditions, methyl sulfate[9,10] in a molar ratio of 1.7:1 was usually added over 1–2 hr. After the reaction, the excess was hydrolyzed and the I recrystallized. Benzenesulfinic acid in ether (reflux, 14 hr.) gave no crystalline product. Its salt (3 g.) in methyl sulfate[9,10] alone (5 ml.; 85°, 22 hr.) gave I in 24% yield, m.p. *ca.* 86°. Its salt in acetone (55°, 2.5–26 hr.) gave I with ranges in yield of 38–12% and in m.p. of 80–87°; in *t*-butyl alcohol containing 5% of water (reflux, 4.5 hr.), the salt gave I in 19% yield, m.p. 86–87.5°.

Methyl p-tolyl sulfone (II). The procedure given for I was followed exactly except that 484 g. of *p*-toluenesulfonyl chloride[9] was substituted for benzenesulfonyl chloride. In four experiments,[12] the II ranged in yield from 69 to 74%, and in m.p. from 83° to 87.5° (a typical product had m.p. and mixture[13] m.p. 86.5–87.5°).

A 20-hr. reflux period was established as sufficient for II by also effecting the alkylation using a 36-hr. period; the yield was 76% m.p. 86.5–87.5°.

Ethyl phenyl sulfone. A mixture of 20.0 g. of sodium benzenesulfinate, 20.1 g. of sodium bicarbonate, and 16.4 ml. of ethyl sulfate was heated at 50° with stirring while 50 ml. of water was added during 2 hr. The mixture was then heated under reflux for 20 hr. and the sulfone extracted with benzene; yield, 8.0 g. (39%), m.p. 41.5–42°; m.p. reported,[14] 41–42°.

Repetition of the procedure resulted in a yield of only 44% with twice the amount of ethyl sulfate and of only 48% with four times the amount both of ethyl sulfate and of sodium bicarbonate. Hydrolysis of the sulfate therefore does not seem to be the limiting factor. Indeed, when the procedure was repeated except that the mixture of the sulfinate and sulfate was heated and stirred alone at 120° for 4 hr. before addition (in one portion) of the sodium bicarbonate and water, only a dark oil, which could not be crystallized, was isolated. No favorable effect resulted either from interchanging the water and the sulfate in the original procedure (34%, m.p. 41.5–42°), from doubling the time of reflux (38%, m.p. 41.5–42°), or from other variations.

Ethyl p-tolyl sulfone. The procedure used for ethyl phenyl sulfone was repeated with 21.7 g. of sodium *p*-toluenesulfinate and 32.8 ml. of ethyl sulfate; yield 10.0 g. (45%), m.p. and mixture[13] m.p., 53–54°.

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(8) Melting points are corrected.

(9) Eastman Organic Chemicals, Yellow Label grade.

(10) Methyl sulfate is quite toxic and should be used in a hood; see N. I. Sax, *Handbook of Dangerous Materials*, p. 147, Reinhold Publishing Co., New York, N. Y., 1951. Glassware used for transfers may be cleaned with dilute ammonia water, containing detergent. It seems quite unlikely[6] that any methyl sulfate survives the 20-hr. period of reflux during alkylation, and no difficulty whatever has been experienced in handling the mixture after this period without gloves, hood, or other special precautions; nevertheless, the possible presence of methyl sulfate should be borne in mind.

(11) L. Field, *J. Am. Chem. Soc.*, **74**, 3919 (1952).

(12) We wish to thank O. D. Keaton and W. E. Stamper for two of these.

(13) L. Field and J. W. McFarland, *J. Am. Chem. Soc.*, **75**, 5582 (1953).

(14) R. Otto, *Ber.*, **13**, 1274 (1880).

Organic Polynitriles. II. 1,1,2,2-Tetracyanocyclopropanes and Their Conversion to Substituted Itaconic Acids[1]

RAYMOND P. MARIELLA[2] AND ARTHUR J. ROTH, III[3]

Received April 27, 1956

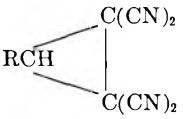
Several alkylidene bismalononitriles were prepared by the reaction of the appropriate aldehyde with malononitrile[4] (Table I).

TABLE I

$RCH[CH(CN)_2]_2$

R	M.P., °C.	Analyses: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	Yields, %
CH_3	93	60.75	3.80	35.52	60.68	3.84	35.60	70
CH_3CH_2	65	62.79	4.65	32.56	62.98	4.73	32.67	80
$CH_3CH_2CH_2$	75	64.52	5.37	30.11	64.58	5.30	30.15	80

TABLE II



R	M.P., °C.	M.W. Calcd.	M.W. Found	Analyses: Calculated C	Calculated H	Found C	Found H	Yields, %
CH_3	192	156	156	61.54	2.56	61.40	2.51	60
CH_3CH_2	197	184	170	63.53	3.53	63.64	3.51	90
$CH_3CH_2CH_2$	131	197	184	65.21	4.34	65.35	4.69	80

$$RCHO + 2CH_2(CN)_2 \xrightarrow[\text{base}]{\text{trace of}} RCH[CH(CN)_2]_2 + H_2O$$

R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$. The reaction of the alkylidene bismalononitriles with bromine caused the instant discoloration of the bromine, but the products did not contain any halogen. By analogy with somewhat related work[5] it is concluded that cyclopropane derivatives were obtained, a conclusion supported by molecular weights and analyses (Table II). Infrared studies also indicated that cyclopropane structures were obtained[6] (Figure 1). A probable mechanism is

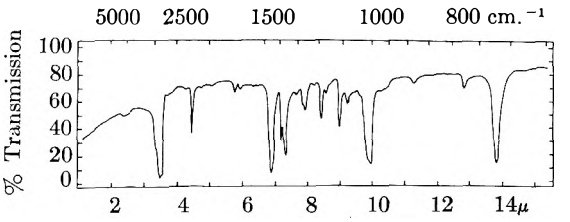
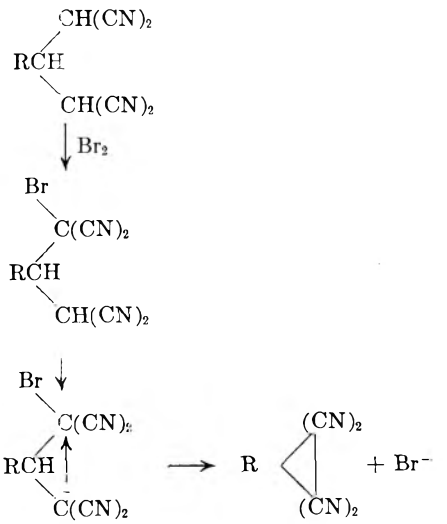


FIG. 1.—1,1,2,2-TETRACYANO-3-METHYLCYCLOPROPANE



Acid hydrolysis of the cyclopropane tetranitriles, for 8 hr., yielded what were probably the cyclo-

(1) This investigation was supported by Research Grant C-1746 (C2) from the National Cancer Institute, of the National Institutes of Health, Public Health Service. For Part I see R. P. Mariella, R. J. Clutter, and H. G. Ebner, *J. Org. Chem.*, **20**, 1702 (1955). This paper was presented April 13, 1956, before the Organic Division at the Dallas meeting of the American Chemical Society.

(2) To whom inquiries should be addressed.

(3) Taken in part from the M.S. thesis of Arthur J. Roth, III.

(4) (*a*) Diels, Gartner, and Kaack [*Ber.*, **55**, 3444 (1922)] originally reported the reaction of formaldehyde and acetaldehyde with malononitrile and (*b*) Gal, Fung, and Greenberg [*Cancer Research*, **12**, 565 (1952)] duplicated part of this. (*c*) Westfahl and Gresham [*J. Org. Chem.*, **21**, 319 (1956)] reported the reaction of formaldehyde and malononitrile. Whereas formaldehyde and acetaldehyde react with malononitrile to give products in addition to the alkylidene bismalononitriles, propionaldehyde and butyraldehyde react smoothly to give the bismalononitrile in very good yields, no other products being isolated.

(5) Wideqvist, *Arkiv. Kemi, Mineral. Geol.*, **B20**, No. 4 (1945); *Chem. Abstr.* **41**, 1621 (1947), reports that the reaction of acetaldehyde, bromomalononitrile and potassium iodide gave 1,1,2,2-tetracyano-3-methylcyclopropane, m.p. 192°. Our sample did not depress the melting point of a sample prepared by the method of Wideqvist.

(6) Hart and Curtis, Jr. [*J. Am. Chem. Soc.*, **78**, 112 (1956)] report that two bands are particularly characteristic of the cyclopropane ring, one at 3100 and the other at approximately 1020 cm^{-1}. The three cyclopropanes in this work all showed bands around 3050 and strong bands at 1005 or 1035 cm^{-1}. The three cyclopropanes prepared have almost identical spectra, and only one is used as an illustration.

propane tetra-acids. However, acid hydrolysis of the tetranitriles for 36 hr. did not yield the expected cyclopropane-1,2-diacids. The compounds so obtained were unsaturated as indicated by reaction with bromine and potassium permanganate, and their infrared spectra showed almost identical absorption with that of itaconic acid[7] (Figure 2).

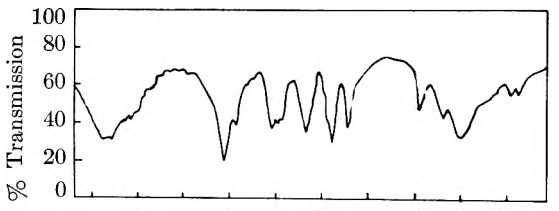


FIG. 2.—ITACONIC ACID

The spectra of our γ-methylitaconic acid was identical with that of an independent sample[8] and a mixture melting point was undepressed. Since the three substituted itaconic acids have almost identical spectra, only one is used as an illustration (Figure 3). The melting point of the three γ-substituted

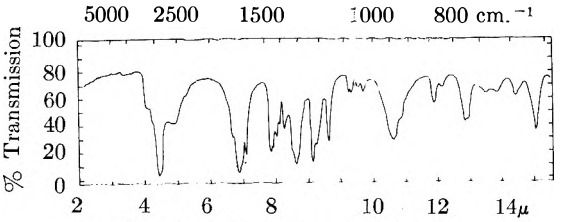


FIG. 3.—γ-ETHYLITACONIC ACID

itaconic acids agreed closely with those reported in the literature (Table III) and the amounts of C and H found in analysis agreed within 0.25% with the theoretical.[9]

TABLE III

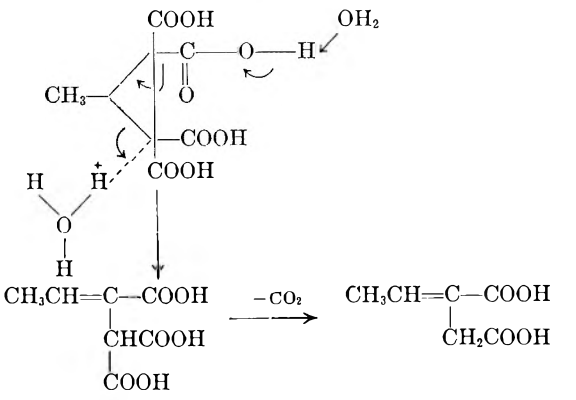
MELTING POINTS OF γ-SUBSTITUTED ITACONIC ACIDS

RCH=CHCOOH
|
HCHCOOH

R	M.P., °C.	Literature[a]	Yields, %
CH_3[b]	170	167°	20
CH_3CH_2	169	165°	35
$CH_3CH_2CH_2$	163	159°	40

[a] Fittig, *Annalen*, **255**, 39 (1889); **304**, 181 (1899). Compounds prepared by the reaction of appropriate aldehyde with succinic anhydride followed by isomerization by distillation or treatment of the esters with ethoxide. [b] Independent sample[8] had m.p. 169–170°.

A likely concerted mechanism is:



EXPERIMENTAL[11]

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The Rast method for molecular weights was used. The infrared curves were determined by means of a Perkin-Elmer Model 21, double beam spectrophotometer. All the samples were run in a Nujol suspension.

Ethylidene bismalononitrile. To a chilled solution of 6.6 g. of malononitrile and 4.5 g. of acetaldehyde, one drop of modified catalyst (1/3 piperidine and 2/3 dioxane) was added. This was kept at 5° overnight. Crystallization may be hastened by scratching the sides of the flask. After 12 hr., the reaction mixture contained a crystalline mass and some sirupy liquid. The acetaldehyde may be allowed to evaporate off at room temperature without heating, leaving a solid mass, or the crystals may be filtered from the mother liquor directly. The crystals were then washed thoroughly with a small portion of ethyl ether and dried in air. Recrystallization from 95% ethanol gave clean, white crystals, which melted sharply at 92–93°.[12] When acetaldehyde was replaced by propionaldehyde or butyraldehyde, the corresponding alkylidene bismalononitriles were obtained (see Table I).

1,1,2,2-Tetracyano-3-alkylcyclopropanes. Two grams of alkylidene bismalononitrile were dissolved in 10 ml. of 95% ethanol. The mixture was warmed gently until the solid dissolved. The solution was cooled slightly and 22–23 drops of bromine, or enough to retain the bromine color, were added slowly. (Vigorous agitation is necessary as this reaction is highly exothermic.) The cyclopropane compound crystallized out immediately.

The solution was well chilled and the crystals filtered off and recrystallized from absolute ethanol. (See Table II).

3-Ethylcyclopropane-1,1,2,2-tetracarboxylic acid. Ten grams of the 1,2,2,2-tetracyano-3-ethylcyclopropane were refluxed with 50 ml. of concentrated HCl for 8 hr. Upon cooling, the clear mixture yielded a large mass of crystals. These crystals

(7) In a somewhat analogous reaction, the acid hydrolysis of 3-methylcyclopropane-1,1,2-tricarboxylic ester yielded 3-methylparaconic acid, Harper and Reed, *J. Chem. Soc.*, 779 (1955).

(8) Kindly supplied by M. C. Ettlinger, Rice Institute, Houston, Tex., and prepared by the method of Kloetzel, *J. Am. Chem. Soc.*, **70**, 3571 (1948).

(9) Ramberg and Wideqvist, *Arkiv. Kemi, Mineral. Geol.*, **14B**, No. 37 (1941). *Chem. Abstr.*, **36**, 79 (1942) reported that the hydrolysis of 1,1,2,2-tetracyano-3,3-dimethylcyclopropane in base gave a diacid $C_7H_{10}O_4$, m.p. 165°, of unknown structure. From our work, it would seem that the diacid actually is γ, γ-dimethylitaconic acid, whose m.p. is reported as 164° by Stobbe [*Ber.*, **36**, 197, (1903)] who prepared it by the reaction of acetone on diethyl succinate.

(11) Micro-analyses by Micro-Tech Laboratories, Skokie, Ill.

(12) Diels, Ref. 4a, reported a melting point of 113°. Numerous attempts to raise the melting point of our analytical sample were uniformly unsuccessful.

were washed with a small amount of ice water and the tetra acid separated from the remaining ammonium chloride by extraction with absolute ethanol. Evaporation of the ethanol yielded a crude product which was then recrystallized from acetic acid, (25% yield), m.p. 286° (dec.), mol. wt. (Calcd.) 246; mol. wt. (found) 234. The results of a C—H analysis were found to differ from the theoretical by about 1.3% and so are not included here.

The sample did not decolorize a bromine solution. In a similar manner a small amount of the 3-*n*-propylcyclopropane-1,1,2,2-tetracarboxylic acid was obtained, m.p. 271° (dec.). Similar attempts to isolate the 3-methyl isomer were unsuccessful. The tetra acids were difficult to obtain and purify and no further attempts were made to isolate them.

γ-Alkyl itaconic acids. 10 grams of 1,1,2,2-tetracyano-3-alkylcyclopropane were refluxed with 50 ml. of concentrated HCl for 36 hr. Upon cooling a large mass of crystals was formed. The solid was filtered off and washed with a small amount of ice water. The acid was separated from the remaining ammonium chloride by extracting with boiling anhydrous benzene. After the benzene solution cooled, a small amount of petroleum ether was added and the crude product slowly came out of solution. This product was recrystallized from anhydrous benzene. (See Table III).

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Communications TO THE EDITOR

Synthesis of 3-Vinylindoles

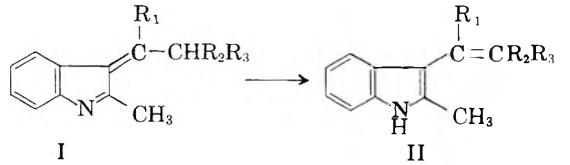
Sir:

The recent disclosure[1] that the 2-methylindole adduct of methyl vinyl ketone can be converted to 2-methylcarbazole prompts us to report on some of our studies with 3-vinylindoles, since it has seemed likely to us that carbonyl-containing 2-methyl-3-vinylindoles, such as IIa–IId, may also serve as carbazole precursors.

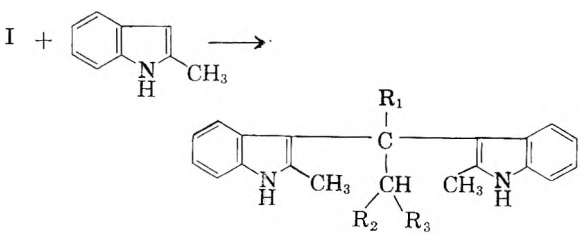
The colorless 1:1 condensation product, m.p. 124–125°, from 2-methylindole and ethyl acetoacetate with hydrochloric acid, to which Scholtz[2] and later Cook and Majer[3] assigned the indolenine structure Ia, is now assigned the 3-vinylindole structure IIa since it has NH and conjugated carbonyl absorption in the infrared [ν(cm.$^{-1}$) 3440, 3330, 1684, 1608 in $CHCl_3$; 3350, 3150, 1670, and 1652 (doublet), 1617 in Nujol] and conjugated absorption in the ultraviolet [λ_{max} in 95% EtOH, with intensities in log ϵ in parentheses, 224 (4.65), 266[4] (3.79), 283 (3.94), 289 (3.93), 331 (3.93)]. Similarly, the yellow condensation product, m.p. 121–123°, from refluxing 2-methylindole with acetylacetone in acetic acid solution, to which Scholtz[5] assigned the bisindole structure IIIb on the basis of apparently erroneous analytical data, is now assigned the 3-vinylindole structure IIb: ν (cm.$^{-1}$) 3440, 3310, 1657 in $CHCl_3$; 3230, 1649 in Nujol; λ_{max} in 95% EtOH 224 (4.48), 281 (3.92), 285[4] (3.91), 358 (4.09). *Anal.* Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57; Mol. wt. 213.27. Found: C, 79.06; H, 7.01; N, 6.64; Mol. wt. 220 (Rast).

Condensations in refluxing acetic acid solution of 2-methylindole with carbonyl compounds containing a readily enolizable α-hydrogen appear to represent a quite general route to 3-vinylindoles. By this method we have obtained, in addition to IIa and IIb, IIc (from benzoylacetone), yellow, m.p. 157–158°: ν (cm.$^{-1}$) 3440, 1643 in $CHCl_3$; 3230, 1631 in Nujol; λ_{max} in 95% EtOH 222 (4.49), 263 (4.27), 279[4] (4.15), 286[4] (4.06), 391 (4.15); *Anal.* Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09; Found: C, 82.64; H, 6.32; N, 5.14; IId (from dibenzoylmethane), orange, m.p. 193–195°: ν (cm.$^{-1}$) 3440, 1633 in $CHCl_3$; 3240, 1627 in Nujol; λ_{max} in 95% EtOH 221 (4.58), 282 (4.28), 406 (3.70); *Anal.* Calcd. for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15; Found: C, 85.52; H, 5.81; N, 4.22; IIe (from α-phenylacetoacetonitrile), pale yellow, m.p. 193–194°: ν (cm.$^{-1}$) 3440, 3310, 2200 in $CHCl_3$; 3340, 2190 in Nujol; λ_{max} in 95% EtOH 224 (4.54), 279 (3.98), 288 (3.92), 352 (3.86); *Anal.* Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29; Found: C, 83.95; H, 6.21; N, 10.38; IIf (from desoxybenzoin), colorless, m.p. 163–164°: ν (cm.$^{-1}$) 3450 in $CHCl_3$; 3400 in Nujol; λ_{max} in 95% EtOH 226 (4.56), 279 (4.37), 353 (3.90); *Anal.* Calcd. for $C_{23}H_{19}N$: C, 89.28; H, 6.19; N, 4.53; Found: C, 89.53; H, 6.44; N, 4.81.

Some of the limits to the 3-vinylindole synthesis are suggested by the facts that under analogous conditions acetone and acetophenone give bisindoles (like III)[6] and phenylacetone (in contrast to



I II



III

Ia–IIa: $R_1 = CH_3$, $R_2 = COOC_2H_5$, $R_3 = H$
IIb–IIIb: $R_1 = CH_3$, $R_2 = COCH_3$, $R_3 = H$
IIc: $R_1 = CH_3$, $R_2 = COC_6H_5$, $R_3 = H$
IId: $R_1 = C_6H_5$, $R_2 = COC_6H_5$, $R_3 = H$
IIe: $R_1 = CH_3$, $R_2 = CN$, $R_3 = C_6H_5$
IIf: $R_1 = R_2 = C_6H_5$, $R_3 = H$
IIIg: $R_1 = CH_3$, $R_2 = C_6H_5$, $R_3 = H$

desoxybenzoin) with 2-methylindole gives a bisindole (IIIg), colorless, m.p. 269–271°: ν (cm.$^{-1}$) 3460 in $CHCl_3$; 3380 in Nujol; λ_{max} in 95% EtOH 229 (4.79), 285 (4.11), 292 (4.09); *Anal.* Calcd. for $C_{27}H_{26}N_2$: C, 85.67; H, 6.92; N, 7.40; Found: C, 85.30; H, 6.93; N, 7.64; as does indole (in contrast to 2-methylindole) with acetylacetone: colorless,

(1) J. Szmuszkovicz, *J. Am. Chem. Soc.*, 79, 2819 (1957).
(2) M. Scholtz, *Ber.*, 46, 1082 (1913).
(3) A. H. Cook and J. R. Majer, *J. Chem. Soc.*, 1944, 486. Although it has not been experimentally verified by us, it seems likely that other 1:1 condensation products of indoles with β-ketoesters described in this reference should also be formulated as 3-vinylindoles (like II), and not as indolenines (like I), since they were not obtained as salts, even though prepared in the presence of hydrochloric acid.
(4) Inflection.
(5) M. Scholtz, *Arch. Pharm.*, 253, 629 (1915).
(6) W. E. Noland, M. H. Fischer, D. N. Robinson, and H. Sorger-Domenigg, Paper 39 presented before The Organic Division at the 131st National Meeting of The American Chemical Society, Miami, Fla., April 9, 1957, Abstracts, p. 24-O.

m.p. 221–223°: ν (cm.$^{-1}$) 3490, 1696 in $CHCl_3$; 3410, 1692 in Nujol; λ_{max} in 95% EtOH 224 (4.80), 283 (4.07), 291 (4.00); *Anal.* Calcd. for $C_{21}H_{20}N_2O$: C, 79.71; H, 6.37; N, 8.85; Found: C, 79.73; H, 6.43; N, 8.72. The differentiation between vinylindole and bisindole formation appears to be the result of a combination of electronic and steric effects on the relative rates with which the probable intermediate, the indolenine I, undergoes tautomerization to a vinylindole or alkylation by an indole to yield a bisindole.

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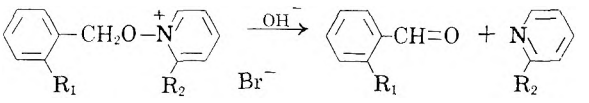
Alkaline Decomposition of Quaternary Salts of Amine Oxides[1]

Sir:

Since the time of Meisenheimer's classic experiments on quaternary salts of amine oxides,[2] numerous reports have been made of the alkaline decomposition of such salts to tertiary amine and aldehyde.[3] Ochiai and his colleagues[4] have applied the reaction to salts of pyridine-*N*-oxide and observed the formation of formaldehyde and acetaldehyde. Recently, Katritsky studied this reaction as a method of deoxygenating pyridine-*N*-oxides under nonreducing conditions and reported the formation of the corresponding bases in fair yield.[5]

In view of this new application and the general lack of quantitative data on these reactions, we would like to report our experience with *N*-benzyloxypyridinium salts which demonstrates that this is both an excellent method for preparing aromatic aldehydes and a convenient way of deoxygenating pyridine-*N*-oxides.

The formation of quaternary salts, such as I, proceeded in high yield by heating the appropriate pyridine-*N*-oxide with benzyl bromide or a similar halide in acetonitrile (I, 95%, m.p. 94–96°, Found: C, 54.15, H, 4.55; II, 92%, m.p. 113–115°, Found: C, 55.81, N, 5.08; III, 67%, m.p. 97–98°, Found: C, 40.32, H, 3, 47). When either I or II was treated with dilute



I, R_1 and R_2 = H IV, R_1 = H VI, R_2 = H
II, R_1 = H, R_2 = CH_3 V, R_1 = NO_2 VII, R_2 = CH_3
III, R_1 = NO_2, R_2 = H

aqueous sodium hydroxide, benzaldehyde could be isolated in 90–92% yield by extraction of the acidified solution with chloroform followed by concentration and distillation. In the case of I and II, work-up of the basic fraction in the usual way gave pyridine and α-picoline in 78 and 84% yields, respectively, after distillation. The decomposition of III was studied to provide a comparison of our procedure with other standard aldehyde syntheses,[6] and gave pure *o* nitrobenzaldehyde, m.p. 42–43°, after chromatography over alumina, in 60% yield. The crude yield of brown crystals was 97%.

When *m*-xylyl dibromide was treated with pyridine-*N*-oxide, the di-salt (m.p. 121–122°, Found: C, 45.54, H, 4.51) formed in 97% yield. Decomposition of this di-salt with base gave isophthalaldehyde as pure crystals, m.p. 88–89°, in 62% yield. Other applications of the method are being investigated. It is apparent that there is a formal analogy between these alkaline decompositions and the formation of aldehydes by the alkaline cleavage of nitronic esters.[7,8]

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(1) Aided by a grant from the National Science Foundation.

(2) Meisenheimer, *Ann.*, **397**, 273 (1913).

(3) *Cf.* Culvenor, *Rev. Pure. Applied Chem.* (*Australia*), **3**, 83 (1953); Katritsky, *Quart. Rev.*, **10**, 395 (1956).

(4) Ochiai, Katada and Naita, *J. Pharm. Soc. Japan*, **64**, 210 (1944); *Chem. Abstr.*, **45**, 5154 (1951).

(5) Katritsky, *J. Chem. Soc.*, 2404 (1956).

(6) *Org. Syntheses*, **Coll. Vol. 3**, 641 (1955).

(7) Weisler and Helmkamp, *J. Am. Chem. Soc.*, **67**, 1167 (1945).

(8) Hass and Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949); *Org. Syntheses*, **30**, 99 (1950).

(9) Predoctoral Fellow, National Institutes of Health, 1956–57.

Selective Reductions with Diborane, an Acidic-Type Reducing Agent

Sir:

Alkali metal borohydrides and aluminohydrides are now widely utilized for the selective reduction of functional groups. Such reductions are believed to involve a transfer of a hydride unit from the complex anion to an electron-deficient center in the organic reactant.[1]

Diborane has long been known to reduce aldehydes and ketones rapidly. In these reactions it is believed to function through an attack on an electron-rich center in the functional group.[2] The possibility that diborane, as an acidic-type reduc-

(1) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949). H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

(2) H. C. Brown, H. I. Schlesinger, and A. B. Burg, *J. Am. Chem. Soc.*, **61**, 673 (1939).

ing agent, might exhibit markedly different selectivity than the saline borohydrides, as basic-type reducing agents, led us to explore the reducing potentialities of diborane. Ample data on the reducing properties of the borohydrides are now available for comparison.[3]

Diborane was prepared by adding a solution of sodium borohydride in diglyme to a solution of boron trifluoride etherate in the same solvent, and the gas was passed into a solution in diglyme or tetrahydrofuran of the compound under examination. After an appropriate interval of time, the residual hydride was determined by analysis. In cases where the group under study was one which is not reduced by sodium borohydride itself, the diborane could be conveniently generated within the reaction mixture by adding boron trifluoride etherate in diglyme to a solution of sodium borohydride and the compound in the same solvent.

Similar results were obtained in both procedures. The following data summarize typical observations using these procedures (the first figure in parenthesis gives the reaction time in hours, the second the moles of hydride utilized per mole of compound). All reactions were studied at room temperature.

Rapid Reduction	Slow or Negligible Reduction
Benzaldehyde (1.0, 1.0)	Benzoyl chloride (2.0, 0.4)
Benzophenone (1.0, 1.0)	Isobutyryl chloride (2.0, 0.4)
γ-Butyrolactone (1.0, 2.0)	Ethyl benzoate (2.0, 0.4)
Styrene oxide (1.0, 1.2)	Nitrobenzene (2.0, 0.1)
Azobenzene (1.0, 1.9)	1-Nitropropane (2.0, 0.1)
Benzoic acid (0.5, 2.8)	Naphthalene (2.0, 0.0)
p-Nitrobenzoic acid (0.5, 2.5)	
Benzonitrile (0.5, 2.0)	
n-Butyronitrile (1.0, 2.0)	

These results reveal remarkable differences in the reducing properties of diborane and the alkali metal borohydrides. Thus, in diglyme solution borohydride reduces acid chloride groups more readily than aldehyde or ketone groups,[4] whereas the reverse is true with diborane. Similarly, lithium borohydride reacts more readily with ester than with nitrile groups,[5] whereas diborane reacts far more rapidly with the nitrile than with the ester grouping. Finally, the rapid reduction of the carboxylic acid group is in marked contrast to its usual stability and inertness. These results suggest that a judicious application of diborane and the alkali metal borohydride would make possible a truly remarkable selectivity in organic reductions.

The following preparations are typical of the two procedures utilized.

The diborane generator consisted of a 250-ml. flask containing a dropping funnel, an inlet for nitrogen, and an outlet for the diborane. In the flask was placed 28.5 g. (0.20 mole) of boron trifluoride etherate in 50 ml. of diglyme; in the dropping funnel, a solution of 5.1 g. (0.135 mole) of sodium borohydride in 125 ml. of diglyme. The flask was connected to the reaction flask containing 29.6 g. (0.20 mole) of *m*-nitrobenzonitrile in 150 ml. of tetrahydrofuran. The system was flushed out with nitrogen. The diborane (0.08 mole) was generated at an even rate over a period of an hour by dropping the sodium borohydride solution into the boron trifluoride etherate and passed into the flask containing the nitrile. (The exit gases were passed through a wash bottle containing acetone to catch and destroy unreacted diborane.) The reaction mixture was permitted to stand at room temperature for a second hour, ethanol was added to destroy excess diborane, followed by dry hydrogen chloride to convert the amine to the hydrochloride. After removal of solvent under reduced pressure, the reaction mixture was allowed to cool, the solid hydrochloride was collected on a filter, washed with ethanol, and dried. There was obtained 33.2 g., 88%, of the crude amine hydrochloride, m.p. 223–225°. Recrystallization from ethanol yielded pure *m*-nitrobenzylamine hydrochloride, m.p. 225–227°, in 79% yield.

p-Nitrobenzoic acid, 0.20 mole, was slowly added and dissolved in 0.18 mole of sodium borohydride in 150 ml. of diglyme (nitrogen atmosphere). Hydrogen was evolved. The flask was cooled in a water bath, stirred, and 0.22 mole of freshly distilled boron trifluoride etherate was added over a period of 1 hr. After a second hour, the contents were hydrolyzed, and the solid product was collected. There was obtained 24.1 g., 79% yield, of *p*-nitrobenzyl alcohol, m.p. 91–93°.

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(3) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, 1956.
(4) Unpublished observations of Dr. K. Ichikawa.
(5) R. F. Nystrom, S. W. Chaikin, and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 3245 (1949).

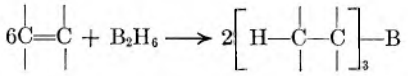
Hydroboration of Olefins. A Remarkably Fast Room-Temperature Addition of Diborane to Olefins

Sir:

Diborane has been reported to react very slowly with simple aliphatic olefins at elevated temperatures[1,2] and with styrene at room temperature[3] to form the corresponding organoboron compounds.

(1) D. T. Hurd, *J. Am. Chem. Soc.*, **70**, 2053 (1948).
(2) A. T. Whatley and R. N. Pease, *J. Am. Chem. Soc.*, **76**, 835 (1954).
(3) F. G. A. Stone and H. J. Emeleus, *J. Chem. Soc.*, 2755 (1950).

In the course of investigating the facile conversion of olefins into trialkylboranes under the influence of the sodium borohydride–aluminum chloride reagent,[4] we have discovered that in the presence of organic ethers diborane adds to olefins with remarkable ease and speed at room temperature to form the corresponding organoboranes in yields of 90–95%.



The reaction is reminiscent of the addition of aluminum-hydrogen bonds to olefins.[5] However, the latter reaction requires somewhat elevated temperatures (~ 100°) and occurs readily only with terminal olefins, >C=CH$_2$. On the other hand, the hydroboration reaction proceeds rapidly at room temperature with olefins of widely varying structural types, including ethylene, propylene, 1-hexene, 2-hexene, *t*-butylethylene, 2,4,4-trimethyl-1-pentene, 2,4,4-trimethyl-2-pentene, cyclopentene, cyclohexene, styrene and 1,1-diphenylethylene.

The reaction can be carried out by passing diborane into the olefin contained in diglyme, tetrahydrofuran, or ethyl ether. The reaction occurs less readily with the pure olefin or with the olefin dissolved in hydrocarbon solvents. However, the traces of ether carried over by diborane generated in ether solvents are sufficient to catalyze the reaction markedly.

We have attempted to measure the velocity of the addition. However, at 25° we have observed half-lives of the order of 1 minute and we are presently engaged in developing methods for following reactions of such high velocities.[6]

The following synthesis of tri-*n*-hexylborane is typical. The apparatus consisted of a diborane generator and a reaction flask as described in the previous Communication.[7] Diborane, 0.067 mole, generated from the addition of 3.8 g. (0.1 mole) of sodium borohydride to 22.8 g. (0.16 mole) of boron trifluoride–etherate, was passed into the reaction flask containing 25.2 g. (0.3 mole) of 1-hexene in 100 ml. of diglyme. The reaction temperature was controlled through a water bath and by regulating the rate of generation of the diborane (30–60 min.). (Excess diborane was destroyed by passing the exit gases through a wash bottle containing acetone.) The reaction flask was disconnected, the solvent removed at room temperature, and the organoborane recovered by distillation at reduced pressure, all under protection of a nitrogen atmosphere. Tri-*n*-hexylborane, b.p. 185–188° at 30 mm., was obtained in 91% yield, 24.2 g. Oxidation with alkaline hydrogen peroxide yielded 3.94% boron (as boric acid) and 1-hexanol, b.p. 156–157° at 745 mm., n^{20}_{D} 1.4152.

Similar results were obtained with the other terminal olefins. Consequently, the addition of diborane to a terminal olefin occurs to place the boron atom on the terminal carbon atom.

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(4) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956).

(5) K. Ziegler, *Angew. Chem.*, **68**, 721 (1956).

(7) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

(6) Research in progress with Dr. Laura Case.

Selective Conversion of Olefins into Organoboranes Through Competitive Hydroboration, Isomerization, and Displacement Reactions

Sir:

The reactions of diborane with 1- and 2-pentene and 1- and 2-hexene in ether solvents are exceedingly fast reactions, being complete in a matter of minutes at room temperature.[1] In spite of its high velocity, the hydroboration reaction exhibits considerable selectivity. Treatment of an equimolar mixture of 1- and 2-pentene or 1- and 2-hexene with a deficiency of diborane results in the selective conversion of the terminal olefin into tri-*n*-pentylborane and tri-*n*-hexylborane.

One- and 2-pentene were converted into the organoboranes and the products were oxidized with alkaline hydrogen peroxide without isolation.[2] The organoborane from 1-pentene yielded 1-pentanol of at least 95% purity, as indicated by infrared examination. The organoborane from 2-pentene yielded a mixture of 63% 2-pentanol and 37% 3-pentanol (infrared analysis). However, after heating the crude organoborane from 2-pentene, 2-hexene, or 2-octene under reflux in diglyme solution for 4 hr., the products obtained in the oxidation were essentially pure primary alcohols. Apparently, under the influence of heat the 2- and 3-alyklboranes undergo a rapid isomerization into the corresponding 1-alkylboranes.[3] Indeed, it was possible to take a mixture of 2-, 3-, 4-, and 5-decenes and transform them by this procedure into 1-decanol in a yield of 80%. Similarly, mixed tetra-

(1) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).

(2) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956).

(3) The isomerization of tri-*sec*-butylborane and tri-*tert*-butylborane to tri-*n*-butylborane and triisobutylborane, respectively, upon distillation at atmospheric pressure has recently been reported. G. F. Hennion, P. A. McCusker, E. C. Ashby, and A. J. Rutkowski, Abstracts of Papers, 130th Meeting of the AMERICAN CHEMICAL SOCIETY, September 16–21 (1956), p. 53-O.

decenes were converted into 1-tetradecanol in a yield of 70%.

Finally, we have observed that it is readily possible to displace a lower alkyl group in the trialkylborane with a higher alkyl group by heating the borane with the appropriate olefin and distilling the more volatile olefin from the reaction mixture.[4] In this way tri-*n*-hexyl-, tri-*n*-octyl- and tri-*n*-decylboranes have been synthesized by treating tri-*n*-pentylborane with 1-hexene, 1-octene, and 1-decene, respectively.

The facile isomerization and displacement reactions suggest the existence of a rapid and mobile equilibrium between the organoborane, olefin and boron-hydrogen bonds.

$$\begin{array}{c|c} | & | \\ C{=}C & + \; H{-}BR_2 \rightleftharpoons \end{array} \begin{array}{c|c} | & | \\ H{-}C & {-}C{-}BR_2 \\ | & | \end{array}$$

Addition of a less volatile olefin displaces the more volatile olefin from the system. Similarly, internal olefins are rapidly isomerized by a series of addition and elimination reactions, and are converted finally into the more stable 1-alkylborane derivatives.

The following experiments are typical.

A mixture of 0.3 mole each of 1-hexene and 2-hexene in 100 ml. of diglyme was treated with 0.05 mole of diborane. Oxidation of the mixture yielded 1-hexanol in 90% yield, b.p. 156–157° at 750 mm., n_D^{20} 1.4150.

2-Hexene, 0.3 mole, in 100 ml. of diglyme, was treated with 0.06 mole of diborane. On oxidation there was obtained 24.7 g. of 2- and 3-hexanol, b.p. 136–137.5° at 750 mm. In a duplicate experiment, following the addition of the diborane, the reaction mixture (in diglyme) was heated under reflux (nitrogen atmosphere) for 4 hr. It was then cooled and oxidized as before. There was obtained 25.2 g., 82%, of 1-hexanol, b.p. 154–156° at 743 mm., n_D^{20} 1.4152.

Tri-*n*-pentylboron, 19.9 g., b.p. 150–152° at 30 mm., and 1-decene, 37.0 g., b.p. 170° at 750 mm., were placed in a dry 100-ml. flask and attached to a Todd column (nitrogen atmosphere). Over a period of 3 hr. there was obtained 17.7 g. (93%) of 1-pentene, b.p. 30–31° at 750 mm. The product, tri-*n*-decylborane, was recovered by distillation under reduced pressure: 32.3 g. (85% yield), b.p. 205–208° at 5 mm.

The remarkable ease with which these reactions proceed suggests that the hydroboration reaction should provide a useful and convenient synthetic route for the transformation of olefins into organoboranes, alcohols, and other functional derivatives.

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(4) Similar transformations have been observed in the organoaluminum compounds. K. Ziegler, *Angew. Chem.*, **68**, 721 (1956).