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Further Studies Concerning the Ozonolysis of Phenanthrene

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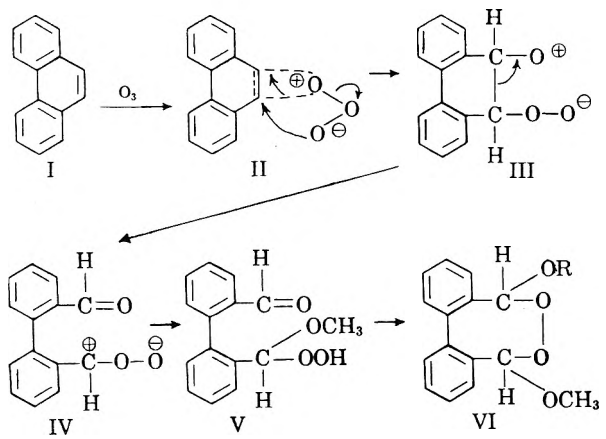
This paper presents further information concerning the nature and behavior of the peroxidic products from ozonolysis of phenanthrene in "inert" and in "reactive" solvents.

In earlier papers the ozonolyses of phenanthrene in methanol[1] and in chloroform[2] were reported. The present paper presents the experimental details of the ozonolysis of phenanthrene in chloroform[2] and additional results of ozonolyses both in "reactive" and in "inert" solvents.[3]

Subsequent to our earlier papers in this series, Wibaut and de Boer[4] published a "preliminary communication" in which they assigned to the first isolable product from the ozonolysis of phenanthrene in methanol the cyclic structure (VIa) rather than the open-chain structure (V) assigned by us.[1] Our crude product (m.p. 84–88°) showed a positive, though weak, lead tetraacetate test for a hydroperoxide[5] and its infrared spectrum, taken either in solution or in KBr disk, showed strong hydroxyl and carbonyl bands.[1] Wibaut and de Boer[4] were able to obtain a purer product (m.p. 96.5–97.5°) and found that the infrared spectrum taken in Nujol mull showed no carbonyl band.



a) R = H; b) R = CH_3; c) R = CH_2CH_3

Repetition of our earlier work leads to the following conclusions. At the end of the ozonolysis the cold methanolic reaction mixture contains high concentrations of V, produced from IV probably *via* II and III[6]. This is evidenced by a strong lead tetraacetate test for a hydroperoxide.[5] With time and/or increase of temperature the equilibrium shifts toward the more stable and less soluble cyclic tautomer VIa, which can be precipitated by addition of cold water or by cooling a reaction mixture containing a minimum of solvent. At room temperature the acidic nature of V, in equilibrium with VIa, catalyzes the conversion of VIa to the peracetal, VIb.

Both the freshly precipitated VIa (m.p. 86–88°) and that purified to the extent reported by Wibaut and de Boer[4] (m.p. 97–98°) contain V as an impurity; their infrared spectra taken in a Nujol mull still show faint carbonyl bands. The highly purified product (m.p. 116–117°) had no carbonyl band in its infrared spectrum, taken in Nujol. The infrared spectra taken in chloroform or bromoform, however, showed strong carbonyl bands.

Wibaut and de Boer[4] showed that the strong carbonyl bands in the KBr disk spectrum were due

(1) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956).

(2) P. S. Bailey and S. B. Mainthia, *J. Org. Chem.*, **21**, 1335 (1956).

(3) The terms "reactive" and "inert" refer to possible reaction of the solvent with the zwitterion intermediate. See reference 1 for details of the Criegee mechanism.

(4) J. P. Wibaut and T. J. de Boer, *Koninkl. Ned. Akad. Wetenschap. Proc. Ser. B.*, 59, 421 (1956).

(5) R. Criegee, H. Pilz, and H. Flygare, *Ber.*, **72**, 1799 (1939).

(6) P. S. Bailey, *Chem. & Ind. (London)*, 1148 (1957).

to decomposition. Those in the solution spectra apparently are the result both of decomposition and of equilibrium with V. After a dilute chloroform solution of pure VIa had been irradiated with infrared light for fifteen minutes, the recovered product was pasty and contained 10% less active oxygen.

The fact that crude VIa can be purified by recrystallization from benzene indicates that at least in this solvent the equilibrium between V and VIa lies far in the direction of VIa. This also appears to be true with methanol. Whereas crude VIa in methanol or ethanol was converted to VIb and VIc, respectively,[1] no such reaction was obtained with pure VIa until a drop of hydrochloric acid was added.

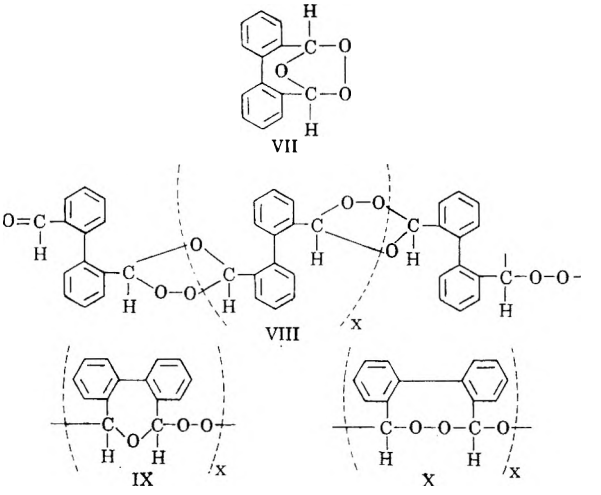
The first paper of this series[1] reported the isolation, one time only, of a crystalline material thought to be a cyclic dimer of V. It is now apparent that this material was VIa of approximately the same purity as obtained by Wibaut and de Boer[4]. We were misled by an erroneous molecular weight determination and by the unfortunate circumstance that, this one time, no appreciable decomposition occurred during the observation of the infrared spectrum in a KBr disk. This spectrum is different from those of crude VIa taken in a KBr disk, which showed strong carbonyl bands.[1] It is similar to those of pure VIa taken in a Nujol mull, except that it has a very weak carbonyl band.

As stated in the second paper of this series[2] and as reported also by Wibaut and de Boer,[4] ozonolysis of phenanthrene in chloroform gives a polymer of zwitterion IV, rather than a monomeric monoozonide (VII) as reported by Schmitt, Moriconi, and O'Connor.[7] The latter authors were misled by a Rast molecular weight determination (during which decomposition occurred[4]) and the infrared spectrum which showed bands in the 5.7–5.9μ region. These bands, which since have been shown to be due to carbonyl-containing impurities,[8,9] had earlier been reported to be characteristic of ozonides.[10] O'Connor, Schmitt, and Moriconi[11] have acknowledged the misassignment of structure.

Our material (m.p. 139–140°) was obtained from ozonolyses of phenanthrene in chloroform, carbon tetrachloride, 1,2-dichloroethane, or methyl chloride. Molecular weight determinations carried out cryoscopically in various solvents showed it to be at least a hexamer. We have assigned it a polyozonide structure (VIII) on the basis of infrared spectra, which show only a weak carbonyl band and bands at 9.5 and 9.6μ which have been shown to be typical of most simple ozonides.[8] Alternative structures are IX and X. In each of these cases (VIII, IX, or X) the chain could be terminated by the addition of a small molecule such as water. If the material were IX or X, however, the infrared spectrum should show no trace of a carbonyl band. The band at 9.5μ probably is due to the ether linkage of the ozonide ring. Five-membered cyclic ethers have been shown to absorb at 9.1–9.3μ whereas open-chain and cyclic ethers of larger size absorb at 8.6–9.1μ.[12]

Wibaut and de Boer,[4] on the basis of a cryoscopic molecular weight determination in benzene, concluded that their polymer of IV (precipitated from the chloroform ozonolysis reaction mixture by addition of ether, and carefully washed with ether, m.p. 128–129°) was trimeric. As would be expected of a lower molecular weight polymer of structure VIII, a relatively strong carbonyl band was reported in the infrared spectrum[4]. An active oxygen determination indicated that the material was not contaminated with nonperoxidic decomposition products.[4] It seems probable that the ozonolysis product is a mixture of polymers of various lengths and that Wibaut and de Boer[4] concentrated the trimer whereas we concentrated higher polymers. An alternative explanation is that during our recrystallization further polymerization occurred through abstraction of some of the small chain terminating molecules.

It was evident that the material of Schmitt, Moriconi, and O'Connor[7] (m.p. 65–90°) contained both the polymeric ozonide and nonperoxidic ozonolysis products. We were able to obtain a material similar to this only by allowing the ozonolysis reaction mixture to stand before precipitation, or by redissolving the product in chloroform and allowing this solution to stand. In each case the



(7) W. J. Schmitt, E. J. Moriconi, and W. F. O'Connor, *J. Am. Chem. Soc.*, **77**, 5640 (1955).

(8) R. Criegee, A. Kerckow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).

(9) E. Briner and E. Dallwigk, *Compt. rend.*, **243**, 630 (1956); *Helv. Chim. Acta*, **39**, 1446 (1956).

(10) E. Briner, *et al.*, *Helv. Chim. Acta*, **35**, 340, 345, 353, 1377 (1952); *Helv. Chim. Acta*, **36**, 1166, 1757 (1953); *Helv. Chim. Acta*, **37**, 620, 1558, 1561 (1954); *Compt. rend.*, **234**, 1932 (1952); *Compt. rend.*, **237**, 504 (1953).

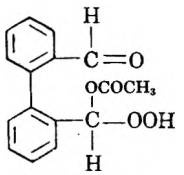
(11) W. F. O'Connor, W. J. Schmitt, and E. J. Moriconi, *Ind. Eng. Chem.*, **49**, 1701 (1957).

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

resulting material was much lower melting, contained much less active oxygen, and showed strong carbonyl bands in its infrared spectrum.

The polymeric ozonide(VIII) was reduced to 2,2′-biphenyldicarboxaldehyde and was oxidized to diphenic acid. The yields were much lower, however, than from the methanol ozonolysis products (VI)[1]. Decomposition of VIII gave a mixture of 2,2′-biphenyldicarboxaldehyde, diphenic acid, 2′-formyl-2-biphenylcarboxylic acid, and an oily phenolic material.

Ozonolysis of phenanthrene in glacial acetic acid gave a material which appears to be a mixture of the polymeric ozonide (VIII) and an acetoxy hydroperoxide (XI).



XI

EXPERIMENTAL[13]

The ozonator and techniques used in this research were the same as described in an earlier paper.[14] The phenanthrene was Eastman Kodak Co. White Label 599. The melting point of 99–100° is indicative of its high purity. The methanol was distilled over magnesium methoxide.[15] The chloroform (Baker and Adamson) was carefully purified[16]; the purity of the peroxidic ozonolysis product from chloroform solution was dependent on the purity of the chloroform. All other liquid ozonolysis solvents were carefully dried and redistilled.

Ozonolysis of phenanthrene in methanol to give 3-hydroxy-8-methoxy-4,5,6,7-dibenzo-1,2-dioxacyclooctane (VIa). An ozone-oxygen stream containing 4% ozone by weight was passed at a rate of 40 l. per hour into a suspension of 4.0 g. of phenanthrene in 80 ml. of methanol at −20°, until all of the phenanthrene had dissolved and ozone had begun to pass into the potassium iodide trap. A total of 1.1 moles of ozone per mole of phenanthrene reacted. The dissolved, unreacted ozone was swept out by a stream of dry oxygen. The solution gave a strong lead tetraacetate test for a hydroperoxide.[5] To the cold reaction mixture was added slowly 200 ml. of ice water while the sides of the containing vessel were scratched. The bulky precipitate was filtered, washed, and dried; 4.6 g. (79%), m.p. 86–88°. Trituration with petroleum ether raised the melting point to 97–98°.[17] Both this and the material before trituration gave weak lead tetraacetate tests and had faint carbonyl bands (5.9 μ) in their infrared spectra. After several recrystallizations from benzene, the material melted at 116–117°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 69.75; H, 5.46; active O, 6.20; mol. wt., 258. Found: C, 70.25; H, 5.58; active O, 6.01; mol. wt. (cryoscopic in 1,2-dibromoethane) 270.

The pure substance gave a negative lead tetraacetate test, strongly released iodine from sodium iodide solution, was stable to shock, remained undecomposed indefinitely at 0°, but decomposed at room temperature after a few days. Its infrared spectrum taken in a Nujol mull showed a strong hydroxyl band (3.0 μ) but no carbonyl band. The spectra in chloroform or bromoform were quite different and had strong carbonyl bands at 5.9 μ.

When the ozonolysis was repeated just as before, except that 4 g. of phenanthrene in only 50 ml. of methanol was used, and the ozonolysis solution was cooled to −50°, a 34% yield of crude VIa (m.p. 87–89°) precipitated.

Infrared irradiation of a chloroform solution of 3-hydroxy-8-methoxy-4,5,6,7-dibenzo-1,2-dioxacyclooctane (VIa). An approximately 1% solution of pure VIa was irradiated with infrared light for 15 min., after which the solvent was rapidly evaporated under vacuum on a Rinco evaporator. A paste remained.

Anal. Calcd. for $C_{16}H_{14}O_4$: active O, 6.20. Found: active O, 5.4.

In another instance the pasty residue was triturated with petroleum ether. A low recovery of crystals melting at 95–96° was obtained. Similar results were obtained by allowing the chloroform solution to stand for 15 min. without irradiation.

Conversion of 3-hydroxy-8-methoxy-4,5,6,7-dibenzo-1,2-dioxyacyclooctane (VIa) *to 3,8-dimethoxy-4,5,6,7-dibenzo-1,2-dioxacyclooctane* (VIb) was accomplished by dissolving 1 g. of pure VIa in 25 ml. of methanol and adding 1 drop of concentrated hydrochloric acid. Precipitation began immediately and was complete in 10 min. A yield of 0.9 g. (85%) of VIb melting at 175–176° was obtained. Identification was by the mixture melting point method.[1] When this was repeated with no hydrochloric acid present no precipitate formed. After several days the solution lost its active oxygen content. Likewise, substitution of a drop of sulfuric acid for hydrochloric acid brought about decomposition rather than conversion to VIb.

Ozonolysis of phenanthrene in methanol to give 3,8-dimethoxy-4,5,6,7-dibenzo-1,2-dioxyacyclooctane (VIb). The ozonolysis was carried out with 2 g. of phenanthrene in 40 ml. of methanol just as described in the first experiment. At the end of the reaction, 4–5 drops of concentrated hydrochloric acid were added. Precipitation began immediately and was complete after 10 min. The yield of VIb melting at 177–178° was 2.5 g. (82%); recrystallized from methyl ethyl ketone, m.p. 180–181°, no depression in melting point in admixture with an authentic sample.[1]

Ozonolysis of phenanthrene in inert solvents to give the polymeric ozonide (VIII). Into a solution of 5.9 g. of phenanthrene and 60 ml. of chloroform cooled to −60° was passed an ozone-oxygen stream, containing 4% by weight ozone, at a rate of 40 l. per hour. The ozone was absorbed quantitatively until one mole per mole of phenanthrene had reacted. Dissolved ozone was swept out with a dry oxygen stream and the reaction mixture was allowed to come to room temperature. Upon addition of ligroin 7.3 g. (97% yield) of material melting at 129–130° precipitated. Similar results were obtained by addition of methanol. Several recrystallizations by dissolving in benzene and reprecipitating with ligroin raised the melting point to 139–140° (77% yield). The material is colorless, amorphous in appearance, stable to shock, releases iodine from sodium iodide solutions, remains undecomposed indefinitely at 0°, but decomposes in a few days at room temperature. Its infrared spectrum taken either in chloroform or in Nujol mull showed a weak carbonyl band (5.9 μ) and very strong twin bands at 9.5 and 9.6 μ.

(13) Melting points are corrected. Microanalyses were performed by the microanalytical laboratory of the University of Texas Biochemical Institute. The active oxygen determinations were done by the method of R. Criegee, G. Blust, and G. Lohaus, *Ann.*, **583**, 4 (1953).

(14) P. S. Bailey and S. S. Bath, *J. Am. Chem. Soc.*, **79**, 3122 (1957).

(15) A. I. Vogel, *A Textbook of Practical Organic Chemistry*, 3rd Ed., Longmans Green and Co., New York, N. Y., 1956, p. 169.

(16) Reference (15), p. 176.

(17) Wibaut and de Boer[4] reported that they triturated with ether to obtain this material. We found, however, that the material partially dissolved and/or became gummy in ether.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.5; active O, 7.1; Found: C, 74.58; H, 4.8; active O, 7.0.

Ozonolyses in carbon tetrachloride and 1,2-dichloroethane by the same procedure gave the same product. For the *ozonolysis in methyl chloride,* gaseous methyl chloride was passed through concentrated sulfuric acid, solid sodium hydroxide, and anhydrous calcium chloride and then condensed at −80° in the ozonolysis flask containing the phenanthrene. After the ozonolysis the solvent was allowed to evaporate and the residue was purified as described in the chloroform experiment. The product was identical with those from the other inert solvents.

Cryoscopic molecular weight determinations of polymeric ozonide (VIII). The molecular weight was determined cryoscopically in several solvents. The results varied somewhat in the different solvents, probably because decomposition occurred in varying degrees (see next experiment). In nitrobenzene the molecular weight changed rapidly with time. It appears that the material is at least a hexamer; probably it is of higher molecular weight.

Calcd. for $(C_{14}H_{10}O_3)_x$: x = 9, 2034; x = 6, 1356; x = 5, 1130; x = 3, 678; x = 2, 452; x = 1, 226. Found: 2020, 1860 (bromoform); 1392, 1370, 1350 (benzene); 1250, 1200 (nitrobenzene, quickly); 508 (nitrobenzene, 1 hr.); 268 (nitrobenzene, 2 hr.); 540, 550 (acetophenone, 1–2 hr.).

Decomposition of polymeric ozonide on standing in solution. A solution of the polymeric ozonide in chloroform was allowed to stand for 3 days after which time it was evaporated. The residue melted at 125–127°.

Anal. Calcd. for $(C_{14}H_{10}O_3)6$: active O, 7.1; mol. wt., 1356. Found: active O, 6.4; mol. wt., 416.

A similar solution was allowed to stand for 5 days. The residue melted at 80–90°.

Anal. Calcd. for $C_{14}H_{10}O_3$: active O, 7.1. Found: active O, 3.2.

Similar melting points were obtained when a benzene solution was allowed to stand for corresponding lengths of time.

When the ozonolysis in chloroform solution was carried out as described earlier, except that the reaction mixture was allowed to stand for 12 hr. before precipitation of the product, the crude product melted with decomposition at 90°. The molecular weight determination indicated that it was trimeric. However, an active oxygen determination indicated that it was a mixture of the polymeric ozonide and nonperoxidic decomposition products.

Anal. Calcd. for $C_{14}H_{10}O_3$: mol. wt., 226; active O, 7.1. Found: mol. wt. 670; active O, 3.1.

Reduction of polymeric ozonide (VIII) *to 2,2′-biphenyldicarboxaldehyde.* A mixture of 0.5 g. of the polymeric ozonide, 0.7 g. of sodium iodide, and 30 ml. of acetic acid was allowed to stand overnight, after which the liberated iodine was reduced with sodium thiosulfate. This mixture was extracted with ether, and the ether extract was washed free of acids with sodium carbonate solution and was extracted with sodium bisulfite. From the bisulfite extract, through decomposition with hydrochloric acid, extraction with ether, and evaporation of the ether extract, was obtained 0.25 g. (54% yield) of the dialdehyde melting at 62–63°. Identification was by a mixture melting point with an authentic sample (m.p. 63–64°).[1]

When a solution of 0.25 g. of the polymeric ozonide, 20 ml. of dry pyridine, and 0.15 g. of hydroxylamine hydrochloride was allowed to stand overnight, after which it was evaporated by a jet of air and the residue was crystallized from dilute ethyl alcohol, 0.05 g. of the dioxime of 2,2′-biphenyldicarboxaldehyde was obtained (crude m.p. 135–144°; recrystallized ethanol, m.p. 170–172°). Identification was by a mixture melting point with a known sample.[1]

Oxidative decomposition of the polymeric ozonide (VIII). A mixture of 1 g. of the polymeric ozonide (VIII), 1.5 ml. of 30% hydrogen peroxide, and 30 ml. of 80% formic acid was warmed gently. Reaction was immediate and after 10 min. the mixture had turned black. The solution was extracted with ether and the ether layer was extracted with sodium bicarbonate solution. Acidification of the bicarbonate solution and filtration and recrystallization of the precipitate from ethanol gave 0.2 g. of diphenic acid (m.p. 210–212°; recrystallized, ethanol, m.p. 216–218°). Identification was by the mixture melting point method.

Decomposition products of the polymeric ozonide (VIII). The polymeric ozonide decomposes to a tar on standing at room temperature for several days. Bicarbonate extraction of the tar gave a low yield of 2-formyl-2′-biphenylcarboxylic acid, m.p. 132–134°. Sodium hydroxide extraction gave a low yield of an oily phenolic material. Bisulfite extraction yielded a small amount of 2,2′-biphenyldicarboxaldehyde, m.p. 60–62°. Identifications were by the mixture melting point method.[1]

In another instance a solution of 1 g. of the polymeric ozonide and 50 ml. of methanol was refluxed for 1.5 hr., after which it gave a negative active oxygen test with sodium iodide. The solution was evaporated, the residue was dissolved in ether, and the ether solution was extracted first with sodium bicarbonate solution, second with sodium hydroxide solution, third with sodium bisulfite solution, and then evaporated. The residue resisted crystallization. Nothing was obtained from the sodium hydroxide extract, showing the absence of phenolic material. From the bisulfite extract was obtained 2,2′-biphenyldicarboxaldehyde (m.p. 62–63°) in 16% yield. The bicarbonate extract was acidified and extracted with ether. The ether solution was extracted with a bisulfite solution and evaporated, and the residue was crystallized from ethanol; the yield of diphenic acid (m.p. 210–212°, recrystallized ethanol, m.p. 214–216°) was 14%. From the bisulfite extract was obtained 2-formyl-2′-biphenylcarboxylic acid (m.p. 132–134°) in 20% yield. Identifications were by the mixture melting point method.

Ozonolysis of phenanthrene in glacial acetic acid. An ozone-oxygen stream containing 4% by weight ozone was passed at a rate of 40 l. per hour through a suspension of 4 g. of phenanthrone in 30 ml. of glacial acetic acid cooled to 16%. No ozone passed over into the KI trap until one mole of ozone per mole of phenanthrene had been absorbed; at this point all of the phenanthrene had gone into solution. Upon cooling the solution in an ice bath, 3.7 g. of a colorless, amorphous appearing solid precipitated, m.p. (decomposition) 90°. Evaporation of the filtrate gave only a tar. The solid material was slightly soluble in ether released iodine from iodide solution, and gave a weak lead tetraacetate test.

Anal. Calcd. for $(C_{14}H_{10}O_3)_x$ (VIII): C, 74.33; H, 4.5; active O, 7.1; mol. wt. (monomer) 226. Calcd. for $C_{16}H_{14}O_5$ (XI): C, 67.12; H, 4.9; active O, 5.6; mol. wt., 286. Found: C, 69.10; H, 4.2; active O, 7.1; mol. wt. (cryoscopic, benzene) 515, 444.

In another instance the product was precipitated by addition of ice water. It melted at 102°. Recrystallization by addition of ligroin to a benzene solution of the material raised the melting point to 105°.

Anal. Found: C, 70.76; H, 4.7; active O, 6.9; mol. wt. (cryoscopic, benzene) 648.

The material gave the same results as did the pure polymeric ozonide when treated with formic acid–hydrogen peroxide, or when allowed to decompose.

The infrared spectra of both materials showed weak hydroxyl bands at 3.0μ and moderate carbonyl bands at 5.9μ.

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AUSTIN 12, TEX.

[CONTRIBUTION FROM THE JOHN STUART RESEARCH LABORATORIES OF THE QUAKER OATS COMPANY]

Catalytic Hydrogenation. I. Kinetics and Catalyst Composition in the Preparation of 2-Methylfuran

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The rates of formation of 2-methylfuran and by-products from the vapor phase hydrogenolysis of furfuryl alcohol are reported. 2-Pentanol and 2-methyltetrahydrofuran are formed by further reaction of 2-methylfuran, while some tetrahydrofurfuryl alcohol is formed by a competing reaction. The kinetics indicate that 2-methylfuran may be prepared in substantially quantitative yields over a copper chromite catalyst.

Investigation of the liquid-phase hydrogenolysis of furfural to 2-methylfuran over various copper and copper chromite catalysts has given occasional yields as high as 90% at temperatures ranging from 200° to 290°.[1] Somewhat better results have been reported in vapor phase reactions. Bremner *et al.*[2,3] have reported 85–90% yields from furfural at 200–300°C. Lukes and Wilson[3a] report at best an 80% yield over a copper-iron catalyst under similar conditions. Others[4,5] report similar results around 200° from furfural using an Adkins type copper chromite, but only a 70% yield when furfuryl alcohol was used as a starting material. These results are not in agreement with the present results in which an 88% yield was obtained when furfural was used as the liquid feed and 95% or better using furfuryl alcohol.

The function of calcium or barium oxides in copper chromite catalysts (Adkins type) is generally considered to be that of a selective promotor in hydrogenation reactions. Since in the present work (Table I), no significant difference was observed in yields or in rates of reaction over catalysts which contained the alkaline earth metal oxides, as compared with those which did not, it must be concluded that these oxides have no apparent effect on the type of hydrogenolysis reaction under discussion.

The addition of a small amount of sodium silicate to copper chromite resulted in very poor yields at temperatures up to 300° as shown in Table I and the resulting catalyst behaved more like copper than copper chromite. This effect can be attributed to either a reaction with the active copper chromite catalyst which would decrease its acidity in a Lewis sense, or a physical distortion of the lattice acting then as a lattice defect poison. In any event, it confirms the effect noted by Bremner and Keeys[3] that basic additives decrease catalyst activity from the standpoint of hydrogenolysis.

A copper catalyst, contrary to results reported[6] earlier, gave poor yields of methylfuran and acted primarily as a hydrogenation catalyst with very little tendency toward hydrogenolysis. Apparently at temperatures above 250°, this catalyst has little effect on the rate of formation of methylfuran.

Although any of the catalysts employed may be used without prior reduction, the catalyst actually becomes reduced during the reaction period. This process, which is highly exothermic for copper chromite catalysts, results in uncontrollable hot zones in the catalyst bed causing poor yields of methylfuran. Reduction of the catalysts at temperatures below 250° with controlled mixtures of hydrogen and nitrogen permits a smooth reaction and gives a catalyst of better activity and life than those not previously reduced. Catalysts which were reduced at temperatures of 300° or higher were less active than those reduced below 250° since they required temperatures about 30° higher to give similar conversions and yields. This temperature effect is presumably due to distortion of the physical structure of the catalyst resulting in fewer undisturbed positions for the adsorption of hydrogen or furfuryl alcohol.

Of the three copper chromite catalysts (No. 1, 2, 3) containing only copper chromite which were investigated, the best conversions were obtained on that which contained 80% copper oxide prior to reduction. The active catalyst is reported[7] to be $Cu_2Cr_2O_4$ + Cu which would be approximately 60% copper oxide before reduction. There is little difference between catalysts 1 and 2 except in conversion at the lower temperatures. These two catalysts bracket the desired 60% and would be expected to be similar. The reasons for the lower conversions observed with catalyst 1 are not understood at the present time, but the results appear to indicate that excess chromium oxide has a detrimental effect.

(1) See for example K. Tsuda *et al.*, *Chem. Abstr.*, **45**, 6182 (1951). M. Okawara, *Chem. Abstr.*, **47**, 4832 (1953).

(2) J. Bremner, R. Keeys, and D. Jones, Brit. Patent 634,079 (1947).

(3) J. Bremner and R. Keeys, *J. Chem. Soc.*, 1068 (1947).

(3a) R. Lukes and C. Wilson, *J. Am. Chem. Soc.*, **73**, 4790 (1951).

(4) R. F. Holdren, U. S. Patent 2,445,714 (1948).

(5) L. W. Burnett, Ph.D. thesis, Iowa State College, 1943.

(6) H. Guinot, U. S. Patent 2,456,187 and French Patent 973,322.

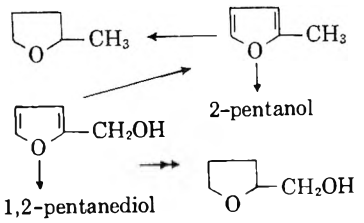
(7) J. D. Stroupe, *J. Am. Chem. Soc.*, **71**, 569 (1949).

TABLE I

Catalyst No.	Composition[a] (%)	T (°C.)	MeF (%)[b]	MeTHF (%)	2-Pentanol (%)	THFA (%)	FA (%)	Diol (%)
1	52 CuO	200	92.1	3.7	1.5	0.5	0.1	2.1
	36 Cr_2O_3	175	33.3	—	0.2	0.1	65.3	1.1
		150	8.6	0.7	—	—	90.5	0.2
2	80 CuO	200	92.2	1.8	1.8	1.7	—	2.5
	17 Cr_2O_3	175	70.8	1.6	0.8	0.2	23.6	2.0
	2 Graphite	150	25.4	0.4	0.5	—	72.7	1.0
3	94 CuO	200	83.8	3.2	5.7	1.0	2.1	4.2
	6 Cr_2O_3	175	66.4	1.2	4.5	0.1	23.4	4.4
		150	16.7	0.5	0.4	—	81.2	1.2
4	46 CuO	200	93.1	3.6	1.7	1.0	0.2	0.4
	50 Cr_2O_3	175	87.9	2.1	0.6	0.2	8.5	0.7
	4 CaO	150	17.7	0.8	0.4	0.1	80.7	0.3
5	72 CuO	300	44.8	11.5	4.6	2.1	35.1	1.9
	15 Cr_2O_3	275	41.8	10.1	4.9	1.0	39.6	2.6
	12 Na_2SiO_3	250	32.8	4.0	3.1	1.4	55.6	3.1
6	96 CuO	300	2.8	0.5	0.2		96.0[c]	0.5
	4 Graphite	250	4.1	14.8	0.6		78.0[c]	2.5
		200	1.2	2.9	0.2		95.0[c]	0.7

[a] Non-reduced tablets, prepared and analyzed by The Harshaw Chemical Co., Catalyst Div. [b] For method of analysis see experimental section. MeF = 2-methylfuran, MeTHF = methyltetrahydrofuran, THFA = tetrahydrofurfuryl alcohol, diol = 1,2-pentanediol, FA = furfuryl alcohol. [c] Qualitative analysis indicates that this is largely FA in agreement with the results of Bremner and Keeys.[3]

On the basis of the products observed and the data obtained, the reaction sequence involved must be as shown



The 1,2-pentanediol must be a product of direct reaction of furfuryl alcohol since tetrahydrofurfuryl alcohol did not form this product under these conditions. Also 2-methyltetrahydrofuran and 2-pentanol are formed by further reaction of 2-methylfuran since neither of these products are formed from tetrahydrofurfuryl alcohol in yields of greater than 1%. This conclusion is also drawn from the results shown in Table II where the yield of pentanol is reported under similar conditions of feed rate and gas flow. Traces of 2-pentanone were found occasionally, in contrast to the reported[8] results which were obtained at very low gas to feed ratio.

TABLE II

CONVERSION TO PENTANOLS OVER CATALYST 2

MeTHF feed T (°C.)	MeTHF feed % Conversion	MeF feed T (°C.)	MeF feed % Conversion
200	<2	120	3
300	9	150	21
400	35	180	63

(8) C. Wilson, *J. Am. Chem. Soc.*, **70**, 1313 (1948)

The rate of formation of 2-methylfuran (hydrogenolysis of side chain) is increased more rapidly by a temperature increase than either the rate of formation of tetrahydrofurfuryl alcohol (hydrogenation of nucleus) or pentanediol (hydrogenolysis of the nucleus). From the kinetic data, there is a temperature at which the conversion of furfuryl alcohol to 2-methylfuran reaches a maximum. Any further increase in temperature serves mainly to increase the rate of formation of other products. The actual temperature would be expected to depend on rate of feed as well as contact time. However, Table III shows that the rate of hydrogen flow had essentially no effect on the composition of the product in the range of 8:1 to 30:1 mole ratio of hydrogen to feed. A rather significant decrease in the amount of hydrogenolysis products (pentanediol and pentanol) was observed when the rate of feed was increased, while no such change was observed in the amounts of hydrogenated products. Since it was previously established that copper acts primarily as a hydrogenation catalyst, it may be concluded that the hydrogenation reactions must require an active site on a portion of the catalyst which is copper whereas the hydrogenolysis requires copper chromite.

TABLE III

Effect of gas flow and feed rate at 218°C. over catalyst 2

Feed rate	20 g./hr.	20 g./hr.	5 g./hr.
Gas flow	30:1	10:1	10:1
MeF	91.5	93.1	84.8
MeTHF	3.2	3.4	4.0
2-Pentanol	1.5	0.8	2.1
THFA	1.4	0.4	0.8
1,2-Pentanediol	2.5	2.3	8.3

Since the three hydrogenolysis reactions are competing, with the formation of 2-methylfuran being the lower energy process, an increase in feed rate leads to the preferential formation of 2-methylfuran. A saturation point would probably be reached where the formation of pentanol would not occur and the formation of pentanediol would be minimized.

In the calculation of kinetic data, the rate constants were taken as percentage yields. For 2-methylfuran the rate constants, shown in Table IV, were taken as the yield of 2-methylfuran plus the yields of 2-methyltetrahydrofuran and pentanol in keeping with the assumption that these products arise from further reaction of methylfuran. Further evidence for this assumption was obtained by taking samples at various depths in the catalyst bed. When about half of the catalyst bed length was used the yield of methylfuran was 99%. A plot of $-\log k$ *vs.* 1/T did not shown any differences in slope for each copper chromite catalyst which could not be attributed to experimental error. Therefore the values were averaged and plotted to obtain 24.1 ± 1.8 k cal/mole for the heat of activation in the formation of methylfuran. Similar calculations for the formation of tetrahydrofurfuryl alcohol gave increasing heats of activation as the copper content of the catalyst increased. The figures are 26.7 ± 3.0 for catalyst 1, 35.7 ± 3.0 for catalyst 2, 38.7 ± 3.0 for catalyst 3, and 28.7 ± 3.0 for catalyst 4.

TABLE IV

LOGARITHM OF RATE CONSTANTS FOR FORMATION OF MeF

Catalyst	200°	175°	150°	125°	100°
1	1.984	1.525	0.973	—	—
2	1.982	1.874	1.420	0.204	−0.689
3	1.967	1.858	1.248	0.431	—
4	1.986	1.988	1.093	0.380	+0.041

EXPERIMENTAL

Apparatus. The reaction chamber was a vertical glass tube 20 in. long and 20 mm. in diameter, externally heated by means of nichrome wire, containing 2 thermocouples at 6 and 12 in. depths, and a glass wool plug as support for the catalyst. A glass vaporizer was constructed to permit admixture of the preheated hydrogen and feed before entering the reaction chamber. The product was cooled by means of a cold water condenser followed by dry ice traps. The hydrogen gas was vented to the atmosphere after the cooling traps.

Typical run. A catalyst charge of 160 g. was used. The catalyst was reduced by heating to 140° under a nitrogen flow of 413 liters/hr. and a hydrogen flow of 45 liters/hr. The nitrogen flow was gradually cut to zero over 3 hr. and the temperature was then raised to 210° until no further evolution of water of reduction occurred. The water given off from catalyst 2 corresponded to a reduction of 71% of the catalyst. When the reduction reached this point, the hydrogen flow was raised to 63 l./hr. and furfuryl alcohol (Q.O. FA) was added to the vaporizer by means of a peristaltic action pump at a rate of 20 g./hr. At least a 1 hr. conditioning run was used in all cases and the actual run was made over a period of 3 to 4 hr. In all runs used for the kinetic data, this feed rate and gas flow were used.

Catalysts. All catalysts used were prepared and analyzed by The Harshaw Chemical Company and were one-eighth inch tablets.

Analysis of products. The organic layer was analyzed using a Perkin-Elmer Vapor Fractometer containing a column packed with material in which didecyl phthalate was the stationary liquid phase. Analysis of the water layer showed not more than 0.2% of any one component and was not used in the calculations. To arrive at an analysis of the product for furfuryl alcohol, the product was distilled up to 101° and the residue was analyzed by the Hughes-Acree technique.

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BARRINGTON, ILL.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Synthesis and Infrared Spectra of Some Indole Compounds[1]

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Examination of the infrared spectra in the solid state of a number of indole compounds substituted in the pyrrole ring shows regularities in the 3200–3400 cm.$^{-1}$ (NH) region and in the 1610–1780 cm.$^{-1}$ (CO and COOH) region. Two effects were observed: (1) in each region the band appeared at a lower frequency for the 3-substituent as compared with the 2-substituent, and (2) electron-withdrawing groups in the 2- or 3-position shifted the NH vibration to lower frequencies and electron releasing groups shifted it to higher frequencies. Four new indole compounds were synthesized: 1,1′-oxalylbis(3-methylindole), bis(1-methyl-3-indolyl)glyoxal, ethyl 1-methylindole-3-carboxylate, and 1-methylindole-3-carboxylic acid. A compound previously assigned both the 2-indolyl diketone and 3-indolyl diketone structures was synthesized independently and shown to be the latter.

The molecular structures of a number of indole compounds have been examined by means of infrared spectral analysis; however, systematic studies reflecting the peculiarities of the indole nucleus are lacking. Of note in this direction is the contribution of Brown, Henbest, and Jones,[3] who listed the principal infrared bands of six indoles and generalized that the strong bands at 1410 and 1550 cm.$^{-1}$ in 2-methylindole and at 1090 cm.$^{-1}$ in 3-methyl- and 3-*n*-propylindole differentiate 2- and 3-alkylindoles. Snyder and Eliel[4] have reported infrared spectra for four indole compounds. Fuson, Josien, Powell, and Utterback[5] studied the NH stretching frequency of indole as a function of concentration in carbon tetrachloride and assigned the band at 3420 cm.$^{-1}$ to associated NH. Recently, Ballantine, *et al.*,[6] have reported that in 3-acylindoles, the NH band and the CO band occur at lower frequencies than for the corresponding 2-substituted compounds. The purpose of the present investigation was to examine more extensively the infrared spectra of indole compounds with the intention of extending the previous studies, particularly that of footnote 6.

Syntheses. Ethyl 1-methylindole-3-carboxylate was synthesized by the action of methyl iodide and ethanolic sodium ethylate on ethyl indole-3-carboxylate. Quantitative saponification gave 1-methylindole-3-carboxylic acid. Non-depression of the mixture melting point and the identity of their infrared spectra showed this sample and the one prepared from bis(1-methyl-3-indolyl)glyoxal by alkali fusion to be identical.

The action of oxalyl chloride upon indole at 37° gave indole-3-glyoxalyl chloride. The structure of this compound was incorrectly assigned by Giua[7] who first reported it in 1924. His proof was based upon fusion with potassium hydroxide which gave indole-2-carboxylic acid. This acid is somewhat unstable at the fusion temperature employed and rearrangement may have taken place during fusion. Thus, Ciamician and Zatti[8] oxidized skatale during fusion with potassium hydroxide, and obtained both indole-2- and indole-3-carboxylic acids, indicating carbon-carbon rupture. In 1954 Speeter and Anthony[9] firmly established the correct structure for indole-3-glyoxalyl chloride when (1) by ammonolysis and reduction with lithium aluminum hydride, tryptamine was obtained, and (2) by alcoholysis the acid chloride was converted to ethyl indole-3-glyoxylate, a compound known for some time.

The assignment of position of carbonyl attachment in bis(3-indolyl)glyoxal also has been a subject of controversy. In 1922 Sanna[10] first isolated this compound from the reaction of oxalyl chloride with indolylmagnesium bromide. This Grignard reagent is active only in the 1- and 3-positions. The assignment of structure as bis(2-indolyl)glyoxal was based upon analysis for the elements, fusion with potassium hydroxide, and oxidation with hydrogen peroxide to indole-2-carboxylic acid. In 1924, however, Majima and Shigematsu[11] repeated the work and criticized the assignment because they found that oxidative fusion with potassium hydroxide had given them indole-3-carboxylic acid. The experience of the latter authors was confirmed in the present study.

Bis(3-indolyl)glyoxal is an unexpectedly stable compound, remaining unreactive to a refluxing solution of potassium hydroxide in propylene glycol, to benzyl ketone under a wide variety of conditions,

(1) Taken from part of the thesis submitted to the Graduate Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the M.S. degree, 1956.

(2) To whom inquiries should be directed.

(3) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3174 (1952).

(4) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 1857 (1948).

(5) N. Fuson, M. L. Josien, R. L. Powell, and E. Utterback, *J. Chem. Phys.*, **20**, 145 (1952).

(6) J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings, and A. Robinson, *J. Chem. Soc.*, 2227 (1957).

(7) M. Giua, *Gazz. chim. ital.*, **54**, 593 (1924).

(8) G. Ciamician and C. Zatti, *Ber.*, **21**, 1930 (1888).

(9) M. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(10) G. Sanna, *Gazz. chim. ital.*, **52 II**, 165 (1922).

(11) R. Majima and T. Shigematsu, *Ber.*, **57B**, 1449 (1924).

and to periodic acid. However, a positive carbonyl test is obtained with 2,4-dinitrophenylhydrazine. Absorption in the infrared at 3311 and 3425 cm.$^{-1}$ suggests that the compound may exist as an enolic ketone. Evidence presented here in support of the 3,3′-assignment, aside from inferences drawn from spectral analysis, is derived from a new synthesis based on the action of an equivalent amount of indolylmagnesium bromide upon indole-3-glyoxalyl chloride which gave a 93% yield of bis(3-indolyl)-glyoxal. Identity was proved by mixture melting point with a sample obtained from a repetition of the Sanna procedure and duplication of infrared spectra of the two samples.

EXPERIMENTAL[12]

General. All of the compounds were prepared and crystallized as indicated in Table 1. Many of the compounds were synthesized from indole or skatole, which were generously supplied by Norda Essential Oils and Chemicals Co., New York. Molecular weights were calculated from cryoscopic measurements in benzene using 0.300 g. of the compound in about 5 ml. of benzene. The procedure was checked for accuracy with benzophenone whose molecular weight was obtained within 5% on each of three successive trials.

1,1′-Oxalylbis(3-methylindole). 3-Methylindolylmagnesium bromide was prepared by adding a solution of skatole (36.1 g., 0.275 moles) in anhydrous ether (50 ml.) to ethylmagnesium bromide (0.275 moles) in anhydrous ether (300 ml.) under nitrogen in a 1 l. flask equipped with a stirrer, vertical water-condenser, and mercury valve. Following the evolution of ethane showed that one hour of reflux was required after addition for completion of the reaction. At 0°, oxalyl chloride (17.0 g., 0.134 mole) in anhydrous ether (50 ml.) was added dropwise. The mixture was refluxed for 1 hr. cooled, and decomposed by the slow addition of 5% sodium bicarbonate (200 ml.). After acidifying cautiously with 5% hydrochloric acid (250 ml.) with stirring, the aqueous layer was discarded and the ether solution was washed until neutral with water and dried over anhydrous sodium sulfate. After filtration, the ether was distilled, the residue was dissolved in acetone (Darco G-60), and recrystallized by the addition of water to incipient precipitation while hot. Another recrystallization from acetone (20 ml.) and water (10 ml.) gave the white product (10.1 g., 23.9%), m.p. 183.6–184.2° (λ_{min} 222 mμ, log ε 4.21; 281 mμ, log ε 3.91; λ_{max} 255 mμ, log ε 4.57; 306 mμ, log ε 4.10).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86; mol. wt., 316. Found: C, 76.00; H, 5.02; N, 8.90; mol. wt., 297.

Boiling a small amount of the compound with 5% sodium hydroxide and chilling at 5° for a few hours yielded skatole, which was identified by melting point and mixture melting point with an authentic sample. The compound failed to give a hydrazone when warmed with methanolic 2,4-dinitrophenylhydrazine in the presence of hydrochloric acid. It failed to condense with benzyl ketone in ethanolic potassium hydroxide solution at room temperature or at reflux, conditions under which the compound saponifies. It also failed to condense with *o*-phenylenediamine after one hour's reflux in glacial acetic acid.

Bis(1-methyl-3-indolyl)glyoxal. Oxalyl chloride (6.3 g., 0.05 mole) in anhydrous ether solution (50 ml.) was added dropwise with stirring under nitrogen to a solution of 1-methylindole (13.1 g., 0.10 mole) in anhydrous ether (200 ml.) at room temperature in 2 hr. and allowed to stand overnight. After distilling the mixture to dryness at reduced pressure, the residue was dissolved in acetone (Darco G-60) and recrystallized by the addition of water to incipient precipitation while hot. The solution was cooled, filtered, and dried. Two further recrystallizations from benzene (150 ml.) gave a lustrous white compound (8.1 g., 51.2%), m.p. 268–269°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86; mol. wt., 316. Found: C, 76.02; H, 5.08; N, 8.90; mol. wt. 305.

The compound (160 mg.) proved completely unreactive when refluxed with benzyl ketone (100 mg.) and potassium hydroxide (20 mg.) for 4 hr. in propylene glycol (5 ml.), dilution with water returning the original material (150 mg.). The compound was insoluble in 5% hydrochloric acid; it gave an immediate red-brown precipitate with methanolic 2,4-dinitrophenylhydrazine and hydrochloric acid, but failed to react with an equivalent amount of *o*-phenylenediamine when refluxed for 1 hr. in glacial acetic acid.

The compound (1.00 g.) was fused with potassium hydroxide pellets (10.0 g.) in a nickel crucible at 200° for 0.5 hr. with frequent stirring. After cooling, the contents were dissolved in hot water (carbon), filtered, cooled, and brought up to *p*H 3 with 5% hydrochloric acid. Cooling and standing at 5° for 2 hr. gave a slightly red product which was washed with water and dried. Sublimation at 150° (1 mm.) gave a white compound (0.77 g., 69.6%), m.p. 205–206°. A mixture melting point was not depressed, and the infrared spectrum proved identical with that of 1-methylindole-3-carboxylic acid prepared below.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00; neut. equiv., 175. Found: C, 68.34; H, 5.40; N, 7.97; neut. equiv., 174 ± 3.

Ethyl 1-methylindole-3-carboxylate. Metallic sodium (0.100 g., 4.35 milligram atoms) was dissolved in ethanol (5 ml.) previously dried over sodium and distilled. After solution of the sodium was complete, ethyl indole-3-carboxylate (0.700 g., 4.35 mmoles) was added and the solution was refluxed for 15 min. After cooling, methyl iodide (3 ml.) was added. The solution, 15 min. later, was refluxed for 1 hr. and then distilled to dryness at reduced pressure. Ether and water were added for complete solution and the aqueous layer was discarded. The ether solution was washed with water, dilute hydrochloric acid, water again, and then dried over anhydrous sodium sulfate, filtered, evaporated, dissolved in warm ethanol (2 ml.), precipitated with water (2 ml.), and allowed to crystallize overnight at 5°. Filtration, air drying, and then sublimation at 100° (1 mm.) gave a white compound (0.710 g., 80%), m.p. 69.7–70.2°, insoluble in dilute hydrochloric acid.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89; sapon. equiv., 203. Found: C, 71.04; H, 6.33; N, 6.92: sapon. equiv., 204 ± 4.

1-Methylindole-3-carboxylic acid. Ethyl 1-methylindole-3-carboxylate (0.216 g.) was refluxed 4 hr. with 0.0995*N* sodium hydroxide (25.00 ml.), cooled, and titrated to the disappearance of phenolphthalein end point with 0.1030*N* hydrochloric acid (13.90 ml.), indicating the saponification equivalent reported above for the ester. Complete acidification precipitated the acid, which was filtered, air-dried, and sublimed as above to give the white compound (0.181 g., 98.4%), m.p. 205–206°.

Bis(3-indolyl)glyoxal. Indole-3-glyoxalyl chloride was prepared at −20° in 91% yield following the procedure of Giua.[7] It could be stored for short periods in a vacuum desiccator. A solution of indole (5.90 g., 0.05 mmole) in anhydrous ether (10 ml.) was added to ethylmagnesium bromide (0.05 mole) in anhydrous ether (200 ml.). Ethane was evolved for 1 hr. while the solution was refluxed after the addition was completed. The Grignard solution was cooled to −10° and the granular indole-3-glyoxalyl chloride (0.05 mole) was added all at once with efficient stirring and maintained at this temperature for 1 hr. The mixture was allowed to warm to room temperature and stand overnight. After the cautious addition of 200 ml. of cold 5% aqueous sodium

(12) All melting points are corrected.

bicarbonate with stirring, the mixture was filtered. The solids were distilled with steam to remove unreacted indole, filtered hot, air-dried, and then extracted with methanol in a Soxhlet apparatus for 6 hr. After filtering the methanol extract (250 ml.) (Darco G-60), water was added to incipient crystallization and the solution was cooled. Recrystallization of the precipitate from acetone-water (Darco G-60) gave the canary yellow product (13.4 g., 93%), m.p. 279–280°. (λ_{min} 237 mμ, log ε 4.24; 254 mμ, log ε 4.25; 288 mμ, log ε 3.98. λ_{max} 247.5 mμ, log ε 4.28; 266.5 mμ, log ε 4.27; 326 mμ, log ε 4.27.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72; mol. wt., 288. Found: C, 75.45; H, 4.41; N, 9.13; mol. wt., 281.

A mixture melting point with the compound described by Oddo and Sanna[13] was not depressed, and the two infrared spectra were identical.

The compound proved completely unreactive when refluxed for 16 hr. with benzyl ketone and potassium hydroxide in propylene glycol, dilution with water returning the original material. An immediate precipitate was obtained from a methanolic solution of the diketone when treated with methanolic 2,4-dinitrophenylhydrazine and hydrochloric acid. The diketone is slightly soluble in aqueous 10% potassium hydroxide. It is unreactive in 16 hr. to periodic acid in 80% ethanol containing concentrated sulfuric acid at room temperature.

Ethyl indole-3-glyoxalate. Sample A was prepared by allowing indole-3-glyoxalyl chloride (1.1 g.) to dissolve in anhydrous ethanol (20 ml.) at 5° overnight. The mixture was warmed to 50° under a slow stream of nitrogen for a few minutes to complete solution of the ethyl ester. Water (5 ml.) was added, and the solution was allowed to cool slowly with final chilling to 0°. Filtration gave a lustrous white compound (0.6 g., 55%), m.p. 187°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11. Found; C, 66.81; H, 4.93.

Sample B was prepared by the procedure of Elks, Elliott, and Hems.[14]

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11. Found: C, 66.00; H, 5.19.

Either sample, when heated with concentrated aqueous ammonia, gave indole-3-glyoxamide, m.p. 252°. A mixture melting point of the esters or of the amides gave no depression. An ethanol solution of either sample gave the same ultraviolet spectrum (λ_{min} 230 mμ, log ε 3.62; 262 mμ, log ε 3.98; 283 mμ, log ε 3.46. λ_{max} 256 mμ, log ε 4.00; 267 mμ, log ε 3.99; 322 mμ, log ε 3.99).

The forms of this ester are interconvertible. Recovery of ester after seven days from either solution by concentration at 40° and dilution with an excess of water, followed by filtration and air-drying, gave A.

If, in the preparation of A given above, periods of long heating at reflux or heating in the presence of hydrogen chloride were not avoided, B resulted. At times, samples were obtained that showed absorptions of both the spectra of A and B.

X-ray powder diagrams showed the two samples to be polymorphic. The major peaks and a qualitative estimate of their intensities are listed in Table I. Two different infrared spectra were found for those samples of the ester, and they are given more completely in Table II. Unfortunately no solvent could be found with sufficient transparency in the interesting carbonyl region, which would dissolve a suitable concentration of the keto-ester so as to give solution spectra.

Indole-2-carboxylic acid. Recrystallization of indole-2-carboxylic acid from benzene yields variously either of two polymorphic samples (see Table II). Further, on one occasion crystallization of the acid from a supersaturated solution in ethylene dichloride, the spectrum showed absorption frequencies characteristic of both samples.

TABLE I

X-RAY POWDER DIFFRACTION LINES (Cu Kα-λ = 1.5418)

Preparation A			Preparation B		
2θ	Distance	Intensity	2θ	Distance	Intensity
3i. Ethyl indole-3-glyoxalate					
7.7°	11.5 Å	Medium	7.0°	12.6 Å	Weak
9.0	9.8	Very strong	7.7	11.5	Very strong
14.5	6.10	Weak	9.6	9.2	Very weak
15.4	5.75	Very weak	14.4	6.14	Medium
15.9	5.57	Very weak	14.9	5.94	Medium
17.4	5.09	Weak	15.4	5.75	Strong
18.2	4.87	Medium	16.8	5.27	Weak
			18.4	4.82	Very weak
2c. Indole-2-carboxylic acid					
5.1°	17.3 Å	Strong	5.9°	15.0 Å	Strong
5.9	15.0	Weak	11.8	7.5	Medium
10.3	8.6	Medium	15.0	5.9	Weak
11.8	7.5	Weak	15.5	5.7	Very weak
19.0	4.67	Medium	16.4	5.4	Weak
19.6	4.53	Weak	17.2	5.15	Weak
20.3	4.37	Strong	25.2	3.53	Weak
22.9	3.88	Weak			
24.2	3.67	Medium			
25.0	3.56	Medium			

Indole-3-glyoxalic acid. This compound was prepared according to the procedure of Elks, Elliott, and Hems,[14] dried, and recrystallized from chlorobenzene (λ_{min} 229.5 mμ, log ε 3.68; 282 mμ, log ε 3.61. λ_{max} 256 mμ, log ε 3.99; 312 mμ, log ε 3.92).

Bis(3-indolyl)glyoxal monosodium salt. Metallic sodium (56 mg., 2 m-atoms), weighed under hexane, was added to dry methanol (2 ml.). Bis(3-indolyl)glyoxal (0.576 g., 2 mmoles) was then added and the solution was allowed to stand overnight under methanol vapor. The solution was distilled to dryness at 1-mm. pressure leaving an orange-yellow powder which was used for an infrared spectrum in a potassium bromide disk.

Potassium carboxylate salts—compounds 2a, 2b, 2i, 3e. Samples of these salts for infrared spectra in potassium bromide disks were obtained as in the preceding paragraph. A small weighed amount was mixed with a few milliliters of methanol and an equivalent quantity of alkali was titrated into the mixture. When solution was complete, the solvent was distilled to dryness at 1-mm. pressure at room temperature during 4 hr.

SPECTRA

Polar effects in infrared spectra are currently receiving increased attention.[15,16] The purpose of part of the present investigation is to present the results of examining the spectra of a variety of indole derivatives for regularities. Table III lists the

(13) B. Oddo and G. Sanna, *Gazz. chim. ital.*, **51 II**, 337 (1921).

(14) J. Elks, D. F. Elliott, and B. A. Hems, *J. Chem. Soc.*, 629 (1944).

(15) L. J. Bellamy and R. L. Williams, *J. Chem. Soc.*, 4294 (1957) and preceding papers.

(16) W. R. Vaughan and G. K. Finch, *J. Org. Chem.*, **21**, 1201 (1956).

TABLE II

INFRARED ABSORPTION FREQUENCIES[a]

2a.	Potassium 2-indolylcarboxylate	3425m; 3226w; 3240s; 1529m; 1410s; 1342m; 1330m; 1287w; 1237w cm^{-1}.
2b.	Potassium 3-indolylcarboxylate	3390m; 3257m; 1614vw; 1580w; 1549s; 1515m; 1490w; 1342w; 1331w; 1283w; 1240w cm^{-1}
2j.	Potassium N-methyl 3-indolylcarboxylate	3257m; 1614vw; 1538s; 1508m; 1465s; 1429m; 1376m; 1350w; 1313m; 1242m cm^{-1}
3e.	Potassium 3-indolylglyoxalate	3367m; 3165w; 1623m; 1600s; 1511m; 1406m; 1348m; 1308w; 1244w cm^{-1}
2c-A	Indole-2-carboxylic acid	3413m; 1678s; 1577w; 1543m; 1408w; 1453s; 1342w; 1311m; 1263m; 1196w; 1151w; 1119w; 1103w; 937w; 833m; 775m; 749m; 736m
2c-B	Indole-2-carboxylic acid	3356m; 1709s; 1520m; 1441m; 1416m; 1348m; 1305w; 1238m; 1196s; 1163w; 1117w; 846w; 820m; 769s; 741m; 728m
3i-A	Ethyl indole-3-glyoxalate	3185s; 1733s; 1623s; 1587m; 1515m; 1493m; 1437s; 1403w; 1337w; 1316w; 1263s; 1236s; 1154m; 1147m; 1130s; 1094m; 1020m; 940m; 862m; 789m; 763s; 759m, 658m
3i-B	Ethyl indole-3-glyoxalate	3226s; 1724s; 1634s; 1618s; 1590w; 1506s; 1433s; 1401m; 1339w; 1314w; 1267s; 1241s; 1157w; 1130s; 1101w; 1020m; 1008m; 938m; 874m; 819s; 809w; 773m; 743s; 653m
4c.	Bis(3-indolyl)glyoxal	3425m; 3311s; 1623m; 1610s; 1515s; 1495w; 1468w; 1439s; 1416m; 1339w; 1311w; 1242s; 1185w; 1148w; 1136w; 1120s; 1103s; 1087m; 1010w; 874w; 821w; 784m; 779s; 759m; 747m; 735s
4d.	Bis(3-indolyl)glyoxal sodium	3367s; 1623m; 1595s; 1515s; 1460m; 1422s; 1395m; 1333w; 1307m; 1274m; 1241m; 1215m; 1167w; 1143w; 1117m; 1103m; 1087w; 1010w; 965w; 935w; 881m; 853m; 804w; 778s; 748s

[a] Intensity designations: s = strong; m = medium; w = weak.

data obtained for the NH and the CO regions for compounds in the solid state.

The NH region. Three conclusions may be reached from the data of Table III. The first is that the indoles unsubstituted in the 1-position absorb in the range 3425 to 3144 $cm.^{-1}$ This compares with the range reported previously,[5] 3472 to 3378 $cm.^{-1}$ The range reported by Ballantine, *et al.*,[6] for 3-acylindoles begins at slightly lower frequencies, i.e., 3135 $cm.^{-1}$ and that of Tanner[17] at 3020 $cm.^{-1}$. When the 1-position is substituted (1b, 2i, 2j, 2k, 4a, 4b) no band appears in this region. This observation has been made previously[18] for bis(2-pyrryl)glyoxal with absorption at 3340 $cm.^{-1}$ compared to bis(1-methyl-2-pyrryl)glyoxal which shows no band from 4000 $cm.^{-1}$ to 3300 $cm.^{-1}$ and for a number of indoles.[4,6,17] The NH region is also relatively free of CO overtone frequencies—an observation substantiated by the spectra of N-substituted carbonyl indoles (4a, 4b) and indole acids (1d, 2c, 2d, 2j).

The second conclusion is that the frequency at which the NH band appears is affected by the electronegativity of the substituent itself. As has been mentioned earlier, this was first observed by Ballantine on a more limited group of compounds. Thus, with electron-releasing groups the NH band is shifted to frequencies higher than the NH band of indole (1a, c, d, e, f). Electron-attracting groups shift the NH band to lower frequencies, as far as 3144 $cm.^{-1}$ for 3-indolealdehyde (3b).

The third observation is that for a given substituent placed in the 2- or in the 3-position, the one in the 3-position has a larger effect. Thus, the NH band in skatole appears at 3425 $cm.^{-1}$ while that for 2-methylindole is at 3401 $cm.^{-1}$. For an example of an electron-withdrawing group the NH band of indole-2-aldehyde appears at 3185 $cm.^{-1}$ and that for the 3-isomer at 3144 $cm.^{-1}$. Other examples are given in Table I.

Among indole compounds it is well known that polar effects are greater with the 3-substituent than with the 2-substituent. Thus, indole-3-carboxylic acid (K_a = 0.00056) is a weaker acid than indole-2-carboxylic acid (K = 0.0177). Electron release from the vinylogous nitrogen to the carboxylic group has been offered as the reason for the greater effect at 3. For the influence of substituents on the NH band compare 1e and 3e (CH_3); 2a and 2b (—COOK); 2c-A and 2c-B with 2d (—$COOCH_3$); 3a and 3b (—CHO).

The relative order of substituent effect on the NH absorption agrees also with that established by

(17) E. M. Tanner, *Spectrochim. Acta*, 9, 282 (1957).

(18) M. Litt, M. S. Thesis, Polytechnic Institute of Brooklyn, 1953.

TABLE III

PHYSICAL CONSTANTS AND INFRARED ABSORPTION FREQUENCIES (cm.$^{-1}$)

	Compound	M.P., °C. and Recrystallization Solvent	Ref.	N—H	COO	C=O
1 a.	Indole	52.5 Hexane	[a]	3390		
b.	1-Methylindole	[B.p. 115° (12/mm.)]	[b]	——		
c.	2-Hydroxymethylindole	76–77 Hexane and C Cl$_4$	[c]	3378		
d.	3-Indole-3-acetic acid	168 ethylene dichloride	[d]	3378	1706	
e.	2-Methylindole; Methylketole	62 hexane	[e]	3401		
f.	3-Methylindole; Skatole	96 hexane	[a]	3425		
g.	Indole-3-acetaldehyde		[3]			1705
2 a.	Potassium indole-2-carboxylate		[f]	3413	Table	
b.	Potassium indole-3-carboxylate		[f]	3390	Table	
cA.	Indole-2-carboxylic acid	206–207 Benzene	[c,13]	3413	1678	
cB.	Indole-2-carboxylic acid	206–207 Benzene	[g]	3356	1712	
d.	Indole-3-carboxylic acid	222 Aqueous acetone	[h]	3300	1642	
e.	Methyl indole-2-carboxylate	151–152 Aqueous methanol	[h]	3300	1689	
f.	Methyl indole-3-carboxylate	147–148 Aqueous methanol	[i,13]	3257	1669	
g.	Ethyl indole-2-carboxylate	125–126 Aqueous ethanol	[h]	3322	1695	
h.	Ethyl indole-3-carboxylate	124 Aqueous ethanol		3257	1669	
i.	Potassium 1-methylindole-3-carboxylate		[f]	——	Table	
j.	1-Methylindole-3-carboxylic acid	205–206 (Sublimed)	[f]	——	1639	
k.	Ethyl 1-methylindole-3-carboxylate	69–70 Aqueous Ethanol		——	1681	
3 a.	Indole-2-aldehyde	138 Ethyl ether	[j]	3185		1675
b.	Indole-3-aldehyde	198 Dilute ethanol	[k]	3144		1634, 1618
c.	Methyl 3-indolyl ketone	191 Ethanol	[l]	3165		1618
d.	Indole-3-glyoxalyl chloride	138 Ethyl ether	[8]	3236	1792	1629
e.	Potassium indole-3-glyoxalate		[f]	3367	Table	1631
f.	Indole-3-glyoxylic acid	224 Chlorobenzene	[13]	3226	1714	1621
g.	Indole-3-glyoxamide	252 Dilute ethanol	[8]	3425, 3257	1669	1621
h.	Methyl indole-3-glyoxalate	224 Methanol	[8]	3226	1736	1621
iA.	Ethyl indole-3-glyoxalate	187 Ethanol	[8]	3185	1733	1626
iB.	Ethyl indole-3-glyoxalate	187 Ethanol	[13]	3226	1724	1634, 1621
4 a.	Bis(3-methylindol-1-yl) glyoxal	183–184 Aqueous acetone	[f]	——	1689	
b.	Bis(1-methylindol-3-yl) glyoxal	268–269 Aqueous acetone	[f]	——		1623, 1610
c.	Bis(3-indolyl) glyoxal; 3,3-indil	279–280 Aqueous acetone	[f]	3425, 3311		1623, 1610
d.	Bis(3-indolyl) glyoxal monosodium salt		[f]	3367		1623, 1610

[a] Commercially available. [b] R. Stolle, *J. prakt. Chem.*, (2) **128**, 1 (1930); P. Julian, *J. Am. Chem. Soc.*, **71**, 3206 (1949). [c] W. J. Brehm, *J. Am. Chem. Soc.*, **71**, 3514 (1949). [d] C. Heidelberger, *J. Biol. Chem.*, **179**, 139 (1949). [e] L. Marion and C. W. Oldfield, *Can. J. Research*, **25B**, 1 (1947). [f] *Cf.* Experimental. [g] B. Oddo, *Gazz. chim. ital.*, **42I**, 361 (1912). [h] J. R. Johnson, R. B. Hasbrouck, J. D. Dutcher, and W. F. Bruce, *J. Am. Chem. Soc.*, **67**, 427 (1945). [i] A. Michael, *Ber.*, **38**, 2091 (1905). [j] W. I. Taylor, *Helv. Chim. Acta.* **33**, 164 (1950). [k] A. C. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, *J. Am. Chem. Soc.*, **68**, 1156 (1946). [l] B. Oddo and L. Sessa, *Gazz. chim. ital.*, **41I**, 240 (1911).

Sutton from an analysis of dipole moment data.[19] Qualitatively, the shifts are in agreement with the Hammett sigma values[20] and the nuclear magnetic resonance shifts given by Gutowsky *et al.*[21] The comparison of the infrared shifts with the Hammett sigma values, which refer to rates of reaction or to equilibria, is strained since the sigma values involve a dependence upon the transition state. A better comparison would be the nuclear magnetic resonance spectra but too few are presently available.

For the two indole-2-carboxylic acids, the NH frequencies at 3413 cm.$^{-1}$ and 3356 cm.$^{-1}$ bracket that of indole, 3390 cm.$^{-1}$. The band at 3356 cm.$^{-1}$ may be a consequence of intermolecular hydrogen bonding, but that at 3413 cm.$^{-1}$ can be rationalized in terms of the *p*-activating effect COO^- group toward nucleophilic substitution.[22] This hypothesis is in agreement with the similar shifts found in the indole carboxylic acid salts (2a, 2b). An alternative explanation may lie in association phenomena,[5] but concentration studies were not made in the present work.

Two different NH bands are evident in 3-indolylglyoxamide, 3427 and 3257 cm.$^{-1}$. The former may be assigned to the unaffected amidic hydrogen, while the latter is consistent with other imidic ring hydrogens.

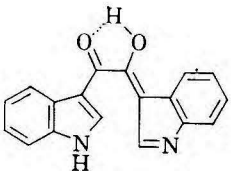
Of interest also are the two absorption frequencies in bis(3-indolyl)glyoxal at 3425 and 3311 cm.$^{-1}$. Models show that with the carbonyl groups cissoid or transoid there can be no intramolecular hydrogen bonding of NH to oxygen. However, tautomerism to a mono-enol would account for the two bands. The sequence of NH frequencies in the series given in Table IV (3-indolyl-CO-R) would tend to

(19) L. E. Sutton, *Proc. Roy. Soc. London*, **133 A**, 668 (1931); C. P. Smyth, *Dielectric Behavior and Structure*, McGraw-Hill Book Co., New York, 1955, p. 314.

(20) H. H. Jaffe, *Chem. Revs.*, **53**, 222 (1953).

(21) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Am. Chem. Soc.*, **74**, 4809 (1952).

(22) J. F. Bunnett, R. J. Morath, and T. Okamoto, *J. Am. Chem. Soc.*, **77**, 5055 (1955).



support this conclusion, since normal indole-3-glyoxalic compounds have now been shown to exhibit NH absorption at frequencies about 3200 cm.$^{-1}$ which is considerably out of line with that occurring in (4c).

TABLE IV

R	Compound and Type	NH Frequencies
$-COOC_2H_5$	3i-A keto-ester	3185 cm^{-1}
	3i-B	3226
$-COOCH_3$	3h	3226
$-COOH$	3f keto-acid	3226
$-COCl$	3d keto-acid-chloride	3236
$-CONH_2$	3g keto-amide	3257
$-C(OH)=C-CH=N-Ph$	4c vinylogous keto-imine	3311

Two absorption bands also appear for 2-hydroxymethyl indole. The band at 3378 likely NH while that at 3247 cm.$^{-1}$ is hydroxyl.

The carbonyl region. The most striking feature of indole spectra in this region is the pronounced shift to lower frequencies which accompanies conjugation with the indole nucleus. Compare, for instance, compounds 2d, 2f, 2h, 2j, and 2k which have carboxyl groups attached directly to the 3-position in indole with compounds 1d, 3f, and 3g where the carboxyl group is separated from the ring by a CH_2 or a CO group (see also footnote 6).

As with the NH region the shift to lower frequencies is greater with 3-substituents than with 2-substituents. For example, see the isomeric aldehydes in Table III.

Carbonyl frequencies have previously been reported as low as 1637 cm.$^{-1}$ for *p*-hydroxyacetophenone and 1634 cm.$^{-1}$ for *p*-aminoacetophenone.[23] The carbonyl absorptions are seen to be restricted to a much narrower range—of the twelve indolealdehydes and ketones, all twelve have absorptions between 1675 and 1618 cm.$^{-1}$

The absorption of indole-3-glyoxalyl chloride at 1792 cm.$^{-1}$ appears to be in order as do the absorptions of the two amides, compounds 3g and 4a, at 1669 and 1689 cm.$^{-1}$, respectively, while the glyoxalyl chloride also shows medium intensity absorption at 1605 and 1590 cm.$^{-1}$ in addition to carbonyl absorption at 1621 cm.$^{-1}$.

The infrared spectra for the four carboxylate salts are listed in Table IV for the range 3500 to 1250 cm.$^{-1}$. No attempt was made to avoid formation of hydrates and the medium band at 3250 cm.$^{-1}$ indicates their probable presence. One regularity is the medium absorption at 1529 cm.$^{-1}$ for the 2-derivative and 1515–1508 cm.$^{-1}$ for the 3-derivatives.

Bis(3-indolyl)glyoxal shows strong absorption at 1613 cm.$^{-1}$. Because of the unsaturation absorption which occurs in this region for all of the indoles, it difficult to make a definite assignment. Assignments in this region have been given to $-C(OH)=NH$, the enol form of acetylurethan (w 1608 cm.$^{-1}$);[24a] the $Ph-C(H)=N$ in 2-phenyl-2-thiazoline (s 1605 cm.$^{-1}$),[24b] and the $CH_3-C(H)=N$ in 3,5-dimethylpyrazole (1595 cm.$^{-1}$).[24c] Although it thus appears feasible to assign the band at 1613 cm.$^{-1}$ in bis(3-indolyl)glyoxal to an enolic form, bis[1-methyl-3-indolyl)glyoxal also absorbs at 1610 cm.$^{-1}$ and here tautomerism is not possible.

Throughout this paper it has been noted that there is a greater conjugation with a substituent in the 3-position as compared with one in the 2-position. For pyrrole just the opposite has been observed.[25]

Indoles in general may be classified as to solubility as those soluble in organic solvents, typified by indole and alkyl indoles, and those insoluble in organic solvents, typified by indoles with a strongly electron-attracting group in the 2- or 3-position. With the latter category it is not feasible to obtain infrared spectra in solution in solvents which do not themselves absorb in the critical NH and CO regions. Thus, the infrared study of indoles in solution in inert solvents where intermolecular interaction would be minimized compared with the solid state is strongly handicapped. For maximum utility, therefore, comparative infrared analysis has had to be made on indoles in the condensed phase.[26]

Examination of compounds in the condensed phase raises the question of the effect of concentration, and thus association, on the position of the absorption bands. Fuson *et al.*[5] have determined the effect of association for indole. Nevertheless, it was necessary to examine the compounds in the condensed phase. Since spectra in potassium bro-

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(24) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand, New York, 1949, (a) p. 159, (b) p. 211, (c) p. 223.

(25) M. Scrocco and R. Nicolaus, *Atti accad. nazl. Lincei. Rend., Classe sci. fiz., mat. e nat.*, 22, 500 (1957); *Chem. Abstr.*, 51, 17455e (1957).

(26) After the work reported here had been completed Tanner[17] pointed up the difference between the spectra of some indoles in the condensed state and in solution. For example, he reports the NH stretching frequency for indole-3-aldehyde as 3140 cm.$^{-1}$ (Nujol) and as 3250 cm.$^{-1}$ (solution in tetrahydrofuran).

mide pellets often afford a degree of resolution comparable to that of solution spectra, in the present study such pellets were employed. It was found, as hoped, that gross effects of intermolecular interaction would be the same or regular and that the comparative study could be made. However, in the solid state different infrared spectra may be observed due to polymorphism, and, indeed, two such cases were found in the present study, namely, ethyl indole 3-glyoxalate and indole-2-acid.

In conclusion it is hoped that the correlation of the greater shift for substituents in the 3- as compared to those for the 2-position will prove useful in assigning structure among indole compounds.

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Synthesis of 2-Azetidinones (β-Lactams)

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Eight *N*-substituted α-phenyl-β-amino acids, obtained by the addition of an amine to atropic acid, as well as a number of substituted β-amino acids, prepared by other procedures, were converted into 2-azetidinones. In some cases, esters of the acids were also employed. A useful method for the synthesis of certain 2-azetidinones was found to consist in the interaction of a β-amino acid chloride hydrochloride with dimethylaniline.

Hitherto, only one example of the addition of an amine, hydroxylamine, to atropic acid (α-phenylacrylic acid) has been reported; the reaction product was α-phenyl-β-aminopropionic acid.[3] Atropic acid can be obtained easily from tropic acid by a simple dehydration process.[4] Since tropic acid can now be synthesized readily,[5] it was feasible to prepare atropic acid in relatively large amounts and to study the addition of the following amines to this unsaturated acid: methyl-, allyl-, isopropyl-, cyclohexyl-, hexahydrobenzyl-, benzyl and β-phenylethylamine and aniline.[6] It was of interest to determine the extent to which the β-amino acids obtained (compounds 2, 4, 6, 8, 9, 10, 12, and 14, Table I) and their esters, as well as a number of additional β-amino acids and esters (Tables I and II) prepared by other procedures, could be employed for the synthesis of 2-azetidinones.

The β-amino acids, not obtained by the use of atropic acid, were synthesized in the following manner. Three β-amino acids were obtained by the addition of benzylamine to ethyl acrylate, methyl methacrylate and ethyl crotonate, respectively, and subsequent hydrolysis.

α - Methyl - β - phenyl - β - (benzylamino)-propionic and α,α-dimethyl-β-phenyl-β-(benzylamino)propionic acid were prepared by the alkaline hydrolysis of 1-benzyl-3-methyl-4-phenyl-2-azetidinone and 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone,[8] respectively.

β-Phenyl-β-aminopropionic acid was synthesized by interaction of benzaldehyde, malonic acid, and ammonium acetate.[9] This acid was converted into ethyl β-phenyl-β-aminopropionate which was then benzylated and hydrolyzed to yield β-phenyl-β-(benzylamino)propionic acid.[10] When ethyl β-phenyl-β-aminopropionate was hydrogenated and then benzylated, subsequent hydrolysis produced β-cyclohexyl-β-(benzylamino)propionic acid.

Ethyl cyclohexylcyanoacetate[11] was hydrogenated to form ethyl α-cyclohexyl-β-aminopropionate. The latter ester was converted into ethyl α-cyclohexyl - β - (benzylamino)propionate by treatment with benzyl chloride and also by interaction of the ester with benzaldehyde and hydrogenation of the resulting Schiff base. Hydrolysis of ethyl α-cyclohexyl-β-(benzylamino)propionate yielded the corresponding acid.

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TABLE I

SUBSTITUTED β-AMINO ACIDS AND THEIR HYDROCHLORIDES

$$\begin{array}{l} R'R''CCOOH \\ \quad\quad | \\ R'''CNHR \end{array}$$

	R	R′	R″	R‴	Yield, %	M.P., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1.	H	C_6H_5	H	H	25	222–224[a]					
2.	CH_3	C_6H_5	H	H	78	198–200	$C_{10}H_{13}O_2N$	67.00	66.93	7.31	7.37
3.	HCl of 2					183–184	$C_{10}H_{14}O_2NCl$[b]				
4.	CH_2=$CHCH_2$	C_6H_5	H	H	80	164–165	$C_{12}H_{15}O_2N$	70.22	70.05	7.37	7.30
5.	HCl of 4					168–169	$C_{12}H_{16}O_2NCl$[c]				
6.	$(CH_3)_2CH$	C_6H_5	H	H	65	182–183	$C_{12}H_{17}O_2N$	69.54	69.30	8.27	8.19
7.	HCl of 6					190–191	$C_{12}H_{18}O_2NCl$[d]				
8.	C_6H_5	C_6H_5	H	H	70	128–130	$C_{15}H_{15}O_2N$	74.66	74.69	6.27	6.31
9.	C_6H_{11}	C_6H_5	H	H	95	192–193	$C_{15}H_{21}O_2N$	72.84	72.69	8.56	8.32
10.	$C_6H_{11}CH_2$	C_6H_5	H	H	95	200–202	$C_{16}H_{23}O_2N$	73.53	73.22	8.86	9.05
11.	HCl of 10					160–162	$C_{16}H_{24}O_2NCl$[e]	64.52	64.41	8.12	7.77
12.	$C_6H_5CH_2$	C_6H_5	H	H	97	193–195[f]	$C_{16}H_{17}O_2N$[g]	75.28	75.32	6.71	6.68
13.	HCl of 12					174–176[h]	$C_{16}H_{18}O_2NCl$[i]	65.86	65.92	6.21	6.20
14.	$C_6H_5CH_2CH_2$	C_6H_5	H	H	97	193–194	$C_{17}H_{19}O_2N$	75.81	75.71	7.11	7.10
15.	HCl of 14					180–181	$C_{17}H_{20}O_2NCl$	66.77	66.82	6.59	6.70
16	$C_6H_5CH_2$	H	H	C_6H_5	78	185–187[j]					
17.	$C_6H_5CH_2$	CH_3	H	C_6H_5	67	170–173[k]					
18.	$C_6H_5CH_2$	CH_3	CH_3	C_6H_5	85	143–145[l]					
19.	$C_6H_5CH_2$	H	H	H	75	182–184[m]					
20.	$C_6H_5CH_2$	CH_3	H	H	81	150–152	$C_{11}H_{15}O_2N$[n]	68.37	68.44	7.82	7.83
21.	HCl of 20					131–133	$C_{11}H_{16}O_2NCl$[o]	57.50	57.62	7.02	7.02
22.	$C_6H_5CH_2$	H	H	CH_3	88	179–181[p]					
23.	$C_6H_5CH_2$	C_6H_{11}	H	H	78	213–214	$C_{16}H_{23}O_2N$[q]	73.53	73.39	8.87	8.76
24.	HCl of 23					230–232	$C_{16}H_{24}O_2NCl$[r]	64.52	64.37	8.12	8.03
25.	$C_6H_5CH_2$	H	H	C_6H_{11}	74	165–167	$C_{16}H_{23}O_2N$	73.53	73.59	8.87	8.97
26.	HCl of 25					138–140	$C_{16}H_{24}O_2NCl$	64.52	64.43	8.12	8.24

[a] A. MacKenzie and R. C. Strathern [*J. Chem. Soc.*, 82 (1925)], m.p. 222–224°. [b] Calcd.: N, 6.50; Cl, 16.44. Found: N, 6.66, Cl. 16.56. [c] Calcd.: N, 5.80; Cl, 14.64. Found: N, 5.91; Cl, 14.87. [d] Calcd.: N, 5.75; Cl, 14.55. Found: N, 5.89; Cl, 14.80. [e] Calcd.: Cl, 11.90; Found: Cl, 12.05. [f] J. Decombe [*Ann. chim. (Paris)*, 18, 81 (1932)], m.p. 190–195°. [g] Calcd.: N, 5.48. Found: N, 5.78. [h] J. M. Stewart and C. H. Chang [*J. Org. Chem.*, 21, 635 (1956)], m.p. 171–173°. [i] Calcd.: Cl, 12.14. Found: Cl, 12.23. [j] Ref. 10, m.p. 187–188°. [k] Ref. 7, m.p. 169–173°. [l] Ref. 8, m.p. 145–148°. [m] Ref. 10, m.p. 184–184.5°. [n] Calcd.: N. 7.25. Found: N, 7.23. [o] Calcd.: N, 6.10. Found: N, 6.08. [p] Ref. [f], m.p. about 191°. [q] Calcd.: N, 5.36. Found: 5.54. [r] Calcd.: Cl, 11.91. Found, Cl, 12.17.

Compounds 1 and 24 were recrystallized from water; 8 from aqueous methanol; 6, 19, 20, and 22 from ethanol; 15 from ethanol-ether; 3 and 7 from isopropyl alcohol; 11 and 26 from isopropyl alcohol–ether; 5 and 21 from methyl ethyl ketone; 13 from dimethoxyethane; 18 from chloroform; 2, 4, 9, 10, 12, 14, 16, 17, 23, and 25 from dimethylformamide.

TABLE II

ESTERS OF α-PHENYL-β-(BENZYLAMINO)PROPIONIC ACID AND THEIR HYDROHALIDE SALTS

$$\begin{array}{l} C_6H_5CHCOOR \\ \quad\quad | \\ CH_2NHCH_2C_6H_5 \end{array}$$

	R	M.P., °C. or B.P., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found
1.	CH_3	110 (20 mm.)	$C_{17}H_{19}O_2N$	75.80	75.75	7.10	7.25		
2.	HCl of 1	172–173	$C_{17}H_{20}O_2NCl$	66.78	66.74	6.59	6.77	11.60	11.90
3.	C_2H_5	116 (20 mm.)	$C_{18}H_{21}O_2N$	76.28	76.27	7.48	7.36		
4.	HCl of 3	169–170	$C_{18}H_{22}O_2NCl$	67.60	67.68	6.94	6.90	11.09	11.34
5.	HBr of 3	129–130	$C_{18}H_{22}O_2NBr$	59.34	59.76	6.09	6.35	21.94	22.14
6.	$(CH_3)_2CH$	46–48 124 (23 mm.)	$C_{19}H_{23}O_2N$	76.73	76.69	7.80	7.97		
7.	HCl of 6	163–164	$C_{19}H_{24}O_2NCl$	68.36	68.01	7.24	7.05	10.63	10.79
8.	$C_6H_5CH_2$[b]								
9.	HCl of 8	173–174	$C_{23}H_{24}O_2NCl$	72.35	72.29	6.33	6.28	9.28	9.33

[a] When distilled, the esters decomposed to a considerable extent even under more reduced pressure than that reported in the table. The yields before distillation ranged from 89–97%. [b] Decomposed extensively upon attempted distillation.

Compound 2 was recrystallized from dimethoxyethane; 4 and 5 from methyl ethyl ketone; 6 from aqueous ethanol; 7 and 9 from isopropyl alcohol.

TABLE III

SUBSTITUTED 2-AZETIDINONES

R'R''C—CO
R'''HC—NR

	R	R'	R''	R'''	Method	Yield, %	M.P. or B.P., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1.	$C_6H_5CH_2$	H	H	H	D	40	106–108					
					C	0[a]	(1 mm.)[a]					
2.	H	C_6H_5	H	H	A	28	114–116	C_9H_9ON[b]	73.45	73.64	6.16	6.18
3.	CH_3	C_6H_5	H	H	C	25	86–87 (0.1 mm.)	$C_{10}H_{11}ON$	74.51	74.51	6.88	6.96
4.	CH_2=$CHCH_2$	C_6H_5	H	H	C	48	103–104 (0.1 mm.)	$C_{12}H_{13}ON$	76.97	76.92	7.00	7.05
5.	$(CH_3)_2CH$	C_6H_5	H	H	C	84	90–92	$C_{12}H_{15}ON$	76.15	76.31	7.99	8.11
					B	54	(0.05 min.)					
6.	C_5H_{11}	C_6H_5	H	H	C	44	59–61	$C_{15}H_{19}ON$	78.56	78.70	8.34	8.42
7.	$C_5H_{11}CH_2$	C_6H_5	H	H	C	80	50–51	$C_{16}H_{21}ON$[c]	78.97	79.08	8.70	8.74
					B	31						
8.	$C_3H_5CH_2$	C_6H_5	H	H	C	72	70–72	$C_{15}H_{15}ON$[d]	80.99	81.14	6.37	6.44
					B	43						
					A	40						
9.	$C_6H_5CH_2CH_2$	C_6H_5	H	H	C	67	145–146	$C_{17}H_{17}ON$	81.24	81.01	6.82	6.79
					B	40	(0.05 mm.)					
10.	$C_6H_5CH_2$	CH_3	H	H	C	61	83–84 (0.1 mm.)	$C_{11}H_{13}ON$	75.40	75.16	7.48	7.33
11.	$C_6H_5CH_2$	C_6H_{11}	H	H	C	84	131–132 (0.05 mm.)	$C_{16}H_{21}ON$	78.99	78.69	8.69	8.75
12.	CH_3	H	H	C_6H_5	E	52	90–92 (0.6 mm.)	$C_{10}H_{11}ON$	74.51	74.55	6.88	6.91
13.	$C_6H_5CH_2$	H	H	C_6H_5	C	80	138–139 (0.1 mm.)[e]					
14.	$C_6H_5CH_2$	H	H	CH_3	C	76	85–86 (0.1 mm.)	$C_{11}H_{13}ON$[f]	75.40	75.46	7.48	7.59
15.	$C_6H_5CH_2$	H	H	C_6H_{11}	C	81	136–137 (0.1 mm.)	$C_{16}H_{21}ON$	78.99	79.09	8.69	8.62
16.	C_6H_5	C_6H_5	H	C_6H_5	E	7	132–133[g]	$C_{21}H_{17}ON$	84.25	84.15	5.72	5.83
17.	CH_3	CH_3	H	C_6H_5	E	81	105–106 (0.6 mm.)	$C_{11}H_{13}ON$	75.40	75.41	7.48	7.55
18.	$C_6H_5CH_2$	CH_3	H	C_6H_5	C	92	141–142					
					E	76	(0.1 mm.)[h]					
19.	$C_6H_5CH_2$	CH_3	CH_3	C_6H_5	C	92	153–155					
					E	84	(0.5 mm.)[i]					

[a] Ref. 10, b.p. 98–112° (2 mm.); yield 5%. [b] Calcd.: N, 9.52. Found: N, 9.46. [c] Calcd.: N, 5.76. Found: N, 5.88. [d] Calcd.: N, 5.90; mol. wt. 2.37. Found: N, 6.17; Mol. wt. (Rast) 235. [e] Ref.[a], b.p. 145–150° (2 mm.); yield 45%. [f] Calcd.: mol. wt. 175. Found: mol. wt. (Rast) 175. [g] A. Spasov, S. Robev, and B. Panaiotova [*Godishnik Sofiĭskiya Univ. Fiz.-Mat. Fak.-Kniga 2—Khim.*, 49, 109 (1956); *Chem. Abstr.*, 51, 12031 (1957)], m.p. 134–135°. [h] Ref. 7, b.p. 142–145° (0.1 mm.); the yield was not reported. [i] Ref. 8, b.p. 200° (15 mm.); yields 10%, 60%, and 70%.

Compounds 2 and 16 were recrystallized from ethanol; 7 from petroleum ether (30–40°); 6 and 8 from petroleum ether (60–75°).

The methyl, ethyl, isopropyl, and benzyl esters of α-phenyl-β-(benzylamino)propionic acid (Table II) were allowed to react with methylmagnesium iodide and ethylmagnesium bromide, respectively, to form 1-benzyl-3-phenyl-2-azetidinone. This type of synthesis of 2-azetidinones was introduced by Breckpot[12] and was used later by other investigators.[7,10,13] The highest yield of the azetidinone obtained by us by this process was 40%.

Incidentally, in an attempt to convert α-phenyl-β-(benzylamino)propionyl chloride hydrochloride into α-phenyl-β-(benzylamino)ethyl diazomethyl ketone by the use of diazomethane, it was discovered that the reaction product was not the diazomethyl ketone but was 1-benzyl-3-phenyl-2-azetidinone; the azetidinone was formed in 43% yield. α-Phenyl-β-(isopropylamino)-, α-phenyl-β-(hexahydrobenzylamino)- and α-phenyl-β-(β-phenylethylamino)propionyl chloride hydrochloride, when treated with diazomethane, yielded 1-isopropyl-3-phenyl- (54%), 1-hexahydrobenzyl-3-phenyl- (31%) and 1-(β-phenylethyl)-3-phenyl-2-azetidinone (40%), respectively. Since it seemed that diazomethane may have served merely in the removal of hydrogen chloride, it was replaced, successfully, by dimethylaniline in a series of experiments. Fourteen 2-azetidinones (Table III), eleven

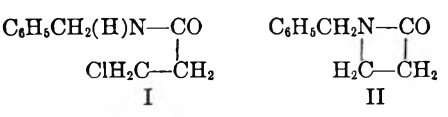
(12) R. Breckpot, *Bull. soc. chim. Belges*, 32, 412 (1923).

(13) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, 71, 2129 (1949).

of which are new compounds, were prepared by the interaction of a β-amino acid chloride hydrochloride and dimethylaniline. In all except three instances, the yields ranged from 61–92%.

We were unable to obtain 1-benzyl-2-azetidinone by the β-amino acid chloride hydrochloride–dimethylaniline process but it was found that the azetidinone could be prepared in 40% yield by the interaction of *N*-benzyl-β-bromopropionamide and sodium hydride.[14] This azetidinone was isolated by Holley and Holley,[10] in 5% yield, from the interaction of ethyl β-(benzylamino)propionate and ethylmagnesium bromide.

Certain N-benzylamides, such as Hibicon (N-benzyl-β-chloropropionamide) (I), have been shown



I II

to be effective anticonvulsants.[15,16] It can be seen that 1-benzyl-2-azetidinone (II), except for the absence of the chlorine atom, is a cyclic analog of I. As far as we are aware, anticonvulsant action of compounds of type II has not been reported.

In addition to the 2-azetidinones obtained by procedures which have been described, three azetidinones (compounds 12, 16, and 17, Table III) were synthesized by a Reformatsky-type reaction.

Two azetidinones (9 and 16, Table III) were hydrolyzed with alkali to known β-amino acids. One azetidinone (9, Table III) yielded ethyl α-phenyl-β-(benzylamino)propionate hydrobromide when it was refluxed with ethanol and hydrogen bromide. When treated with lithium aluminum hydride, 1-benzyl-3-phenyl-2-azetidinone was converted into 2-phenyl-3-(benzylamino)-propanol; the latter compound was also obtained by treatment of ethyl α-phenyl-β-(benzylamino)propionate with lithium aluminum hydride.

The carbonyl absorption of each of the 2-azetidinones prepared was found to be within the 1750–1730 cm.$^{-1}$ range.

EXPERIMENTAL

β-Amino acids obtained from atropic acid. Compounds 2, 4, 6, 9, 10, 12, and 14 (Table I) were synthesized by the following method.

A solution of 0.1 mole of the required amine in 50 ml. of absolute ethanol was added to a solution of 7.4 g. (0.05 mole) of atropic acid[4,17] in 60 ml. of absolute ethanol. After 4 days,[18] the solvent was removed and the residue was recrystallized from a suitable solvent.

α-Phenyl-β-(dimethylamino)propionic acid. This acid was obtained in 80% yield by the method described above; m.p. 143–145°[19] after recrystallization from 95% ethanol.

α-Phenyl-β-anilinopropionic acid (compound 8, Table I). This acid was prepared by heating for 4 hr. on a steam bath, a mixture of 7.4 g. of atropic acid, 9.3 g. of aniline, and 2 ml. of acetic acid. The precipitate was filtered and recrystallized from aqueous methanol. The acid is insoluble in water, soluble in dilute acid and alkali.

Esters of α-phenyl-β-(benzylamino)propionic acid. The ester hydrochlorides (compounds 2, 4, 7, and 9, Table II) were obtained by a general method previously described.[10] The ester bases (compounds 1, 3, 6, and 8) were liberated from the salts and distilled. The ester hydrobromide (compound 5) was obtained by addition of hydrogen bromide to the ester base dissolved in ether.

Ethyl α-phenyl-β-aminopropionate hydrochloride. From 2.0 g. of α-phenyl-β-aminopropionic acid[3], by the general process mentioned above, there was obtained 2.3 g. (82%) of product; m.p. 160–162° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{11}H_{16}O_2NCl$: N, 6.10; Cl, 15.44. Found: N, 6.09; Cl, 15.69.

Methyl α-phenyl-β-anilinopropionate. Diazomethane,[20] which had been obtained from 43.0 g. of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[21] dissolved in 500 ml. of ether, and 16.5 g. of α-phenyl-β-anilinopropionic acid yielded 11.5 g. (65%) of ester; b.p. 154–155° (0.5 mm.).

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.34; H, 6.85; N, 5.36.

β-(Benzylamino)propionic acid (compound 19, Table I). This acid was obtained when a suspension of 0.2 mole of ethyl β-(benzylamino)propionate[22] in 500 ml. of water was refluxed for 6 hr. The water was removed under reduced pressure and the residue was recrystallized from ethanol; yield 75%.

β-(Benzylamino)butyric acid (compound 22, Table I). Ethyl β-(benzylamino)butyrate[23] was hydrolyzed in the manner described above.

Ethyl α-methyl-β-(benzylamino)propionate. A mixture of 98.1 g. of methyl methacrylate, 107.0 g. of benzylamine, and 500 ml. of methanol was allowed to remain at room temperature for 7 days. The solvent was removed and the residue was distilled; b.p. 97–100° (0.3 mm.); yield 123.7 g. (60%).

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.39; H, 8.22; N, 6.66.

The *hydrochloride* was prepared by the use of ethereal hydrogen chloride; m.p. 101–103°.

Anal. Calcd. for $C_{12}H_{18}O_2NCl$: N, 5.74; Cl, 14.55. Found: N, 5.90; Cl, 14.70.

α-Methyl-β-(benzylamino)propionic acid (compound 20, Table I). Ethyl α-methyl-β-(benzylamino)propionate was hydrolyzed in the manner described above in order to obtain this acid.

Ethyl β-cyclohexyl-β-aminopropionate. Ethyl β-phenyl-β-

(14) Several 2-azetidinones have been obtained by I. L. Knunyant and N. P. Gambaryan [*Izvest. Akad. Nauk S. S. S. R., Otdel. Khim. Nauk* **1955**, 1037; *Chem. Abstr.* **50**, 11277 (1956)] by reaction between a β-halo amide and potassium or sodium amide in liquid ammonia.

(15) S. Kushner, R. I. Cassel, J. Morton, and J. H. Williams, *J. Org. Chem.*, **16**, 1283 (1951).

(16) B. K. Harned, R. W. Cunningham, M. C. Clark, C. H. Hine, M. M. Kane, F. H. Smith, Jr., R. E. Vessey, N. N. Yuda, and F. W. Zabransky, *J. Pharmacol. Exptl. Therap.*, **107**, 403 (1953).

(17) In the preparation of tropic acid,[5] it was found necessary to stir the reaction mixture, after the addition of formaldehyde, for 12 hrs. in order to obtain the reported yield.

(18) In some instances the amino acid had partially precipitated.

(19) C. Mannich and E. Ganz [*Ber.*, **55**, 3486 (1922)], m.p. 143°.

(20) T. J. De Boer and H. J. Backer, *Org. Syntheses*, **36**, 16 (1956).

(21) "Diazalid," Aldrich Chemical Co.

(22) G. Stork and S. M. McElvain, *J. Am. Chem. Soc.*, **69**, 971 (1947).

(23) J. Decombe, *Ann. chim.* (*Paris*), **18**, 81 (1932).

aminopropionate[10] (19.3 g.), dissolved in 150 ml. of acetic acid, was hydrogenated at 50° in the presence of 0.5 g. of platinum dioxide under an initial pressure of 50 pounds until the calculated amount of hydrogen had been absorbed. After filtration and removal of the solvent from the filtrate under reduced pressure, the residue was dissolved in water, the solution was made alkaline and extracted with ether. The solvent was removed from the dried extract and the residue was distilled; b.p. 81–82° (0.4 mm.); yield 13.8 g. (70%).

Anal. Calcd. for $C_{11}H_{21}O_2N$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.21; H, 10.44; N, 7.00.

The *hydrochloride*, prepared by the use of ethereal hydrogen chloride, melted at 108–110° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{11}H_{22}O_2NCl$: Cl, 15.04; N, 5.94. Found: Cl, 15.37; N, 6.01.

Ethyl β-cyclohexyl-β-(benzylamino)propionate. (a) Ethyl β-cyclohexyl-β-aminopropionate (39.8 g.) and 12.6 g. of benzyl chloride were heated at 70° for 5 hr. After the addition of 500 ml. of anhydrous ether, the mixture was cooled in a refrigerator for 12 hr., filtered, and the solvent was removed from the filtrate. The residue was distilled; b.p. 150–152° (0.1 mm.); yield 16.0 g. (55%).

Anal. Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40. Found: C, 74.68; H, 9.49.

(b) Ethyl β-cyclohexyl-β-aminopropionate (19.9 g.), 10.6 g. of benzaldehyde, a catalytic amount of zinc chloride, and 200 ml. of benzene were refluxed for 12 hr. in a 500-ml. flask to which a Dean-Stark trap was attached. The benzene was removed from the filtered mixture under reduced pressure and the product, ethyl β-cyclohexyl-β-(benzylideneamino)propionate, was distilled; b.p. 170° (1 mm.); yield 23.0 g. (80%).

Anal. Calcd. for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.23; H, 8.81; N, 4.73.

The ester (23.0 g.), dissolved in 150 ml. of absolute ethanol, was hydrogenated in the presence of 0.5 g. of platinum dioxide under an initial pressure of 50 pounds until the calculated amount of hydrogen had been absorbed. The solvent was removed from the filtered mixture and the residue was distilled; b.p. 170–172° (0.7 mm.); yield 17.3 g. (75%).

A mixture of 0.5 g. of the propionate and 5 ml. of hydrochloric acid was evaporated to dryness and the *hydrochloride* was recrystallized from isopropyl alcohol; m.p. 179–180°.

Anal. Calcd. for $C_{18}H_{29}O_2NCl$: C, 66.33; H, 8.66; Cl, 10.88. Found: C, 66.24; H, 8.60; Cl, 11.01.

β-Cyclohexyl-β-(benzylamino)propionic acid (compound 25, Table I). Ethyl β-cyclohexyl-β-(benzylamino)propionate (16.0 g.), 4.0 g. of sodium hydroxide, and 100 ml. of 95% ethanol were refluxed for 12 hr., the solvent was removed and the residue was dissolved in 100 ml. of water. Upon careful neutralization of the solution with 10% hydrochloric acid, the product precipitated.

Ethyl α-cyclohexyl-β-aminopropionate. Ethyl cyclohexylcyanoacetate[11] (19.5 g.), dissolved in 150 ml. of acetic acid, was hydrogenated for 4 hr. in the presence of 5 ml. of concentrated sulfuric acid and 0.2 g. of platinum oxide under an initial pressure of 50 pounds. After removal of the solvent from the filtered mixture, the residue was dissolved in water, the solution was made alkaline and extracted with ether. The ether was removed from the dried extract and the residue was distilled; b.p. 76–77° (0.3 mm.); yield 17.5 g. (90%).

Anal. Calcd. for $C_{11}H_{21}O_2N$: C, 66.29; H, 10.62; N, 7.02. Found: C, 66.23; H, 10.57; N, 7.00.

The *hydrochloride* was prepared with ethereal hydrogen chloride; m.p. 143–145° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{11}H_{22}O_2NCl$: N, 5.94; Cl, 15.04. Found: N, 6.02; Cl, 15.26.

Ethyl α-cyclohexyl-β-(benzylamino)propionate. Ethyl α-cyclohexyl-β-aminopropionate (19.9 g.) was benzylated with 6.3 g. of benzyl chloride in the manner described above; b.p. 143–145° (0.2 mm.); yield 10.0 g. (70%).

Anal. Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40. Found: C, 74.71; H, 9.44.

The *hydrochloride* was obtained by the use of ethereal hydrogen chloride; m.p. 171–173°.

Anal. Calcd. for $C_{18}H_{28}O_2NCl$: C, 66.33; H, 8.66; Cl, 10.88. Found: C, 66.23; H, 8.66; Cl, 11.08.

α-Cyclohexyl-β-(benzylamino)propionic acid (compound 23, Table I). This acid was prepared in the same manner as the corresponding β-cyclohexyl compound from ethyl α-cyclohexyl-β-(benzylamino)propionate.

Hydrochlorides of β-amino acids (Table I). These compounds were obtained by dissolving the amino acid in 10% hydrochloric acid and evaporation of the solution to dryness. The salts were then recrystallized from a suitable solvent.

2-Azetidinones (Table III). Method A. The interaction of the methyl, ethyl, isopropyl, and benzyl esters of α-phenyl-β-(benzylamino)propionic acid with methylmagnesium iodide and ethylmagnesium bromide, respectively, was studied. In some experiments, the molar ratio of the ester and Grignard reagent was 1:1, in others 1:2. The best yield of 1-benzyl-3-phenyl-2-azetidinone was obtained in the manner described below.

1-Benzyl-3-phenyl-2-azetidinone (compound 8). A solution of ethylmagnesium bromide (approximately 0.06 mole), prepared from 1.5 g. of magnesium, 8 ml. of ethyl bromide and 150 ml. of ether, was added, dropwise, to 8.9 g. (0.03 mole) of isopropyl α-phenyl-β-(benzylamino)propionate in 100 ml. of ether. After about one half of the Grignard reagent had been added, the white precipitate turned into a grey ball. The mixture was stirred for 2 hr. at room temperature. Aqueous 10% ammonium chloride (100 ml.) was added and the material was stirred until the two layers became clear. The aqueous layer was separated and extracted with ether. The combined ether solutions were dried and the solvent was removed. The semisolid residue was placed on a porous plate; 1.8 g. of crystalline material was obtained.

3-Phenyl-2-azetidinone (compound 2). Ethyl α-phenyl-β-aminopropionate (0.05 mole), prepared from the ester hydrochloride, was allowed to react with approximately 0.15 mole of ethylmagnesium bromide in the manner described above.

We were unable to obtain 1,3-diphenyl-2-azetidinone from methyl α-phenyl-β-anilinopropionate and ethylmagnesium bromide.

Method B. The required β-amino acid (compound 6, 10, 12, or 14, Table I) (0.02 mole) was treated with 10 ml. of pure thionyl chloride. The acid chloride hydrochloride obtained was suspended in 250 ml. of ether and the suspension was added slowly from a large-bore dropping funnel to a stirred solution of approximately 4.0 g. (0.1 mole) of diazomethane, prepared from 28.4 g. of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[20] in 500 ml. of ether which was cooled in an ice-salt bath. The mixture was stirred for 1 hr. and then allowed to remain at room temperature for 12 hr. The solution was filtered and the ether and excess diazomethane were removed. The residue was either recrystallized or distilled.

Method C. The acid chloride hydrochloride obtained from 0.05 mole of the required acid (compound 2, 4, 6, 9, 10, 12, 14, 16, 17, 18, 20, 22, 23, or 25, Table I) and 25 ml. of pure thionyl chloride was suspended in 250 ml. of dry benzene and the suspension was added slowly through a wide-bore dropping funnel to a refluxing solution of 18.2 g. (0.15 mole) of dry dimethylaniline dissolved in 250 ml. of benzene. The mixture was refluxed for 4 hr., cooled and extracted thoroughly with water. The unreacted dimethylaniline was then extracted with 10% hydrochloric acid. After the benzene layer had been extracted with water again, it was dried over magnesium sulfate, the solvent was removed, and the residue was distilled or recrystallized.

Method D. 1-benzyl-2-azetidinone (compound 1). *N*-Benzyl-β-bromopropionamide[15] (24.2 g., 0.1 mole) was added, in small amounts, to a stirred mixture of 3.0 g. (0.12 mole) of sodium hydride and 150 ml. of dry toluene. The mixture was

refluxed for 12 hr., cooled, and 150 ml. of water was added. The mixture was stirred until both layers became clear, the aqueous layer was separated and extracted with 100 ml. of toluene. The combined toluene solutions were dried over magnesium sulfate, the solvent was removed, and the residue was distilled.

Method E. By the use of a described method,[24] products were obtained from the interaction of benzylidenebenzylamine and ethyl α-bromopropionate (compound 18) or ethyl α-bromoisobutyrate (compound 19); from benzylidenemethylamine and ethyl bromoacetate (compound 12) or ethyl α-bromopropionate (compound 17); from benzylideneaniline and ethyl α-bromophenylacetate (compound 16).

2-Phenyl-3-(benzylamino)propanol. (*a*) 1-Benzyl-3-phenyl-2-azetidinone (1.2 g., 0.005 mole), dissolved in 50 ml. of ether, was added, dropwise, to a stirred suspension of 0.19 g. (0.01 mole) of lithium aluminum hydride in 30 ml. of ether, and the mixture was refluxed for 24 hr. Water (0.5 ml.) was added to the cooled mixture and it was stirred for 4 hr., filtered, the filtrate was dried with magnesium sulfate and the solvent was removed. The residue was recrystallized from ether–petroleum ether (30–40°); m.p. 52–54°[25]: yield 0.9 g. (75%).

Anal. Calcd. for $C_{16}H_{19}ON$: C, 79.64; H, 7.93. Found: C, 79.52; H, 7.79.

The *hydrochloride*, prepared by the use of ethereal hydrogen chloride, melted at 131–133°[26] after recrystallization from 2-butanone.

Anal. Calcd. for $C_{16}H_{20}ONCl$: C, 69.18; H, 7.26; Cl, 12.76. Found: C, 69.23; H, 7.13; Cl, 12.65.

(*b*) Ethyl α-phenyl-β-(benzylamino)propionate (27.4 g.), dissolved in 200 ml. of ether, was added, dropwise, to a stirred suspension of 2.3 g. of lithium aluminum hydride in 300 ml. of ether. The mixture was stirred for 3 days at room temperature; 6 ml. of water was added, dropwise, and the stirring was continued for 24 hr. The mixture was filtered, the filtrate was dried, and the solvent was removed. The oily residue, after it had crystallized, was recrystallized from ether–petroleum ether (30–40°); m.p. and mixed m.p. 52–54°; yield 21.8 g. (94%). The hydrochloride melted at 132–133° after recrystallization from 2-butanone.

ANN ARBOR, MICH.

(24) H. Gilman and M. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).

(25) Ref. 22, m.p. 64°.

(26) Ref. 22, m.p. 135–136°.

[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Reaction of Alkyl Isocyanides with Ozone. A New Isocyanate Synthesis[1]

HENRY FEUER, HARRY RUBINSTEIN,[2] AND ARNOLD T. NIELSEN

Received January 16, 1958

The reactions of alkyl isocyanides with ozone have been shown to give exclusively the corresponding isocyanates. The formation of the isocyanates varied from 7–73%, based upon the conversion of the isocyanates with ammonia to the urea. It appears that increasing concentrations of ozone will result in excellent yields of isocyanates.

The reactions of isocyanides have been studied since their discovery in 1867.[3,4] The only reference in which the oxidation of isocyanides has been investigated dates back to the work of Gautier who found that methyl isocyanide and ethyl isocyanide were oxidized by mercuric oxide[5]; he obtained a complex mixture from which he was able to isolate a small amount of isocyanate.

The purpose of this research was to study the course and the products of the oxidation of isocyanides. Ozone was chosen because it was thought best to employ a very strong oxidizing agent which would also make the separation of products, reactants and starting material fairly easy.

The first isocyanide to be ozonized was isopropyl isocyanide. The materials obtained upon distillation of the reaction mixture were isopropyl isocyanate (identified as the diisopropylurea), unreacted isocyanide, and some residual tars. It became apparent after two preliminary runs that much of the isopropyl isocyanide was being lost through entrainment (*i.e.*, evaporation), and that the separation of the isocyanate from any unreacted isocyanide by distillation was unfeasible because extensive tar formation took place during the distillation.

To avoid these losses, the reaction vessel was provided with a Dry Ice condenser, and the isocyanate was derivatized. It is well known that isocyanates react with amines to give excellent yields of the urea.[3,7] Thus, in all the ozonolysis experiments, the isocyanate was reacted with ammonia and the yield of isocyanate was based upon the amount of urea formed. As a check upon the validity of this method, hexyl isocyanate, prepared by the phosgenation of hexylamine hydrochloride, was reacted with ammonia to give the urea. This was found to proceed in yields of 95–97% in each of four determinations.

The reaction of ethyl, isopropyl, *n*-butyl, *n*-hexyl, and *n*-octyl isocyanides with ozone was studied and the results are shown in Table I.

From the data in the table it may be noted that

(1) Abstracted in part from the Ph.D. thesis of Harry Rubinstein, (February 1958).

(2) Purdue Research Foundation Fellow, 1956–58.

(3) A. W. Hofman, *Compt. rend.*, **65**, 484 (1867).

(4) A. Gautier, *Ann. Chim. (Paris)* (4), **17**, 228 (1869).

(5) A. Gautier, *Ann.*, **149**, 313 (1869).

(6) W. Siefken, *Ann.*, **562**, 99 (1949).

(7) Houben-Weyl, *Methoden Der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, Germany (1952) Volume 8, p. 157.

TABLE I

REACTION OF VARIOUS ISOCYANIDES WITH OZONE

Isocyanide	B.P., °C.	Mole	Reaction Time, Hr.	Vol. of O_2, L.	Approx. Amt. of O_3 Produced, Mole	Isocyanate,[a] % Conversion	Isocyanide Lost by Entrainment, Moles $\times 10^{-3}$	Isocyanide Unreacted, Moles $\times 10^{-3}$	Isocyanate, % Yield
Ethyl[b]	77	0.105	10	84.0	0.10	7.1	4.84	91	83
Isopropyl[c,d]	85–87	0.143	14	174.5	0.14	34	—	—	—
n-Butyl[c]	123–124.5	0.127	13	152.7	0.13	37	—	—	—
n-Hexyl[c]	168–169	0.121	15	199.0	0.15	55	5.05	40	88
n-Octyl[c]	89–91/12 mm.	0.081	25	272	0.25	73.5	5.90	3.2	82

[a] Based on the formation of the urea. [b] Reaction temperature 0°. [c] Reaction temperature 25°. [d] In ethylene chloride as solvent.

the higher molecular weight isocyanides gave conversions to the isocyanates than the lower ones. This seems to be due primarily to the volatility of the isocyanides and isocyanates involved. For example, when ethyl isocyanide was ozonized at 25°, the loss through entrainment (despite the use of the Dry Ice condenser and a Dry Ice trap), was so large that the reaction had to be carried out at 0°. Even then the loss was appreciable and the flow of oxygen and the reaction time had to be decreased. These factors and the lower reaction temperature, account for the low conversion in the case of ethyl isocyanide.

In order to establish that isocyanates were the only products in the ozonolysis of isocyanides, the ozonolysis mixture of octyl isocyanide was reacted with ammonia. The filtrate from this reaction mixture gave on distillation only unreacted isocyanide, without significant tar formation. When, however, the crude ozonolysis product was distilled, tar formation took place. This very likely was caused by decomposition or polymerization of the isocyanate present.

It is apparent, therefore, that the reactions of isocyanides with ozone are potentially capable of giving excellent yields of isocyanates. In order to achieve this, it would be necessary to produce higher concentrations of ozone, thereby decreasing the over-all reaction time. This is especially desirable in the case of the lower boiling isocyanides.

EXPERIMENTAL

Preparation of isocyanides. Ethyl isocyanide. Ethyl isocyanide was prepared according to the procedure of H. L. Jackson and B. C. McKusick[8] in 75% yields, b.p. 77° (lit. val., 78°).

All other isocyanides were prepared by minor modification of a published procedure.[9]

Isopropyl isocyanide. Isopropyl isocyanide was prepared in a yield of 71%, b.p. 85–87° (lit. val., 87°).[10]

n-Butyl isocyanide. In the preparation of *n*-butyl isocyanide the reaction mixture was heated to 120–140° for 2 hr. and the oil layer formed was separated by decanting it from the frozen water layer. Yield 84%, b.p. 123–124.5° (lit. val.,[11] 124–125°).

n-Hexyl isocyanide. In the synthesis of *n*-hexyl isocyanide the reaction mixture was heated at 115–120° for only 1 hr. and after distillation a 63% yield was obtained, b.p. 168–169°.

Anal. Calcd. for $C_7H_{13}N$: C, 75.6; H, 11.7; N, 12.6. Found: C, 75.32; H, 12.00; N, 12.50.

n-Octyl isocyanide. This compound was prepared in exactly the same manner as the hexyl isocyanide affording an 89% yield of liquid, b.p. 89–91°/12 mm.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.2; N, 10.05. Found: C, 77.48; H, 12.45; N, 10.06.

Octyl isocyanate. Except for variations in reaction time and amount of ozone produced (*cf.* Table I) this preparation is typical of the procedure employed.

The ozonizer used was that proposed by Henne and Perilstein,[12] except that the reaction cell was provided with a Dry Ice condenser.

n-Octyl isocyanide (11.3 g., 0.08 moles) was placed into the reaction cell and treated with ozonized oxygen at 25°. This was done on two successive days using 272 l. of oxygen (approx. 0.25 mole of ozone) in 25 hr. The reaction cell was stored in Dry Ice between the runs. At the end of 25 hr. the system was flushed with oxygen and the product weighed. A total of 9.15 g. of liquid was obtained and this was treated with excess ammonia gas at Dry Ice temperature. The

TABLE II

UREA DERIVATIVES PREPARED FROM ISOCYANATES

Urea	Recrystallized	M.P., °C.
Isopropyl[13,a]	Ethyl acetate	154
n-Butyl[14]	Benzene	96
n-Hexyl[15]	Benzene	108–110
n-Octyl	Benzene	100–101

[a] Was prepared by the addition of concentrated ammonium hydroxide to the ozonolysis reaction mixture.

(8) *Org. Syntheses*, **35**, 62 (1955).
(9) Reference (**7**), p. 135.
(10) A. Gautier, *Ann.*, **149**, 155 (1869).
(11) T. L. Davis, *J. Am. Chem. Soc.*; **59**, 1998 (1937).
(12) A. L. Henne and W. L. Perilstein, *J. Am. Chem. Soc.*, **65**, 2183 (1943).
(13) C. H. Maugin, *Ann. de Chemie, 8E*, **22**, 321 (1911).
(14) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1797 (1929).
(15) C. Norstedt and H. A. Wahlforss, *Ber.*, **25**, 637*c*. (1892).

excess ammonia was then allowed to escape, with intermittent stirring, and the resulting solid was filtered and dried *in vacuo* for 24 hr. This procedure gave 8.25 g. (60%) of a slightly brown material which was recrystallized three times from benzene to give *n*-octylurea, m.p. 100–101°.

Anal. Calcd. for $C_9H_{20}N_2O$: C, 62.70; H, 11.62; N, 16.27. Found: C, 62.47; H, 11.62; N, 16.29.

The ureas which were prepared from the isocyanates, resulting from the ozonolysis of the various isocyanides are listed in Table II.

Acknowledgment. We are indebted to the Purdue Research Foundation and the Office of Naval Research for the financial support of this work.

LAFAYETTE, IND.

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

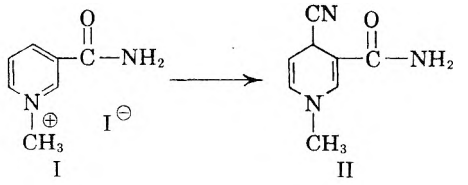
Action of Base on Certain Pyridinium Salts[1,2]

ARTHUR G. ANDERSON, JR., AND GERALD BERKELHAMMER

Received January 23, 1958

The action of ethoxide, hydroxide, and cyanide ions on a number of 1-alkyl-3-substituted pyridinium salts has been studied and interpreted. Evidence for the formation of pseudo bases and, in one case, the dimolecular ether of a hydroxy pseudo base has been obtained.

Among the properties of di- and triphosphopyridine nucleotides (DPN and TPN) which have been attributed to the nicotinamide portion of the molecule is the reaction with nucleophilic species to give a change in the ultraviolet absorption similar to that observed on reduction to the dihydro compounds. This behavior was first noted with cyanide and bisulfite by Meyerhof *et al.*[3] More recently the reaction with cyanide has been studied in some detail with the coenzymes and also with model compounds including a number of 3-substituted 1-methylpyridinium iodides.[4] From deuterium exchange experiments San Pietro[5] concluded that the reaction involved the addition of cyanide to the 4-position of DPN to form a pseudo cyanide. Recently a stable, crystalline cyanide addition product (II) has been isolated from I.[6] Also the spectral changes observed with the model compounds[4] seem to correspond best to 4-cyano derivatives. Other reactions which probably involve addition of a nucleophilic group at the 4-position are those with acetone,[7] negatively substituted methyl ketones,[8] and hydroxylamine.[9]



I II

The transient existence of pseudo bases has long been suspected in the formation of pyridones from *N*-alkylpyridinium halides[10] and in the reaction of strong alkali with DPN,[11] but there is very little evidence in support of this hypothesis.[10,12]

In connection with the preparation of a number of 1-alkyl-3-substituted-1,4-dihydropyridines as model compounds of DPNH,[13] it was observed that the aqueous solution of the quaternary pyridinium halide and sodium carbonate became yellow before the introduction of the sodium dithionite. In the case of one compound, 1-benzyl-3-acetylpyridinium chloride, a yellow solid also precipitated. Accordingly, the effect of base on the absorption spectra of ethanolic solutions of the substituted pyridinium halides was qualitatively measured and it was found that a similar spectral change occurred for all of the model compounds (Table I). Each of these had a substituent attached *via* a carbonyl group to the 3-position. The spectrum of a compound having no such group, 1-benzylpyridinium chloride, was essentially the same in neutral, basic, and acidic solutions.

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(1) From the Ph.D. thesis of Gerald Berkelhammer.

(2) Supported in part by a research grant (No. RG-3844) from the National Institutes of Health, Public Health Service.

(3) O. Meyerhof, P. Ohlmeyer, and W. Mohle, *Biochem. Z.*, 279, 113 (1938).

(4) S. P. Colowick, N. O. Kaplan, and M. M. Ciotti, *J. Biol. Chem.*, 191, 447 (1951); M. R. Lamborg, R. M. Burton, and N. O. Kaplan, *J. Am. Chem. Soc.*, 79, 6173 (1957). The latter paper appeared after the completion of the present work.

(5) A. San Pietro, *J. Biol. Chem.*, **217**, 579 (1955).

(6) M. Marti, M. Viscontini, and P. Karrer, *Helv. Chim. Acta*, 39, 1451 (1956). This publication appeared after our work had been completed.

(7) J. W. Huff, *J. Biol. Chem.*, **167**, 151 (1947).

(8) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, 206, 283 (1954).

(9) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, 211, 447 (1954).

(10) H. S. Mosher, *Heterocyclic Compounds*, edited by R. C. Elderfield, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 415.

(11) N. O. Kaplan, S. P. Colowick, and C. C. Barnes, *J. Biol. Chem.*, **191**, 461 (1951).

(12) E. M. Kosower, *J. Am. Chem. Soc.*, **77**, 3883 (1955).

(13) A. G. Anderson and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).

TABLE I

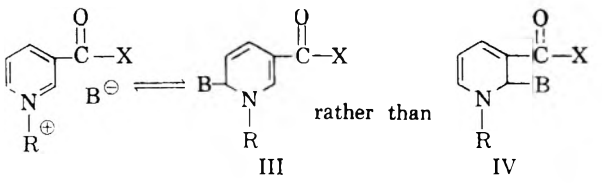
BASE-INDUCED CHANGES IN THE ULTRAVIOLET SPECTRA OF MODEL COMPOUNDS OF DPN IN 95% ETHANOL

Compound	λ_{max} (mμ) in Ethanol	λ_{max} (mμ) in Basic Ethanol[a]
1-Benzyl-3-carbamoylpyridinium chloride	266	259, 318
1-*n*-Propyl-3-carbamoylpyridinium bromide	266	259, 315
1-Benzyl-3-carbomethoxypyridinium chloride	264	258, 316[b]
1-Benzyl-3-acetylpyridinium chloride	264	271, 323
1-Benzyl-3-(*N*-phenylcarbamoyl)pyridinium chloride	End absorption	260–275, 325
1-Benzylpyridinium chloride	259	259

[a] One drop (about 0.04 ml.) of 3*N* aqueous sodium hydroxide added to the ethanolic solution of the compound in a 1-cm. Cary cell. [b] These peaks were unstable and eventually disappeared, leaving the 264 mμ maxima found in neutral solution. This behavior probably is due to hydrolysis to the zwitter ion, which is not attacked by base to an observable extent.

A reasonable explanation of the spectral changes found is the addition of a basic species (*e.g.*, ethoxide ion) to the ring in a reversible process. If so, the band at the shorter wave length (*ca.* 260 mμ) would be the (displaced) absorption of the pyridinium ion. Also, increasing the basicity of the solution would be expected to increase the ratio of the intensity of the long wave length peak (314–325 mμ) to that of the short wave length peak. This was found to occur. Similar spectral changes were observed with 1-benzyl-3-carbamoylpyridinium chloride and 1-benzyl-3-acetylpyridinium chloride in water, although the solutions had to be considerably more basic to give ratios of intensities comparable in magnitude to those obtained in ethanol. This is in keeping with the postulated equilibrium since the higher dielectric constant of water would cause a displacement in favor of the more ionic species (substituted pyridinium hydroxide) rather than the covalently bonded pseudo base.

It was noted that the long wave length absorption bands were 35–48 mμ shorter than those of the corresponding 1,4-dihydro compounds. This was in contrast to the results cited above for products obtained with other anions and suggested that the addition of the ethoxide or hydroxide ion did not take place at the 4-position. Of the two other likely possibilities (2 and 6), the 6-position was judged the more probable (III) since addition at position 2 would result in a chromophore having a nitrogen atom conjugated through two double bonds to a carbonyl (IV) and this would be expected[14] to absorb at considerably longer wave lengths than those observed. It is possible that with other substituted pyridinium salts, including those with different substituents in the 3-position, addition may occur predominantly, or even solely, at the 2-position. This would account for the formation

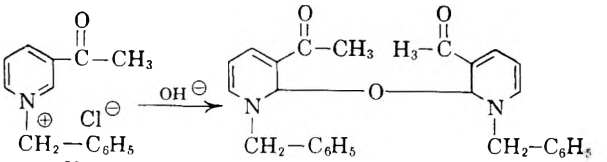


III IV

of different α-pyridones as the main products from, for example, the ferricyanide oxidation of the quaternary salts of nicotinic acid and nicotinamide.[10,15] The selection of the 6-position in the present case is in opposition to the postulated formation (on the basis of the wave length of absorption) of a pseudo base of DPN by reaction at the 4-position.[11]

The finding that the spectrum of 1-benzylpyridinium chloride was unchanged in basic ethanol or in 3*N* aqueous sodium hydroxide is in agreement with the conductivity studies of Hantzsch and Kalb[16] who found no evidence of pseudo base formation by quaternary pyridinium salts. Thus apparently the presence of a substituent capable of imparting resonance stabilization to the pseudo base by conjugation with the ring nitrogen causes a significant increase in the stability of the product relative to that of the quaternary salt.

When the yellow solid obtained from the action of sodium hydroxide on 1-benzyl-3-acetylpyridinium chloride (V) in aqueous solution was treated with acid, V was recovered in quantitative yield. This result was that expected from a pseudo base and efforts were made to characterize the compound. The material was stable in a refrigerator but darkened at room temperature. It could not be crystallized or otherwise further purified. Elementary analysis showed, however, that it was most probably not the pseudo base but rather a dimolecular ether of it, possibly VI. Precedent for this structure is found in analogous derivatives of



V VI

other nitrogen heterocycles[16,17] and in the product of the reaction of the tropylium cation with base.[18]

(14) K. Bowden, E. A. Braude, E. R. H. Jones, and B. Weedon, *J. Chem. Soc.*, **45** (1946).

(15) W. Holman and C. Wiegand, *Biochem. J.*, **43**, 423 (1948); H. Bradlow and C. Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951); J. W. Huff, *J. Biol. Chem.*, **171**, 639 (1947).

(16) A. Hantzsch and M. Kalb, *Ber.*, **32**, 3109 (1899).

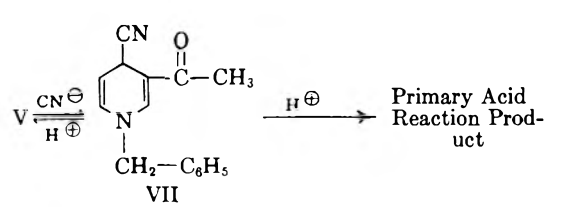
(17) J. G. Aston and P. Lasselle, *J. Am. Chem. Soc.*, **56**, 426 (1934); W. La Coste, *Ber.*, **15**, 186 (1882); J. G. Aston, *J. Am. Chem. Soc.*, **53**, 1448 (1931).

(18) W. E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **76**, 3203 (1954).

To our knowledge no other example in the pyridine series has been reported.

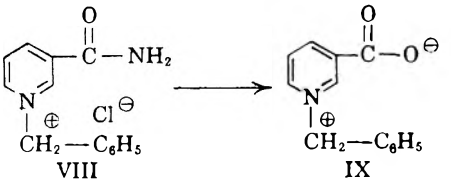
Just as the addition of ethoxide or hydroxide ion to form the pseudo base was postulated from the position of the ultraviolet absorption maximum to take place at the 6-position, the absorption of the ether at 278 and 351 mμ (dioxane)[19] suggested the 2-position for the attachment of the ether bridge. A second possibility would be that the rings are joined through the oxygen at the 4-positions. This might also account for the band at 351 mμ, though 1-benzyl-3-acetyl-1,4-dihydropyridine is known to absorb at 371 mμ in ethanol.[13] The peak at 278 mμ is less easy to explain. It seems unlikely that this represents pyridinium ion since the latter would be expected to absorb nearer to 270 mμ and, in addition, ionization would not be particularly favored in dioxane. When the dimolecular ether was dissolved in ethanol the initial absorption at 270 and 362 mμ was rapidly replaced by the maxima of the ethoxide addition compound (323 mμ) and the pyridinium alcoholate (270 mμ), the intensity of which increased with time. The formation of the latter products can be readily explained from either VI or the 4-isomer by displacement *via* nucleophilic attack at the 6-position. Whether the initial absorption at 270 mμ in ethanol represents some immediate ionization of the ether or corresponds to the peak at 278 mμ in dioxane (if this is not caused by ionization) is not known. Treatment of the dimolecular ether with acid regenerated the original pyridinium salt.

The reaction with cyanide ion was also investigated and found to alter the spectra of aqueous solutions of the model compounds. In particular, treatment of a dilute solution of 1-benzyl-3-acetylpyridinium chloride (V) with a small amount of sodium cyanide resulted in the gradual disappearance of the absorption at 265 mμ and concurrent growth of a peak at 355 mμ. Acidification of the solution caused the loss of the maximum at 355 mμ and the appearance of a new peak at 298 mμ[20] along with increased intensity at 270 mμ. When excess cyanide ion was then introduced, the 298 mμ peak was unchanged, some increase in absorption occurred at 355 mμ and the intensity at 270 mμ decreased. These results are consistent with the formation of VII and the conversion of this by acid both back to V and to the product of the "primary acid reaction." VII was isolated as a relatively stable crystalline material which showed, in ethanol, a single absorption maximum at 351 mμ. Thus the compound is essentially completely covalent whereas the corresponding product (II) obtained by Karrer[6] apparently is partially ionized in ethanol since it displayed a peak at 265 mμ (as well as at 340 mμ) which was absent in dioxane solution. Explanation for this difference is afforded by the stronger electron-withdrawing resonance interaction with the ring unsaturation of the acetyl group as compared with the carbamoyl group.



VII

Observations of the action of base on aqueous solutions of 1-benzyl-3-carbamoylpyridinium chloride (VIII) at room temperature indicated hydrolysis of the amide group. The odor of ammonia was evident soon after addition of the base and, after two hours, a *ca.* 40% yield of zwitter ion (IX), characterized by comparison with a sample prepared by quaternization of nicotinic acid, was isolated. After a reaction period of only 10 min. a 15% yield of IX was realized. Extraction of the reaction mixture after three minutes gave only a yellow-brown resinous product (30–40%) which showed absorption at 262 and 350 mμ and thus may have arisen from attack on the ring. Its nature discouraged further investigation.



VIII IX

EXPERIMENTAL[21,22]

Pyridinium salts. 1-Benzyl-3-carbamoylpyridinium chloride, 1-*n*-propyl-3-carbamoylpyridinium bromide, 1-benzyl-3-carbomethoxypyridinium chloride, 1-benzyl-3-acetylpyridinium chloride, and 1-benzyl-3-(*N*-ethyl-*N*-phenylcarbamoyl)-pyridinium chloride were prepared from the corresponding 3-substituted pyridines and benzyl or *n*-propyl halides as previously described.[13]

Dimolecular pseudo base ether from 1-benzyl-3-acetylpyridinium chloride. To a solution of 1.24 g. (5 mmoles) of 1-benzyl-3-acetylpyridinium chloride in 200 ml. of water was added 50 ml. of 0.2*N* sodium hydroxide. After 45 min. the lemon yellow solid which had precipitated was collected in a sintered glass funnel, washed four times with 5-ml. portions of water, and placed while still wet over phosphorus pentoxide in a desiccator under vacuum and in a refrigerator. The solid came to constant weight (1.02 g., 93%) in 6 hr. It sintered at 74°, darkened and softened at 80–95° and melted at 95–98°. A qualitative ultraviolet spectrum showed maxima (mμ) at 277 and 346 (chloroform), and 278 and 350

(19) These maxima correspond closely to those of a product obtained from the x-ray induced reduction of 1-methyl-3-carbamoylpyridinium iodide by G. Stein and G. Stiassny, *Nature*, **176**, 734 (1955) which was thought to be the 1,2- or 1,6-dihydro compound.

(20) This behavior is very similar to that associated with the so-called primary acid reaction on the 1,4-dihydro forms of the model compounds.[13]

(21) Melting points are corrected unless otherwise stated. Boiling points are uncorrected. Elementary analyses were performed by B. J. Nist and C. H. Ludwig.

(22) Ultraviolet spectra were determined with a Cary Model 115 Recording Spectrophotometer and/or a Beckman Model DU Spectrophotometer.

(dioxan). An ethanol solution exhibited maxima at 270 and 362 mμ immediately after preparation but after a few minutes the peaks were at 270 and 323 mμ and both increased in intensity with time.

Anal. Calcd. for $C_{28}H_{29}N_2O_3$: C, 76.35; H, 6.39; N, 6.36. Found: C, 76.73; H, 6.20; N, 6.06.

1-Benzyl-3-acetylpyridinium chloride from the dimolecular pseudo base ether. Hydrogen chloride was passed into a solution of the dimolecular pseudo base ether (229 mg., 0.52 mmole) in 20 ml. of methanol for one minute. Evaporation of the solvent left a brown solid (235 mg., 91%) the infrared spectrum of which was identical with that of 1-benzyl-3-acetylpyridinium chloride. Recrystallization from methanol–ethyl acetate gave a 64% recovery of tan crystals which melted at 183.5–184° alone and when mixed with an authentic sample.

1-Benzyl-3-acetyl-4-cyano-1,4-dihydropyridine (VII). A solution of 3.25 g. (0.05 mole) of potassium cyanide in 10 ml. of water was added to a solution of 1.24 g. (0.005 mole) of 1-benzyl-3-acetylpyridinium chloride in 10 ml. of water. There was an immediate separation of a yellow oil. The supernatant solution was decanted from the oil and the latter washed with water and taken up in 5 ml. of hot ethanol. The yellow needles (0.87 g., 77%) which separated from the cooled solution melted at 114–115.5° with decomposition. An ethanol solution showed absorption at 351 mμ (ε 9,500).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92. Found: C, 75.61; H, 5.99.

1-Benzylpyridinium-3-carboxylate (IX). 1-Benzyl-3-carbamoylpyridinium chloride (2.49 g., 0.01 mole) was dissolved in 100 ml. of 0.1*N* carbonate-free sodium hydroxide. The odor of ammonia was soon evident. After 2 hr. the solution was extracted with three 50-ml. portions of chloroform and then seven 50-ml. portions of 1-butanol. The combined butanol extracts were washed with 25 ml. of water, dried over sodium sulfate, and concentrated to a volume of 20 ml. Addition of a large excess of ether precipitated an orange solid (1.29 g., 60%). Purification by extraction with cold chloroform, chromatography on acid-washed alumina with methanol, treatment with Norit, and recrystallization from ethanol–ethyl acetate gave 0.8 g. (37.5%) of IX as colorless crystals, m.p. 183–184.5° dec.; λ_{max} (ethanol) 264 mμ. Treatment of this product with hydrochloric acid gave 1-benzyl-3-carboxypyridinium chloride, identical with a sample prepared from benzyl chloride and nicotinic acid. Acidification of the aqueous layer from the 1-butanol extraction with hydrochloric acid, extraction with chloroform and then 1-butanol (two 60-ml. portions), and evaporation of the butanol solution afforded 227 mg. of somewhat impure 1-benzyl-3-carboxypyridinium chloride.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE ROHM & HAAS CO.]

Nitrile Groups. V. Substituted Aminoacetamidoximes[1]

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The reaction of substituted aminoacetonitriles with hydroxylamine hydrochloride gave, after neutralization, substituted aminoacetamidoximes. The reaction is interpreted to reflect activation of the nitrile group by the ammonium ion. *N*-Benzyl-*N*-cyanomethyl-*N*,*N*-dimethylammonium chloride similarly gave a quaternary ammonium substituted acetamidoxime by reaction with free hydroxylamine. Aminonitriles derived from isobutyraldehyde and from cyclohexanone failed to give the reaction, and instead amine displacement reactions occurred. Tetrakis(cyanomethyl)ethylenediamine gave the corresponding tetrakisamidoxime.

Other papers in this series have shown that a nitrile group in a position near to an electron-withdrawing substituent undergoes reaction with amines with unusual ease.[1,2] The reactions to be described illustrate how a proximate cation (substituted ammonium group) favors the addition of hydroxylamine to the nitrile function.

The usual conditions for the formation of amidoximes require treating the corresponding nitrile with free hydroxylamine in aqueous alcoholic solution for an extended period of time. It is significant that unusually rapid reactions have been reported for succinonitrile,[3] cyanogen,[4] and tribromoacetonitrile.[5]

When, in this study, hydroxylamine was added to substituted aminoacetonitriles, it was not necessary, and not desirable, to free the hydroxylamine from its hydrochloride by the addition of a base. The reaction of the nitrile with hydroxylamine hydrochloride proceeded rapidly with evolution of heat to give the hydrochloride of the corresponding aminoacetamidoxime. The addition of sodium carbonate in equivalent amount then freed the amidoxime for isolation. The data for a number of aminoacetamidoximes are given in Table I.

The aminonitrile is believed to take part in the reaction in its ammonium form, by equilibration with the hydroxylamine hydrochloride. The provision in this way of a highly electron-withdrawing substituent then activates the nitrile group. This substituent could also be provided in the form of a quaternary ammonium ion, in which case it would be necessary to add base to free the hydroxylamine for reaction. *N*-Benzyl-*N*,*N*-dimethyl-*N*-cyanomethylammonium chloride was prepared, and to it was added an equivalent amount of hydroxylamine

(1) For the previous paper in this series, see P. L. de Benneville, C. L. Levesque, L. J. Exner, and E. Hertz, *J. Org. Chem.*, 21, 1072 (1956).

(2) (a) L. J. Exner, M. J. Hurwitz, and P. L. de Benneville, *J. Am. Chem. Soc.*, 77, 1103 (1955); (b) M. J. Hurwitz, L. J. Exner, and P. L. de Benneville, *J. Am. Chem. Soc.*, 77, 3251 (1955).

(3) F. Sembritzki, *Ber.*, 22, 2958 (1899).

(4) E. Fischer, *Ber.*, 22, 1930 (1899).

(5) W. Steinkopf and H. Grünupp, *Ber.*, 41, 3571 (1908).

TABLE I

SUBSTITUTED AMINOACETAMIDOXIMES

$R^1R^2NCH_2C(=NOH)NH_2$

R^1	R^2	M.P., °C.	Yield, %	Empirical Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
CH_3	CH_3	112–114	22	$C_4H_{11}N_3O$	41.0	41.5	9.4	9.7	35.9	35.9
C_2H_5	C_2H_5	79–80[a]	51	$C_6H_{15}N_3O$	49.6	49.6	10.3	10.4	29.0	29.2
Morpholine		152–153[b]	52	$C_6H_{13}N_3O_2$	45.3	45.4	8.2	8.1	26.4	26.4
n-C_4H_9	H	84–85[c]	64	$C_6H_{15}N_3O$	49.6	49.4	10.3	10.4	29.0	28.7
t-C_8H_{17}[d]	H	95–96	72	$C_{10}H_{23}N_3O$	59.7	59.5	11.4	11.6	20.9	20.6
C_6H_{11}[e]	H	146–148[a]	71	$C_8H_{17}N_3O$	56.1	56.3	9.9	9.8	24.5	24.3

[a] Recrystallized from water. [b] Recrystallized from isopropyl alcohol. [c] Recrystallized from ethyl acetate. [d] t-C_8H_{17} is 1,1,3,3-tetramethylbutyl. [e] C_6H_{11} is cyclohexyl.

hydrochloride. No reaction took place. An equivalent amount of sodium carbonate solution was then slowly added, and before the addition was half over, heat was evolved, and the corresponding amidoxime was ultimately isolated. The general reaction is therefore probably best formulated:

$$R_2N^+CH_2CN + NH_2OH \longrightarrow R_2N^+CH_2C(=NOH)NH_2$$

Infrared spectra were obtained on a Perkin-Elmer Spectrophotometer, Model 21. Common peaks in the spectra determined in KBr dispersion (*ca.* 5% of the compound) for *N*-*n*-butyl- and *N*,*N*-dimethylaminoacetamidoxime, for acetamidoxime[6] itself, and for *N*-benzyl-*N*,*N*-dimethylammonium acetamidoxime chloride are given in Table II. The same peaks (except where Nujol interferes) were present in Nujol mulls of these compounds, and of *N*-(1,1,3,3-tetramethylbutyl)- and *N*-cyclohexylaminoacetamidoxime.

TABLE II

INFRARED PEAKS (CM.$^{-1}$) COMMON TO X—$CH_2C(=NOH)NH_2$

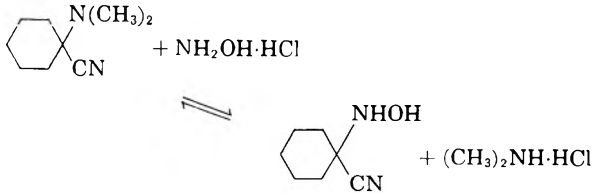
X = n-C_4H_9NH	$(CH_3)_2N$	$C_6H_5CH_2\overset{+}{N}(CH_3)_2$	H
3436	3401	3396	3484
3247	3247	3300	3356
3086	3106 (b)	3115	3106 (b)
2882	2907 (s)	2905 (s)	2924 (s)
2778 (b)	2778 (b)	2778 (m)	2762
1661	1664	1661	1661
1610 (m)	1618	1603 (m)	1590
1499 (w)	1499 (m)	1479 (m)	Absent
1451 (m)	1451	1449 (m)	1414 (m)
1387 (m)	1404	1389 (m)	1399
1340 (w)	1340 (m)	1355 (w), 1342 (w)	1366
995 (w)	992	999 (w)	Absent

(b) = broad; (s) = shoulder; (m) = medium; (w) = weak

Strong absorption was present in the whole range from 3450 to 2780 cm.$^{-1}$ Medium, fairly sharp peaks were obtained for the quaternary salt and for unsubstituted acetamidoxime at 2778 and 2762 cm.$^{-1}$, and a sharp drop in absorption followed to the base line at about 2600 cm.$^{-1}$ On the other hand, the two amino compounds gave strong, broad bands at 2778 cm.$^{-1}$, and a slow regular drop in absorption followed to the base line at about 2300 cm.$^{-1}$ These absorption characteristics are interpreted as reflecting inter- and intramolecular bonding.[7]

Absorptions at 1661–1664 cm.$^{-1}$ for C=N, and at 1590–1618 cm.$^{-1}$ for NH_2 were at the expected locations for these functional groups. Bonded NH and OH gave three peaks at slightly different locations for all four compounds in the 3100–3500 region.

α-Aminonitriles derived from isobutyraldehyde and from cyclohexanone did not give the same reaction. Instead, amine displacement reactions occurred.[8] When 1-dimethylaminocyclohexanecarbonitrile was heated in aqueous alcohol with hydroxylamine hydrochloride, 1-hydroxaminocyclohexanecarbonitrile was produced in significant amounts:



Hydrogen cyanide was also evolved, probably owing to reversion of the aminonitriles in the presence of

(6) Prepared by the method of E. Nordmann, *Ber.*, 17, 2746 (1884).

(7) The 2778 cm.$^{-1}$ peak is the most characteristic element of these spectra, but its assignment is quite conjectural. The broader absorption from 2800 to 2300 cm.$^{-1}$ in the amino compounds may be caused by intra- and intermolecular bonding involving the free electron pair on the amino-nitrogen atom and the amidoxime group. The quaternary salt with no free electrons resembles the unsubstituted amidoxime in lacking this.

(8) The particular carbonyl derivatives were chosen for ease of isolation. The results, which can probably be generalized for ketones and aldehydes other than formaldehyde, indicate that the activation of the nitrile group may involve removal of a proton from the central active methylene group as the first step of the reaction.

water; in another experiment, carried out over a long period of time, cyclohexanone oxime was the major product isolated. The reaction of α-*n*-butylaminoisovaleronitrile with hydroxylamine hydrochloride also evolved hydrogen cyanide, and there was isolated only a small amount of an impure crystalline solid.

The reaction can be carried out with more than one cyanomethyl group on the nitrogen atom. Thus, *N,N,N',N'*-tetrakis(cyanomethyl)ethylenediamine was converted to the tetrakis-amidoxime in good yield by the same procedure.

EXPERIMENTAL

Starting materials. Dimethylaminoacetonitrile,[9] cyclohexylaminoacetonitrile,[10] and 1,1,3,3-tetramethylbutylaminoacetonitrile[11] were prepared from commercial 50–70% aqueous glycolonitrile and isolated as pure compounds. Diethylaminoacetonitrile, *N*-cyanomethylmorpholine, and *n*-butylaminoacetonitrile were prepared from the corresponding amines and aqueous glycolonitrile, and were used as the resulting aqueous solutions, as described herein. *N,N,N',N'*-Tetrakis(cyanomethyl) ethylenediamine[12] was prepared from ethylenediamine, formaldehyde, and hydrogen cyanide.

Substituted aminoacetamidoximes. The following procedures illustrate several isolation procedures, which depend on the water solubility of the product, as well as the use of a substituted aminoacetonitrile prepared and used in aqueous solution.

Dimethylaminoacetamidoxime. To a solution of dimethylaminoacetonitrile (42 g., 0.5 mole) in ethanol (100 ml.) was added over a period of 10 min. at room temperature a solution of hydroxylamine hydrochloride (35 g., 0.5 mole) in water (35 ml.). A slight exotherm resulted which was allowed to dissipate. To the solution was then added solid sodium carbonate (26.5 g., 0.25 mole) in portions, and the mixture was stirred for 1 hr. The precipitated NaCl was removed by filtration and the filtrate evaporated to a moist solid. This was recrystallized from isopropyl alcohol to give 13 g. (22%), m.p. 107–112°, which was purified without loss by another recrystallization. The product was water-soluble.

1,1,3,3-Tetramethylbutylaminoacetamidoxime. To a solution of 1,1,3,3-tetramethylbutylaminoacetonitrile (83 g., 0.5 mole) in ethanol (150 ml.) was added a solution of hydroxylamine hydrochloride (35 g., 0.5 mole) in water (150 ml.), with ice water cooling. The mixture was stirred for 30 min. after which cooling was removed. After about 1 hr., the solution was clear, and a slight exotherm was still apparent. When no more heat was evolved, there was added a solution of sodium carbonate (26.5 g., 0.25 mole) in water (100 ml.). The ethanol was removed *in vacuo*, and the reaction mixture was filtered. The precipitate, m.p. 92–94°, amounted to 56.5 g., and a second crop of 16 g., m.p. 72–77°, was obtained by further evaporation. Both crops, when recrystallized from 1:1 methanol-water mixtures, melted at 92–94°. The total, based on isolated crude, was 72.5 g. (72%).

Diethylaminoacetamidoxime. To a 70% aqueous glycolonitrile solution (27 g., 0.33 mole) was added diethylamine (24.3 g., 0.33 mole) with good cooling. After standing overnight, the water layer was separated, and the rude aminonitrile (39 g.) was diluted with methanol (100 ml.). The solution was added gradually with stirring to a solution of hydroxylamine hydrochloride (23.3 g., 0.33 mole) in water (75 ml.). Heat was evolved. The mixture was allowed to stand overnight, and to it was added a solution of sodium carbonate (17.7 g., 0.167 mole) in water. The solution was evaporated *in vacuo* at room temperature until crystals appeared. It was then cooled in ice water, and filtered to give 24.7 g. (51%) melting at 79–80° after recrystallization from water.

N-Benzyl-N,N-dimethylammoniumacetamidoxime chloride. A solution of dimethylaminoacetonitrile (21 g., 0.25 mole) and benzyl chloride (31.7 g., 0.25 mole) in isopropyl alcohol (50 ml.) was heated at reflux for 3 hr., at the end of which time all of the chlorine was ionizable, by Volhard titration. The solution was diluted with ethanol (100 ml.) and to it was added a solution of hydroxylamine hydrochloride (17.5 g., 0.25 mole) in water (50 ml.). No heat was evolved. A solution of sodium carbonate (13.3 g., 0.125 mole) in water (50 ml.) was slowly added, and heat was evolved when addition was about one-half over. The remainder of the carbonate solution was added and the mixture stirred for 2 hr. The water and ethanol were removed at room temperature *in vacuo* leaving a mixture of solid and oil which solidified overnight. To it was added anhydrous ethyl acetate (300 ml.), and the solid was thoroughly triturated, and filtered off. It was dried, taken up in methanol (200 ml.), and filtered to remove sodium chloride. The filtrate was refrigerated overnight. The crystals which formed were filtered to give 41.5 g. (59%) of the desired quaternary salt, which contained 12.6% ionizable chlorine and corresponded in analysis to a dihydrate. After drying in an Abderhalden pistol, the anhydrous crystals melted at 176–178° with decomposition.

Anal. Calcd. for $C_{11}H_{18}N_2OCl$: C, 54.2; H, 7.4; N, 17.2; Cl, 14.6. Found: C, 54.0; H, 7.5; N, 17.0; Cl (ionizable) 14.3.

1-Dimethylaminocyclohexanecarbonitrile. To an aqueous solution of dimethylamine (225 g. of 40% or 2 moles) was added cyclohexanone (172 g., 1.75 moles) dropwise at 10–15°. There was then added, with cooling, liquid hydrogen cyanide (54 g., 2 moles). The mixture was stirred for 1 hr. The organic layer was distilled through a 4-inch Vigreux column to give 217 g. (82%) of product, b.p. 79–83°/3 mm.

Anal. Calcd. for $C_9H_{16}N_2$: N, 18.4. Found: N, 18.0.

Reaction of 1-dimethylaminocyclohexanecarbonitrile with hydroxylamine hydrochloride. To a solution of the carbonitrile (51 g., 0.33 mole) in ethanol (100 ml.) was added a solution of hydroxylamine hydrochloride (25 g., 0.36 mole) in water (100 ml.). No heat was evolved. The mixture was stirred for 30 min., then heated at reflux for 20 min. HCN was evolved. The mixture was cooled, and to it was added a solution of sodium carbonate (19 g., 0.18 mole) in water (100 ml.). The ethanol was stripped *in vacuo*, the reaction mixture was cooled to 0°, and filtered. The crystalline product, 30.5 g., m.p. 73–80°, was combined with 2 g. obtained by further concentration, and the whole was recrystallized from isopropyl alcohol (HCN evolved) to give 8.5 g. of colorless solid, m.p. 133–135°. Further recrystallization of this from 80:20 isopropyl alcohol–water mixture improved the melting point to 137.5–138°. This material analyzed correctly for 1-hydroxaminocyclohexanecarbonitrile. Infrared spectrum (Nujol mull): Bonded NH and OH at 3240 (broad); —C≡N at 2235 (weak); no absorption in 1500–1700 region.

Anal. Calcd. for $C_7H_{12}N_2O$: C, 60.0; H, 8.6; N, 20.0. Found: C, 59.9; H, 8.6; N, 20.0.

In another experiment of approximately 20 hr. duration, there was obtained from one mole of the carbonitrile, 104.5 g. of colorless solid, m.p. 87–89°, which was identified as cyclohexanone oxime, m.p. 89–90°.[13]

(9) D. B. Luten, Jr., *J. Org. Chem.*, **3**, 588 (1938).

(10) L. J. Exner, L. S. Luskin, and P. L. de Benneville, *J. Am. Chem. Soc.*, **75**, 4841 (1953).

(11) L. S. Luskin, M. J. Culver, G. E. Gantert, W. E. Craig, and R. S. Cook, *J. Am. Chem. Soc.*, **78**, 4042 (1956).

(12) I. G. Farbenindustrie, A. G. French Patent 831,985; *Chem. Abstr.*, **33**, 2913 (1939).

(13) A. Baeyer, *Ann.*, **278**, 102 (1894).

α-n-Butylaminoisovaleronitrile. To isobutyraldehyde cyanohydrin (198 g., 2 moles) was added *n*-butylamine (185 g., 2.5 moles) with cooling to maintain the temperature at 25–30°. The mixture was stirred at room temperature for 6 hr. Benzene (150 ml.) was added and the water layer was separated and discarded. The benzene layer was distilled through a 4-inch Vigreux column, to give 235 g. (77%), b.p. 85–90°/5 mm., n_D^{25} 1.4358.

Anal. Calcd. for $C_9H_{18}N_2$: N, 18.2; neutral equivalent (nonaqueous), 154. Found: N, 17.7; neutral equivalent, 154.

Reaction of α-n-butylaminoisovaleronitrile with hydroxylamine hydrochloride. To a suspension of hydroxylamine hydrochloride (29 g., 0.42 mole) in methanol (150 ml.) was added α-*n*-butylaminoisovaleronitrile (51 g., 0.33 mole) dropwise. A slight exotherm developed, the solution became clear, and HCN was evolved. After 2 hr., there was added a solution of Na_2CO_3 (22 g., 0.23 mole) in water (150 ml.). Further dilution failed to give the expected precipitate. The mixture was evaporated *in vacuo* to remove methanol, and an oil separated. From this oil, after storing overnight, fine needles precipitated, which were filtered off. The solid (7 g.) was crystallized from 1:1 benzene-hexane mixture to give 1.8 g., m.p. 85°, whose analysis was fairly close to that of the amidoxime (% N found, 23.0), but which was not identified as such.

Ethylene bis(iminodiacetamidoxime). To a slurry of ethylene bis(iminodiacetonitrile) (10.0 g., 0.047 mole) in methanol (25 ml.) was added a solution of hydroxylamine hydrochloride (14.0 g., 0.2 mole) in water (15 ml.). Heat was evolved. Stirring was continued for 1 hr., and then sodium carbonate (10.6 g., 0.1 mole) slowly added. After 3 hr. additional stirring, the mixture was filtered, and the residue dried in air. The crude product, 15.5 g. (95%), m.p. 182–184°, was purified by recrystallization from distilled water, m.p. 186–187° with decomposition.

Anal. Calcd. for $C_{10}H_{24}O_4N_{10}$: C, 34.5; H, 6.9; N, 40.2. Found: C, 34.4; H, 6.9; N, 40.3.

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PHILADELPHIA, PA.

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

Dinitro Amines and Their Reduction Products from the Mannich Reaction of Nitrocyclohexane with Aliphatic Diamines or Ammonia

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Nitrocyclohexane was found to react readily with aliphatic primary or secondary diamines or ammonia in the Mannich reaction to give a new series of dinitroamines in good yield. The dinitro compounds were reduced to the corresponding polyamines.

The use of diamines in the Mannich reaction of secondary nitro paraffins was first recorded by Johnson when he described a dinitro diamine obtained from the reaction of 2-nitropropane with formaldehyde and *p*-phenylenediamine.[1] The product, *N,N'*-bis(2-nitroisobutyl)-*p*-phenylenediamine, is the compound obtained when one hydrogen from each of the two amine groups of the diamine is replaced by a 2-nitroisobutyl group leaving the amine groups secondary. More recently, Butler

$$(CH_3)_2\text{—}CHNO_2 + HCHO + H_2N\text{—}C_6H_4\text{—}NH_2 \longrightarrow$$

$$(CH_3)_2\text{—}\underset{\displaystyle NO_2}{\overset{|}{C}}\text{—}CH_2\text{—}NH\text{—}C_6H_4\text{—}NH\text{—}CH_2\text{—}\underset{\displaystyle NO_2}{\overset{|}{C}}\text{—}(CH_3)_2$$

recorded the reaction of 2-nitropropane with formaldehyde and the secondary diamines, piperazine and 2,5-dimethylpiperazine.[2] He also obtained dinitro diamines although the amine groups in these products were both tertiary.

The possibility of using ammonia in place of an amine in this type of reaction of secondary nitro paraffins was investigated by Urbanski with 2-nitropropane.[3] The product he isolated was bis(2-nitroisobutyl)amine in which two of the ammonia hydrogens had been replaced by 2-nitroisobutyl group to produce a secondary amine.

$$(CH_3)_2CHNO_2 + HCHO + NH_3 \longrightarrow$$

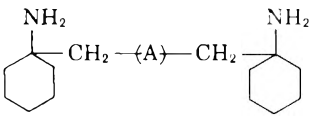
$$(CH_3)_2\underset{\displaystyle NO_2}{\overset{|}{C}}\text{—}CH_2\text{—}NH\text{—}CH_2\text{—}\underset{\displaystyle NO_2}{\overset{|}{C}}(CH_3)_2$$

The use of the secondary nitro compound, nitrocyclohexane, in the Mannich reaction does not appear to have been studied previously, since most work of this type has been limited to the more readily available 2-nitropropane. It has now been found, however, that nitrocyclohexane takes part quite readily in Mannich reactions and that good yields of dinitro diamines may be obtained from either primary or secondary aliphatic diamines or from ammonia. The secondary amines studied were limited to the closed ring diamines, piperazine and *C*-substituted piperazines, but since secondary monoamines such as diisobutylamine react readily,[4]

(1) H. G. Johnson, *J. Am. Chem. Soc.*, **68**, 14 (1946).
(2) G. B. Butler, *J. Am. Chem. Soc.*, **78**, 482 (1956).
(3) J. K. N. Jones and T. Urbanski, *J. Chem. Soc.*, 1766 (1949).
(4) R. A. Smiley, unpublished.

TABLE I

POLYAMINES



Basic Compound from Which Polyamine Is Derived (A)	% Yield	n_D^{25}	M.P. or B.P.	Analysis Calcd. / Found % C	% H	% N
Ammonia	77	1.5050	B.p. 134–135° (0.4 mm.)	70.29 / 70.54	12.12 / 11.60	16.72 / 17.58
Ethylenediamine	48	1.5067	B.p. 167–168° (0.55 mm.)	68.08 / 68.37	12.05 / 11.09	19.85 / 19.34
Hexamethylenediamine	47	1.4995	B.p. 194° (0.1 mm.)	71.00 / 71.01	12.42 / 12.47	16.51 / 16.35
Piperazine	65	—	M.p. 91–92°	70.10 / 69.98	11.69 / 11.69	18.19 / 18.18
2-Methylpiperazine	73	1.5106	B.p. 174–179° (0.3 mm.)	70.80 / 70.11	11.80 / 11.53	17.39 / 17.35
trans-2,5-Dimethylpiperazine	75	—	M.p. 71–72°	71.85 / 71.31	11.97 / 11.81	16.16 / 16.40

it seems probable that open-chain secondary diamines would react just as well as the piperazines.

All of the nitro amines prepared in this study were hydrogenated in ethanol with Raney nickel catalyst to the corresponding polyamines. Table I shows the properties of these compounds. These polyamines are all colorless and have no appreciable odor. When pure they appear to be quite stable and show no discoloration after normal storage for a year. They are all soluble in most organic compounds but are insoluble in water except for the ethylenediamine derivative. This compound is completely miscible in water and in all the organic liquids tested, including hydrocarbons.

EXPERIMENTAL

Materials. The nitrocyclohexane used in this study was prepared by the liquid-phase nitration of cyclohexane. The 2-methylpiperazine and the *cis*- and *trans*-2,5-dimethylpiperazine were obtained from the Wyandotte Chemical Corp. and were used without further purification. The formaldehyde was commercial formaldehyde solution meeting ACS specifications while all other reactants were of the best grade obtainable from commercial sources and were used as received.

Purification of nitrocyclohexane. Straw-colored, technical-grade nitrocyclohexane (500 ml.) was added dropwise to a stirred 500-ml. volume of concentrated sulfuric acid cooled in an ice bath. When the addition was complete, the solution was poured into a mixture of cyclohexane (500 ml.) and ice. The mixture was stirred until the ice melted. The cyclohexane layer was separated and dried over calcium chloride. The cyclohexane then was distilled off at atmospheric pressure, and the residue was distilled through a Claisen head *in vacuo*. Nitrocyclohexane purified in this manner was water white, boiled sharply at 79° at 10 mm., and had an n_D^{25} of 1.4587. Analysis of the distilled nitrocyclohexane by an infrared method failed to detect the presence (0.1%) of any alcohol, nitrate, or nitrite. The ketone content was usually about 0.2–0.6% by weight.

N,N'-Bis[(1-nitrocyclohexyl)methyl]piperazine. A solution of 64.5 g. (0.5 mole) of nitrocyclohexane, 50 g. (0.6 mole) of 37% formaldehyde, and 49 g. (0.25 mole) of piperazine hydrate in 250 ml. of 95% ethanol was stirred for 1 hr. at room temperature and then was refluxed on a steam bath for 2 hr. The thick white slurry which resulted was cooled, and the solid material was removed by filtration. Recrystallization from benzene gave 81 g. (87.5%) of white product, m.p. 186–188°.

Anal. Calcd. for $C_{18}H_{32}N_2O_4$: C, 58.65; H, 8.69; N, 15.21. Found: C, 58.87; H, 8.63; N, 15.49.

The following C-substituted piperazine derivatives were prepared in a similar manner.

N,N'-Bis[(1-nitrocyclohexyl)methyl]-2-methylpiperazine. M.p. 122–123°, yield 73%.

Anal. Calcd. for $C_{19}H_{34}N_4O_4$: C, 59.65; H, 8.90; N, 14.65. Found: C, 59.63; H, 8.57; N, 14.91.

N,N'-Bis[(1-nitrocyclohexyl)methyl]-2,5-dimethylpiperazine. The *trans*-diamine produced a white solid product in 76% yield, m.p. 149–150°, while the *cis*-diamine gave a 79% yield of product, m.p. 122–124°.

Anal. Calcd. for $C_{20}H_{36}N_4O_4$: C, 60.60; H, 9.09; N, 14.13. Found: C, 60.39; H, 9.02; N, 13.93.

N,N'-Bis[(1-nitrocyclohexyl)methyl]ethylenediamine. Ethylenediamine (15 g., 0.25 mole) was added slowly over a period of 30 min. to a stirred mixture of 64.5 g. (0.5 mole) of nitrocyclohexane and 50 g. (0.6 mole) of 37% aqueous solution of formaldehyde at a rate such that the temperature of the reaction mixture did not exceed 40°. After the addition of the diamine was complete, the reaction mixture was stirred for 4 hr. The mixture then was allowed to stand for 16 hr., after which time it was poured into 200 ml. of 18% hydrochloric acid. The white precipitate which formed was removed by filtration, washed with acetone, and dried. A yield of 71 g. (90%) of the dihydrochloride of the dinitro diamine was obtained.

The salt was neutralized with ammonium hydroxide, and the free dinitro diamine was removed by filtration. The product was recrystallized from diethyl ether, and a yield of 53 g. (75%) of white crystalline product, m.p. 72–73°, was obtained.

Anal. Calcd. for $C_{16}H_{30}N_4O_4$: C, 56.10; H, 8.77; N, 16.37. Found: C, 56.06; H, 8.77; N, 16.06.

N,N'-Bis[(1-nitrocyclohexyl)methyl]hexamethylenediamine. Using hexamethylenediamine in a manner similar to that used with ethylenediamine, a 32% yield of product was obtained which after recrystallization from a mixture of ethyl ether and 30–60° petroleum ether melted at 51–52°.

Anal. Calcd. for $C_{20}H_{38}N_4O_4$: C, 60.30; H, 9.55; N, 14.07; neut. equiv., 199.0. Found: C, 61.09; H, 9.40; N, 14.25; neut. equiv., 199.5.

Bis(1-nitrocyclohexylmethyl)amine. To a stirred solution of 258 g. (2 moles) of nitrocyclohexane and 270 g. (2.75 moles) of concd. ammonium hydroxide (28%) in 500 ml. of 95% ethanol was added 180 g. (2.2 moles) of 37% formaldehyde dropwise over a period of 1 hr. When the addition of formaldehyde was complete, the reaction mixture was refluxed for 4 hr. and then allowed to cool to room temperature. The mixture was poured into a liter of 1/1 solution of concentrated hydrochloric acid and water. The hydrochloride salt which precipitated was removed by filtration, washed in ethanol, and dried. The hydrochloride was neutralized with aqueous sodium hydroxide solution, and the free amine was recrystallized from 95% ethanol. The yield of white crystalline product, m.p. 57–58°, was 176 g. or 59%.

Anal. Calcd. for $C_{14}H_{24}N_3O_4$·HCl: C, 50.07; H, 7.74; N, 12.51. Found: C, 50.24; H, 7.66; N, 12.58.

The infrared spectra of all of the dinitro compounds showed a high nitro group absorption at 6.50–6.52, typical of tertiary nitro compounds.[5]

Reduction of dinitro amines to polyamines. All of the Mannich condensation products were reduced to the corresponding polyamines with hydrogen in a Parr hydrogenator by using 2 g. of Raney nickel[6] for 0.1 mole of dinitro compound in 175 ml. of 95% ethanol. The heavy-walled reaction bottle was shaken until the hydrogen required for the reduction of the nitro groups was absorbed. Then the catalyst was filtered off and the ethanol solvent removed under reduced pressure. The liquid products were purified by distillation *in vacuo*. The piperazine derivative was recrystallized from acetone, while the 2,5-dimethylpiperazine compound was recrystallized from 90–120° petroleum ether at −15°. Table I lists the properties of these compounds.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, PLASTICS DIVISION, MONSANTO CHEMICAL CO.]

Synthesis of Polyfunctional Polymers[1]

JOSEPH A. BLANCHETTE AND JOHN D. COTMAN, JR.

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Polyfunctional polymers were synthesized by chemical modification of hydrocarbon and nitrile polymers and by copolymerization of selected monomers. Reactions included aromatic nitration, chloromethylation and acylation, reduction of nitro, oximino, carbonyl and nitrile groups and other carbonyl reactions. Polymers utilized included polystyrene, polyacrylonitrile, and copolymers of methyl vinyl ketone with acrylonitrile and styrene.

Chemical modification of high polymers has been studied extensively. In this study polystyrene was chosen as a base polymer for modification because of the ready reactivity of the benzene ring to well defined products of definite structure for a number of reactions. Nitropolystyrene was prepared as a precursor of a variety of substituted polystyrenes such as aminopolystyrene and the products of reaction of diazotized aminopolystyrene. The nitrated polymer has been previously prepared[2–5] under conditions resulting in varying degrees of polymer degradation because of the vigor of the nitrating techniques (use of concentrated sulfuric and nitric acid mixtures at elevated temperatures). Acetylnitrate is an efficient nitrating agent at moderate temperatures, however, and should effect nitration of polystyrene without simultaneous polymer degradation. To increase the solubility of polystyrene in nitrating media, several polystyrenes of low molecular weight were prepared by polymerization in the presence of bromotrichloromethane (1–6%) as a chain transfer agent (Table I).

Nitropolystyrene was obtained when acetylnitrate was used as the nitrating agent and elemental analysis showed this material to contain less than one nitro group per benzene ring (0.6). Varying the conditions of reaction with acetyl nitrate did not yield a $—NO_2$ to C_6H_5 ratio greater than .6 (Table II).

Concentrated nitric acid did not dissolve polystyrene and, as would be expected, nitration was negligible. Fuming nitric acid reacted with polystyrene at 0° to yield a viscous sirup and considerable nitration occurred. Elemental analysis on the product corresponded to 1.2 nitro groups per benzene ring. Chemical and catalytic hydrogenations were carried out on the low molecular weight nitropolystyrenes. Chemical reduction was ineffectual. Products from catalytic hydrogenation (palladium-on-carbon catalyst) appeared to be aminopolystyrene[7–9] with infrared bands at 1600

(1) This paper was presented at the November 1957 Meeting in Miniature of the Connecticut Valley Section of the American Chemical Society, Hartford, Conn.

(2) G. Komppa, *Ber.*, 26, 677 (1893).

(3) H. Zenftman, *J. Chem. Soc.*, 982 (1950).

(4) A. Langhans, *Explosivstoffe*, 516, 68 (1953); *Chem. Abstr.*, 48, 373 (1954).

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TABLE I

LOW MOLECULAR WEIGHT POLYSTYRENE

Sample	% Chain Transfer Agent	% Yield of Polymer	$[\eta]$	M_v[a]	% Cl in Polymer
1	1	70	.078	10,000	2.07
2	2	55	.058	7,000	2.98
3	4	45	.045	5,000	4.05
4	6	20		Below 5,000	5.24

[a] $[\eta] = 5.74 \times 10^{-5} M^{0.78}$ (Ref. 6).

TABLE II

NITRATION OF POLYSTYRENE

Polystyrene	Nitration Method	Temp. °C.	Time, Hr.	% Yield	NO_2/C_6H_5[a]	% N in Polymer[b]
Sample 3	Acetyl nitrate	40	1	90	.6	5.26
Sample 4	Acetyl nitrate	40	1	98	.6	5.98
Sample 4	Acetyl nitrate	40	4.5	100	.6	5.77
Sample 4	Acetyl nitrate	75	4.5	95	.6	5.45
Mw 67,000	Acetyl nitrate	75	4.5	98	.2	2.30
Mw 67,000	Conc. HNO_3	100	12	98	.2	1.78
Mw 67,000	Fuming HNO_3	0	8			
		25	24	96	1.2	10.98

[a] From elemental analytical data. [b] Theoretical value for mononitrated polystyrene; N = 9.39%.

and 3350 cm.$^{-1}$ but were insoluble in organic solvents and aqueous acids and may be crosslinked. The nitropolystyrene showed strong bands at 1350 and 1550 cm.$^{-1}$ (Fig. 1).

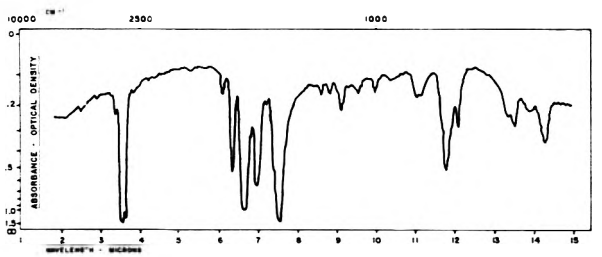


Fig. 1. *p*-Nitropolystyrene infrared curve

Polystyrene was acetylated[10,11] by a Friedel-Crafts reaction[12–14] with acetyl chloride. The elemental analysis and infrared data corresponded to quantitative monoacetylation. The butyryl and stearoyl homologs were prepared and, as expected, the products became less soluble (*i.e.* benzene, methyl ethyl ketone) as the aliphatic carbon chain was lengthened. Softening points (*cf.* EXPERIMENTAL) decreased[15] as the aliphatic chain was lengthened (Table III).

TABLE III

SOFTENING POINTS

Compound	Softening Point
Polystyrene (base polymer)	140–145
Acetylpolystyrene	130–135
Butyrylpolystyrene	95–100
Stearoylpolystyrene	50– 55
p-(α-Hydroxyethyl)polystyrene	120–125
Oxime of acetylpolystyrene	170–175
p-(α-Aminoethyl)polystyrene	170–175
Styrene–methyl vinyl ketone copolymer	100–105
Reduced styrene–methyl vinyl ketone copolymer	135–140
Oxime of styrene–methyl vinyl ketone copolymer	145–150
p-[2-(Cinchoninic acid)]polystyrene	~240
Nitropolystyrene	210–215
Chloromethylpolystyrene[a]	135–145
Stearoylpolystyrene[a]	50– 55

[a] Softening point of polystyrene (base polymer) 100–105°.

Stearoylpolystyrene, in particular, was insoluble in most organic solvents (slightly soluble in polyhalogenated aromatic solvents and soluble in nujol). This material resembled a wax in its physical appearance and behavior. An interesting experimental observation was that the acetyl and butyryl reaction mixtures became heterogeneous early in the reaction; whereas the stearoyl-aluminum chloride complex remained in solution. In the latter reaction, the viscosity increased and gelation occurred toward the end of the reaction. The greater solubility of the stearoyl-aluminum chloride complex than either that of the butyryl or acetyl complexes is probably the consequence of the higher percentage of carbon disulfide compatible aliphatic chain

(9) H. Brandenberger, *J. Polymer Sci.*, **20**, 215 (1956).
(10) W. O. Kenyon, G. P. Waugh, C. C. Unruh (Eastman Kodak Co.), U.S. Patent **2,713,570** (July 19, 1955).
(11) A. W. Ralston, R. J. Vander Wal (Armour and Co.), U.S. Patent **2,197,709** (Apr. 16, 1940).
(12) D. T. Mowry, M. Renoll, W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946).
(13) P. W. Sherwood, *Petrol. Processing*, **8**, 724 (1953).
(14) P. Teyssie, G. Smets, *J. Polymer Sci.* **20**, 351 (1956).
(15) L. L. Ferstandig, J. C. Butler, A. E. Strauss, *J. Am. Chem. Soc.*, **76**, 5779 (1954).

in the R group of the ionic complex $\left[\begin{matrix}RC^{+} \\ \| \\ O\end{matrix}\ AlCl_4^{-}\right]$.

The reaction of phthalic and succinic anhydrides with polystyrene to yield keto acids, another more soluble polyfunctional polystyrene, was not successful. The anhydrides were insoluble in any polystyrene solvent suitable for the reaction.

To introduce amino groups on polystyrene in positions other than on the backbone of the molecule, acetylpolystyrene was converted to the oxime[16] which was then reduced with lithium aluminum hydride[17] to the corresponding primary amine. A Beckman rearrangement on the oxime[18] gave an insoluble resin which could not be identified. Lithium aluminum hydride reduction of the acetylpolystyrene yielded the corresponding secondary alcohol. The number of hydroxyl or amino groups in the polymer was varied from 0 to 1 per benzene ring by controlling the degree of acylation. *p*-Carboxypolystyrene, 1700 and 2500–3000 cm.$^{-1}$ (Fig. 2), was obtained by the oxidation of acetylpolystyrene, 1670 cm.$^{-1}$, with sodium hypochlorite. The sodium salt of the product was completely soluble in water and the solution exhibited detergent properties. The free acid resembled a fatty acid in physical appearance rather than a polymeric material.

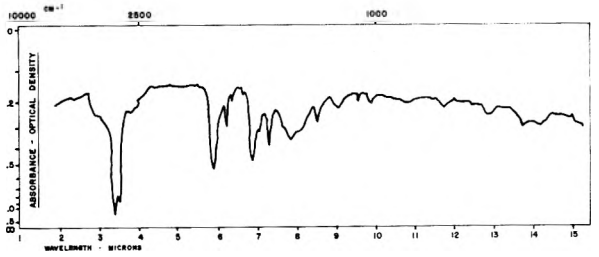
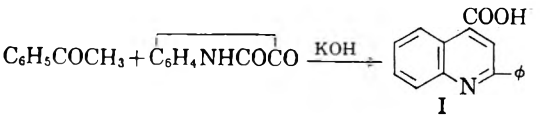


Fig. 2. *p*-Carboxypolystyrene infrared curve

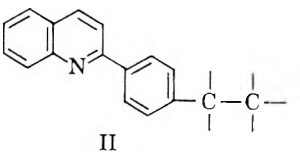
The chloromethylation[19–21] of polystyrene was attempted and numerous runs were made varying reaction conditions and ratios of reactants. In many of these runs no chloromethylation took place and when a chloromethylated product was isolated it was very insoluble. Using low molecular weight polystyrene, a chloromethylated product was isolated which was partially soluble in several solvents but attempts to replace the halogen with hydroxyl and nitrile groups were unsuccessful.

The reaction of isatin with aryl methyl ketones, known as the "Pfitzinger Reaction",[22]



I

has lead to 4-carboxy-2-aryl substituted quinolines (derivatives of cinchoninic acid). Reports in the literature[23–26] suggest possible physiological or pharmacological activity for these compounds. Atophan, (I) has been used in treating gout and rheumatism. Further, it has been shown that if the aryl group of the ketone is alkyl-substituted the activity is enhanced. The condensation of acetylpolystyrene with isatinic acid gave a resin (II)



II

which contained the expected structure as confirmed by infrared comparison with the spectrum of a model compound (I), Fig. 3 and 4. This resin can be considered a styrene-quinoline copolymer.

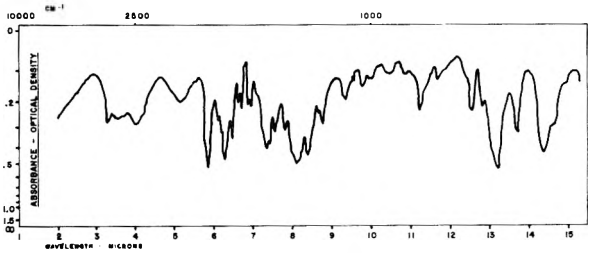


Fig. 3. 4-Carboxy-2-phenyl quinoline infrared curve

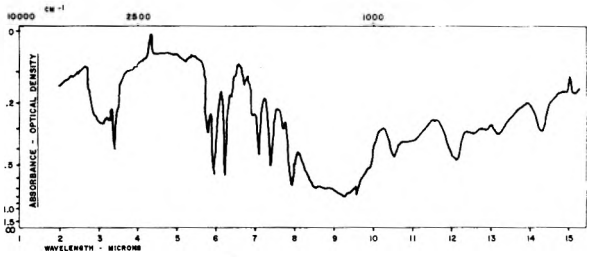


Fig. 4. *p*-(2-[Quinoline-4-carboxylic acid])polystyrene infrared curve

A styrene–methyl vinyl ketone copolymer[27,28] was made as a prototype polymer with a high percentage of carbonyl groups. In this material the

(16) W. E. Bachmann, *J. Am. Chem. Soc.*, **58**, 2097 (1936).
(17) R. E. Lyle, H. J. Troscianiec, *J. Org. Chem.*, **20**, 1757 (1955).
(18) A. Schaffler, *Ber.*, **88**, 767 (1955).
(19) C. H. McBurney, U.S. Patent 2,629,710 (Feb. 24, 1953).
(20) Dow Chemical Co., Brit. Patent 677,350 (Aug. 13, 1952); *Chem. Abstr.*, **47**, 8943 (1953).
(21) G. D. Jones, *Ind. Eng. Chem.*, **44**, 2686 (1952).
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(23) J. A. Knight, H. K. Porter, P. K. Calaway, *J. Am. Chem. Soc.*, **66**, 1893 (1944).
(24) N. P. Buu-Hoï, P. Cagniant, *Bull. soc. chim.*, **11**, 343 (1944).
(25) N. P. Buu-Hoï, R. Royer, *Rec. trav. chim.*, **66**, 300 (1947).
(26) M. Colonna, *Gazz. chim. ital.*, **78**, 502 (1948); *Chem. Abstr.*, **43**, 2210 (1949).
(27) F. M. Lewis, C. Walling, W. Cummings, E. R. Briggs, W. J. Wenisch, *J. Am. Chem. Soc.*, **70**, 1527 (1948).
(28) H. J. Hagemeyer, *J. Am. Chem. Soc.*, **71**, 1119 (1949).

carbonyls are on the chain rather than on the benzene rings. The copolymer was converted to the oxime and reduced to a primary amine. Reduction of the carbonyl groups with lithium aluminum hydride gave the corresponding secondary alcohol. The infrared carbonyl band at 1690 cm.$^{-1}$ was changed to hydroxyl at 3600 cm.$^{-1}$, Fig. 5 and 6.

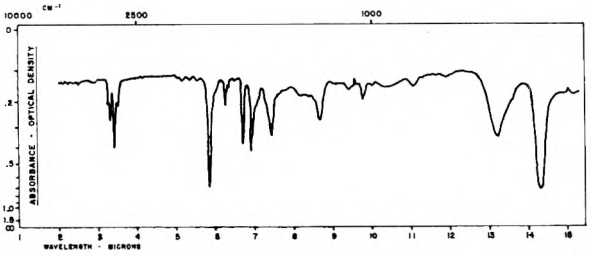

Fig. 5. Styrene-methyl vinyl ketone copolymer infrared curve

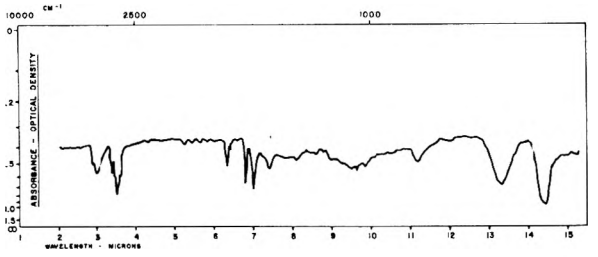

Fig. 6. Reduced styrene-methyl vinyl ketone copolymer infrared curve

An approximately 60/40 methyl vinyl ketone–acrylonitrile copolymer[29,30] was prepared by mass polymerization in sealed tubes. The copolymer was isolated and purified by solution followed by precipitation and then catalytically hydrogenated over Raney nickel in tetrahydrofuran. Infrared analysis showed strong amine and hydroxyl absorption and some nitrile indicating considerable but incomplete reduction. Using similar experimental conditions with polyacrylonitrile[30] in dimethylformamide, a discolored insoluble material was obtained.

It is evident that chemical reactions on polymeric materials are, in many instances, not as easily facilitated as the same reactions with simple organic compounds. Limited solubility, side reactions, and crosslinking are among the more persistent problems. The chemical properties of the modified polymers are quite different from those of the parent compounds (Table III, softening points; solubilities in EXPERIMENTAL section). These chemical compositions lend themselves to further chemical modification and reaction.

EXPERIMENTAL

Low molecular weight polystyrene. Four samples of polystyrene were prepared by mass polymerization in sealed tubes. Bromotrichloromethane was used as a chain transfer agent in 1, 2, 4, and 6% by weight of styrene monomer. Di-tertiary butyl peroxide was the catalyst at .02%. The polymerizations were carried out at 90° for 12 hr. and then brought to 190° for 5 hr. These low viscosity materials were dissolved in methyl ethyl ketone and precipitated from methanol as solids, Table I.

Nitration of polystyrene. Ten grams of polystyrene sample 3 (Table I) was dissolved in 100 ml. of carbon tetrachloride. Fifteen ml. of acetic anhydride was slowly added followed by the cautious addition of 5 ml. of concentrated nitric acid keeping the temperature below 40°. The solution was poured into 300 ml. of methanol with stirring and then filtered. The pale yellow solid was reprecipitated from carbon tetrachloride with methanol. Several runs were made by this procedure and the results are given in Table II.

A sample of polystyrene, prepared without chain transfer agent (M_v 67,000), was nitrated with fuming nitric acid. Twenty grams of polystyrene was added slowly to 160 ml. of fuming nitric acid while keeping the temperature at 0°. After 8 hr. the temperature was allowed to come to room temperature and stand for 24 hr. The thick sirup was poured carefully into water and the yellow solid removed by filtration, washed several times with water, and dried. The molecular weight of the product was 58,000. The molecular weights of the polystyrene $[\eta]$ = 0.343 and of nitropolystyrene $[\eta]$ = 0.290 were calculated from the relationship[6] $[\eta] = 5.74 \times 10^{-5} M^{0.78}$ (toluene at 25°; g./100 ml.). The value for nitropolystyrene is an approximation as used by Zenftman.[3] The nitrated polystyrenes were soluble in dimethylformamide and tetrahydrofuran, and slightly soluble in benzene and toluene.

Reduction of nitropolystyrene. A series of chemical and catalytic reduction experiments was unsuccessful for the reduction of nitropolystyrene. Unreacted nitropolystyrene was recovered along with up to 10% insoluble material in some runs. Palladium-on-carbon gave an aminopolystyrene.

Method of Reduction	Conditions	Result
$LiAlH_4$	THF, reflux 1 hr.	No reduction
Sn, HCl (gaseous)	THF, reflux	No reduction 90%; material insoluble in all common solvents 10%
Raney nickel	60°, 900 lb./sq. in. 4 hr.	No reduction
Raney nickel	100°, 1400 lb./sq. in. 4 hr.	No reduction

Palladium-on-carbon powder. Fifteen grams (.1*M*) of nitropolystyrene (degree of nitration 1.2) was dissolved in 135 ml. of purified dimethylformamide to which 3 g. of 5% palladium-on-carbon was added. This was charged to a Parr low pressure hydrogenator at 50 lb./sq. in. and 50° for 12 hr. The reaction consumed the theoretical amount of hydrogen. The yellow product, isolated as previously described, was almost completely reduced as shown by infrared analysis, but was insoluble in HCl and all solvents.

Acylation of polystyrene. p-acetylpolystyrene (polyvinylacetophenone). In a 2-liter three-necked flask, fitted with a mechanical stirrer, dropping funnel, and a reflux condenser were placed 67 g. (.5 mole) of Eastman grade aluminum chloride and 250 ml. of carbon disulfide. Stirring was begun and 30 g. (.37 mole) of practical acetyl chloride was added. While maintaining vigorous stirring, a dope of 26 g. (.25 mole) of polystyrene, sample 1, in 200 ml. of carbon disulfide was added gradually over a period of about 20 min. The mixture became yellow, a soft bulky precipitate was formed, the carbon disulfide refluxed gently, and hydrogen chloride was evolved. After the addition of polystyrene was complete, the mixture was refluxed for 1.5 hr. until the evolution of hy-

(29) W. E. Elwell, R. L. Meier (California Research Co.), U. S. Patent 2,451,435 (Oct. 12, 1948).

(30) N. H. Shearer, H. W. Coover (Eastman Kodak Co.), U. S. Patent 2,719,144 (Sept. 27, 1955).

drogen chloride ceased. Stirring was maintained during this period. The reflux condenser was replaced by a tube leading to a distilling condenser, stirring was stopped, and about 70% of the carbon disulfide was removed leaving a damp yellow mass which was poured into water containing ice and 100 ml. of HCl. This was then steamed to remove the remainder of the CS_2 and the acidic water was decanted from the solid which adhered to the walls of the container. Cold water was added and the solid hardened on contact and was removed by filtration. The product was dissolved in 800 ml. of acetone and precipitated by 3 l. of water to yield a pale yellow solid in 92% yield.

Anal. Calcd.: C, 82.20; H, 6.90. Found: C, 82.10; H, 6.78. The material was soluble in acetone, ethylene chloride, acetophenone, dioxane/alcohol, dioxane/methanol, and tetrahydrofuran.

When stannic chloride was used no acetylation occurred. With acetic anhydride and aluminum chloride, 25% acetylation (1 CH_3CO/4 benzene rings) was the most obtained.

Butyrylpolystyrene. This compound was prepared by the same method with *n*-butyryl chloride. The purification was more difficult due to decreased solubility and the recovery was 50%.

Anal. Calcd.: C, 82.75; H, 8.05. Found: C, 82.06; H, 8.41. The material exhibited limited solubility in methyl ethyl ketone, xylene, and dichlorobenzene.

Stearoylpolystyrene. This compound was prepared by the same method (using freshly distilled stearoyl chloride) in 80% yield as a white, very waxy solid, with limited solubility in methyl ethyl ketone, xylene, and dichlorobenzene and soluble in hot nujol.

Anal. Calcd.: C, 84.32; H, 11.35. Found: C, 83.78; H, 11.25.

Phthalic and succinic anhydrides could not be used since they are insoluble in all Friedel-Crafts type solvents which will dissolve polystyrene. A run was made using nitrobenzene as solvent but no reaction occurred.

Derivatives of p-acetylpolystyrene. p-(α-Hydroxyethyl)polystyrene. Five grams (.034 mole) of acetylpolystyrene was dissolved in 50 ml. of tetrahydrofuran. Five grams (0.14 mole) of lithium aluminum hydride was suspended in 50 ml. of tetrahydrofuran. The tetrahydrofuran was distilled from calcium hydride and then from lithium aluminum hydride. The polymer solution was added slowly to the lithium aluminum hydride suspension in a 200-ml. flask fitted with a reflux condenser, stirrer, and dropping funnel. The solution became warm during the addition and began to reflux and the viscosity of the mixture increased. After refluxing for 2 hr. the mixture was cooled and excess $LiAlH_4$ was decomposed with ethanol followed by water and HCl to dissolve the aluminum hydroxide. The polymer was removed by filtration, dissolved in methyl ethyl ketone, and reprecipitated from water. The yield was 4.5 g. (90%) and infrared confirmed conversion of carbonyl to hydroxyl.

Anal. Calcd.: C, 81.06; H, 6.99. Found: C, 80.68; H, 7.06.

Oxime of acetylpolystyrene. Seven and one half grams (0.047 mole) of acetylpolystyrene and 6 g. (.085 mole) of hydroxylamine hydrochloride were dissolved in a mixture of 30 ml. of absolute ethanol and 45 ml. of dry pyridine. The mixture was refluxed for 48 hr. and then poured into cold water. The white solid amounted to 7.2 g. (88%). The oxime was purified by dissolving in acetone and reprecipitating from water. It was soluble in acetone and pyridine, slightly soluble in ethanol and benzene, and insoluble in water. The infrared spectrum showed essentially complete conversion of carbonyl to oxime.

Anal. Calcd.: N, 8.70. Found: N, 8.05.

An attempted Beckman rearrangement of the oxime gave a completely insoluble mass.

p-(α-Aminoethyl)polystyrene. Five grams (0.31 mole) of the oxime was dissolved in 50 ml. of purified tetrahydrofuran and added to a slurry of 5 g. (0.14 mole) of lithium aluminum hydride. A vigorous reaction occurred and a gel formed. After 1 hr. of reflux the mixture was carefully decomposed with ethanol and then poured into water. The *p*H was adjusted to 8–10 and the gummy precipitate was removed by filtration, dissolved in methyl ethyl ketone, and reprecipitated from water. The yield of fine yellow powder was 3.7 g. (80%).

Anal. Calcd.: C, 81.60; H, 9.50; N, 8.90. Found: C, 81.00; H, 9.40; N, 8.55.

p-Carboxypolystyrene. Six grams of acetylpolystyrene was added to an aqueous solution of sodium hypochlorite (Merchlor) and the suspension refluxed for 12 hr. during which time the odor of chloroform was observed. At the end of this time the polymer was all in solution and the clear liquid was acidified. An excessive amount of foam was observed at this point. The white solid was removed by filtration (75%). The infrared spectrum showed complete conversion of carbonyl to carboxyl. The material was soluble in methanol, ethanol, and in water as the sodium or ammonium salt, and insoluble in other common organic solvents. Dilute aqueous solutions of the sodium salts exhibited heavy foaming characteristics.

Anal. Calcd.: C, 72.98; H, 5.40. Found: C, 72.83; H, 5.41.

Chloromethylation of polystyrene. In a 1-l. four-necked flask equipped with condenser, stirrer, thermometer, dropping funnel, and drying tubes was added 25 g. (0.25 mole) of polystyrene dissolved in 200 ml. of carbon disulfide. Stirring was started and the solution was cooled to about 0° with an ice-salt bath. Fifty-five g. (0.69 mole) of chloromethyl ether was then added to the cold solution followed by the dropwise addition of 13 ml. (0.11 mole) of $SnCl_2$. The temperature rose a few degrees, the solution slowly darkened until about 15 min. after the first addition of catalyst when the mixture became a dark red gel. The mixture was allowed to stand for 1 hr. after which methanol was added. The color disappeared leaving an off-white solid which was washed repeatedly with methanol and dried. The material was insoluble in dioxane, methyl ethyl ketone, tetrahydrofuran, carbon disulfide, and chloroform.

A second run was made adding the polymer solution and $SnCl_2$ simultaneously to the chloromethyl ether and quenching immediately after the last addition to prevent excessive cross-linking. The product was again insoluble. Using this procedure with the low molecular weight polystyrene (sample 2) a product was obtained which was soluble in CS_2 and partially soluble in dioxane, methyl ethyl ketone, and tetrahydrofuran. Sodium fusion showed the presence of chlorine and the infrared curve deviated from that of the starting material. Softening point of polystyrene used was 100–105°; for the product 135–140°.

Attempts to replace the halogen of the above chloromethylated polystyrene with nitrile and hydroxyl groups were unsuccessful.

Styrene–methyl vinyl ketone copolymer. This copolymer was prepared by mass polymerization in sealed tubes. Seventy g. (0.67 mole) of purified styrene, 35 g. (0.5 mole) of methyl vinyl ketone and .02% di-*tert*-butyl peroxide were placed in tubes, flushed with nitrogen, and sealed. The tubes were placed in an oven at 95° for 8 hr. and brought to 190° for 15 hr. The pale yellow sticky mass was dissolved in methyl ethyl ketone and precipitated from methanol (81% conversion).

Anal. Found: C, 85.31; H, 8.37 which corresponds to about 65% styrene, 35% methyl vinyl ketone.

Derivatives of styrene–methyl vinyl ketone copolymer. Reduced styrene–methyl vinyl ketone copolymer. Twenty grams (0.11 mole) of dry styrene–methyl vinyl ketone copolymer (65/35) was dissolved in 150 ml. of dry tetrahydrofuran. Fifteen grams (0.39 mole) of lithium aluminum hydride was suspended in 150 ml. of tetrahydrofuran. The tetrahydrofuran was previously distilled from calcium hydride and then from lithium aluminum hydride. The polymer solution was slowly added to the lithium aluminum hydride suspension in a 2-l. three-necked flask fitted with a reflux condenser, stirrer, and dropping funnel. The solution became warm during the addition and began to reflux. After

about one half of the polymer solution was added, the mixture became gelatinous and broke up into small lumps. After the addition of the polymer solution was complete (about 45 min.), stirring and refluxing was continued for 2 hr. The mixture was cooled and ethanol was cautiously added after which it was poured into 150 ml. of cold 20% HCl. The polymer was removed by filtration, dissolved in methyl ethyl ketone, and reprecipitated from water. The yield was 20 g., 98%. The infrared spectrum showed complete conversion of carbonyl to hydroxyl. Analysis for hydroxyl content gave 5.86% hydroxyl. Calculated hydroxyl for 33% methyl vinyl ketone composition is 6.01%.

Oxime of styrene–methyl vinyl ketone copolymer. Five g. (.03 mole) of styrene–methyl vinyl ketone copolymer and 5 g. (.071 mole) of hydroxylamine hydrochloride were dissolved in a mixture of 30 ml. of absolute ethanol and 30 ml. of dry pyridine. The mixture was refluxed for 48 hr. and then poured into cold water. The clean white solid amounted to 5.5 g. (96%). The infrared spectrum showed complete conversion of carbonyl to oxime.

Anal. Calcd.: N, 4.77. Found: N, 5.01.

The semicarbazone was prepared by an analogous procedure.

p-[2-(Quinoline-4-carboxylic acid)]polystyrene (II). Five g. (.034 mole) of acetylated polystyrene and 5 g. of isatin (.034 mole) were dissolved in 100 ml. of pyridine and 50 ml. of 30% aqueous potassium hydroxide was added. The dark red solution was refluxed for 3 days after which time it was poured into 250 ml. of methanol. The small amount of insoluble material was removed by filtration leaving a clear, deep red solution. The methanol solution was acidified whereupon a reddish-brown solid precipitated and was removed from the yellow solution by filtration. The solid was dissolved in tetrahydrofuran and reprecipitated from water. There was obtained 7.5 g., 80% yield, of a pale pink solid. A model compound was prepared from isatin and acetophenone. The infrared spectrum showed that these two materials were of similar composition.

Acrylonitrile–methyl vinyl ketone. This copolymer, prepared by mass copolymerization of equimolar quantities of these monomers, was precipitated from methyl ethyl ketone solution in methanol. This was a clear, brittle, glassy material with exceptional adhesive properties.

Reduction of methyl vinyl ketone–acrylonitrile copolymer. The methyl vinyl ketone–acrylonitrile copolymer was reduced in the low pressure hydrogenator with Raney nickel catalyst in tetrahydrofuran solution. The pale yellow solid which was isolated showed hydroxyl, nitrile, and amine groups by infrared. A similar reduction on polyacrylonitrile in dimethylformamide yielded a black, insoluble, amorphous mass.

Softening points. This data was taken on the Fisher-Johns apparatus and reported in Table III. The softening point (range) was measured from initial softening to complete flow of the sample.

Acknowledgment. We wish to express our thanks to Donald Casey for help in the preparative work and to Peter Shapras for his help with infrared spectrometry.

SPRINGFIELD, MASS.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY SECTION MIDWEST RESEARCH INSTITUTE]

An Application of Statistical Design to Organic Synthesis. The Reductive Alkylation of *t*-Butylamine (Leuckart Reaction)

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A series of experiments was designed to simultaneously determine by statistical analysis the effect of five experimental conditions on the yield of *t*-butylmethylamine and *t*-butyldimethylamine in the reductive methylation of *t*-butylamine by the Leuckart procedure. Optimum conditions were determined for the preparation of both amines.

Although tertiary amines are the usual products in the Leuckart reaction of formaldehyde with primary amines in the presence of formic acid,[1] we have observed that *t*-butylamine, treated in this manner, yields significant amounts of the secondary amine, *t*-butylmethylamine. Since we had need of a large amount of this product and there is no satisfactory synthesis reported,[2] we considered it of interest to determine the optimum conditions for its preparation by this method. After consideration of some excellent reviews on the mechanism of the Leuckart reaction,[3] we chose to study the effects of several experimental variables. In a previous study in our laboratories,[4] application of the method of experimental design[5] provided outstanding results in determining ideal conditions for a synthesis problem involving the variation of several experi-

(1) M. L. Moore, *Org. Reactions*, V, 307 (1949).

(2) *t*-Butylmethylamine was prepared in unspecified yield (along with neopentylamine) by the hydrogenation of *t*-butylcarbylamine [P. Sabatier and A. Mailhe, *Compt. rend.*, **144**, 957 (1907)]. This compound was also formed in about 6 per cent yield by the alkylation of *t*-butylamine with methyl iodine [N. Bortnick, *et al.*, *J. Am. Chem. Soc.*, **78**, 4039 (1956)]. Hurwitz [U. S. Patent 2,582,128 (1952)] suggests the possibility of hydrogenating the Schiff base (aldimine) formed on treatment of *t*-butylamine with formaldehyde.

(3) See, for example, (a) E. R. Alexander and R. B. Wildman, *J. Am. Chem. Soc.*, **70**, 1187 (1948); (b) V. J. Webers and W. F. Bruce, *J. Am. Chem. Soc.*, **70**, 1422 (1948); (c) P. A. S. Smith and A. J. MacDonald, *J. Am. Chem. Soc.*, **72**, 1037 (1950); (d) D. S. Noyce and F. W. Bachelor, *J. Am. Chem. Soc.*, **74**, 4577 (1952); (e) E. Staple and E. C. Wagner, *J. Org. Chem.* **14**, 559 (1949); (f) C. B. Pollard and D. C. Young, Jr., *J. Org. Chem.*, **16**, 661 (1951).

(4) Results to be published later.

(5) For a general reference to the method of experimental design, see C. A. Bennett and N. L. Franklin, *Statistical Analyses in Chemistry and the Chemical Industry*, John Wiley & Sons, Inc., New York, (1954).

mental factors. Experimental design permits optimum application of statistical analysis to experimental data and can often be the most efficient method of determining optimum reaction conditions. For this reason we believe that it is ideally suited to many problems in organic synthesis and that it should find ever increasing application in this field. Moreover, the method provides some indication of the reliability of the results. The data provide sufficient information for the calculation of the uncertainty or error inherent in the yield variations. When this uncertainty is compared with the difference which is attributed to a variable under study one may reliably determine the probability that the effect is real.

The effects discussed in this paper were significant at the 95% confidence level, that is, the odds are 20 to 1 that the effects were not due to an unfortunate sampling of data.

After a preliminary run to determine approximate reaction conditions, a series of experiments was designed. These were designed to test the effect of five experimental conditions on the yield of secondary and tertiary amines. The initial block of 16 experiments (a half-replicate of a 2^5 factorial experiment) simultaneously compared high and low values of reaction temperature (50° and 80°), reaction time (4 hr. and 6 hr.), rate of addition of formaldehyde (2 ml./min. and 6 ml./min.), and the concentration of formic acid (2 moles and 3 moles) and formaldehyde (0.75 mole and 1.25 moles). The design and randomization of the experiment are presented in Fig. 1.

TEMPERATURE, °C.				50				80			
REACTION TIME, HR.				4		6		4		6	
FORMALDEHYDE RATE OF ADDITION, ML./MIN.				2	6	2	6	2	6	2	6
FORMIC ACID, MOLES	2	FORMALDEHYDE, MOLES	1.25	7			11		16	5	
			0.75		9	12		2			4
	3		1.25		1	3		8			10
			0.75	6			15		14	13	

Fig. 1. The design and randomization of the experiment

The consecutive numbers in Fig. 1 (1 through 16) represent the individual runs and the position of the number in the block readily shows the experimental conditions of that run.

In these experiments, *t*-butylamine was mixed with formic acid at ice water temperature to produce the formate salt. This mixture was heated to the specified temperature and formaldehyde (a 37% formalin solution) was added at a prescribed rate. At the end of the experiment, the reaction mixture was analyzed for *t*-butylmethylamine, *t*-butyldimethylamine, and unreacted *t*-butylamine by rectification of the mixture. As will be seen, this method of analysis was not precise but it was accurate enough for our purposes. The yields based on primary amine (conversions) are presented in Table I.

TABLE I

YIELDS BASED ON PRIMARY AMINE (CONVERSIONS)

Experiment Number	Recovered Primary Amine, %	Secondary Amine, %	Tertiary Amine, %
1	45	43	6
2	43	28	25
3	24	46	22
4	43	23	25
5	18	22	55
6	59	29	7
7	27	38	28
8	17	22	55
9	48	27	18
10	19	21	58
11	29	36	30
12	49	26	22
13	41	27	25
14	43	31	22
15	51	28	19
16	19	21	53

It is of interest to note that in all the runs at 80° the formaldehyde was completely utilized. The yields based on formaldehyde ranged from 95 to 109%. Yields in excess of 100% are, of course, a reflection of the accuracy of the analysis by distillation.

A statistical analysis of the yields (Table I) was performed. Effects were tested for significance at the 95% confidence level and the following conclusions were drawn:

1. Under the conditions chosen for study, reaction time and rate of addition are not significant. 2. Increasing the temperature from 50° to 80° causes an increase in the yield of tertiary amine and a decrease in secondary amine yield. 3. An increase in the amount of formaldehyde (from 0.75 to 1.25 moles) causes an increase in the yield of both amines. 4. A significant interaction between temperature and formaldehyde concentration exists. At the low temperature (50°) an increase in formaldehyde concentration increases the yields of both secondary and tertiary amines. At the higher temperature an increase in formaldehyde increases the yield of tertiary amine but reduces the yield of secondary amine. 5. Although not statistically significant, the effect representing the formic acid–temperature interaction was relatively large. The data indicate that at the high temperature the formic acid concentration has little effect on yields. At the lower temperatures, a high formic acid concentration appears to favor secondary rather than tertiary amines.

Figure 2 is a representation of the expected yield values based upon the assumption that only form-

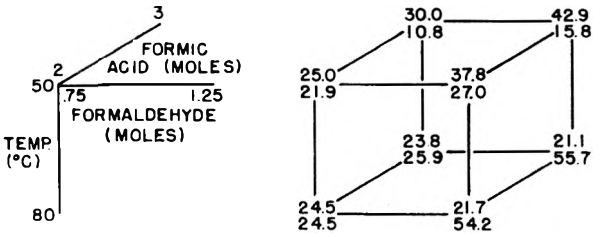

Fig. 2. Expected yield estimates. The yield estimates are based upon a statistical analysis of the experimental data. The upper number represents per cent conversion to secondary amine; the lower number represents per cent conversion to tertiary amine

aldehyde concentration, formic acid level, reaction temperature, and the above-mentioned interactions are important.

Our major objective in these experiments was to find the best conditions for the preparation of the secondary amine. However, it is worth noting that the statistical conclusions and the high ultilization of formaldehyde at 80° both indicate that high yields of the tertiary amine should be formed at high temperatures with excess formaldehyde. Actually, high yields of many tertiary amines have been reported under such conditions but since the reaction of *t*-butylamine had not been reported,[6] one run was made at 90° with excess formaldehyde. The tertiary amine was obtained in almost quantitative (95%) conversion with no detectable amounts of the secondary amine or recovered primary amine.

Our results also indicated that secondary amine formation would be favored by lower reaction temperatures and higher concentrations of formic acid and formaldehyde.

We then designed a series of 24 experiments (a $2^3 \cdot 3$ factorial experiment) to more completely investigate reaction temperatures (46°, 53°, and 60°), high formic acid concentration (3 and 7 moles), high formaldehyde concentrations (1.25 and 2.25 moles), and reaction times (3 hr. and 6 hr.). However, it was found that the reaction did not proceed to any great extent at 46°. It was apparent that the higher levels of formic acid concentration caused a considerable decrease in the reaction rate. This retarding effect of a large excess of formic acid was observed before in reactions of this type.[3e]

The experimental design was changed to eliminate the study at 46° (thus becoming a 2^4 factorial experiment) and the remaining experiments were performed. The design and randomization of this series of experiments was carried out in the same manner as the first block of experiments (Fig. 1). In this series, the reaction conditions varied from those which barely allowed the reaction to proceed to those which permitted fairly extensive reaction. (The yields of carbon dioxide varied widely from 11% to 156%, based on the amount of carbon dioxide required in the formation of the secondary amine.) The effect of high concentrations of formic acid in decreasing reaction rate was especially significant. An increase in formic acid concentration (from 3 to 7 moles) caused a fourfold decrease in the extent of the reaction during 3 hr. at both temperatures and a twofold decrease during the 6-hr. experiments at both temperatures. However, a complete statistical analysis of these experiments was not possible since, under conditions where the reduction had not occurred to a large extent, a considerable quantity of *t*-butylaldimine[7] (a Schiff base) was formed. This seriously interfered with the analysis of the secondary amine because *t*-butyl aldimine boils within a few degrees of the secondary amine and has been shown to be unstable.[8] In all cases, however, the yield of crude secondary amine was no greater than the highest yield found in the first block of experiments.

Thus, the application of statistical design to this reaction has provided a convenient set of experimental conditions for the satisfactory production of the secondary amine. The better runs in the first block of experiments produced the secondary amine in yields as high as 60% with 46% conversion. This is probably very close to the optimum for this reaction since these were the highest yields obtained in a systematic study of the important experimental variables at levels near those which produced these yields.

EXPERIMENTAL[9]

Starting materials. *t*-Butylamine is commercially available and was used without purification. The formaldehyde used was a formalin solution (38% formaldehyde) and the formic acid used was a technical grade (90% formic acid).

General procedure. *t*-Butylamine (73 g., 1.0 mole) was cautiously added dropwise (30 min.) to ice cold formic acid (the amount of formic acid was systematically varied between 2 and 7 moles). The flask was equipped with a reflux condenser and a thermometer well, and the contents were stirred with a magnetic stirrer. The reaction mixture was brought to the required temperature by means of a heating mantle and the temperature was maintained within a degree of the desired temperature by means of a capacitance relay attached at the proper position on the thermometer. This "Thermo-Cap Relay" provided an off-on switch for the heating-mantle variac. Formaldehyde solution was added dropwise at a specified rate by means of an apparatus similar to that used for surgical infusions. It consisted of a graduated addition funnel from which the formaldehyde solution was conducted downward through a Tygon tube to a calibrated dripmeter. This dripmeter consisted of a glass tube $^1/_2 \times 2$ in. which was half filled with the solution. As the solution passed dropwise into the dripmeter, the solution flowed downward to the reaction mixture through another Tygon

(6) This reaction was subsequently reported by L. Spialter and J. Pappalardo, *J. Org. Chem.*, 22, 840 (1957).

(7) M. D. Hurwitz, U. S. Patent 2,582,128 (1952).

(8) *t*-Alkylamines are unique in their reaction with formaldehyde, since they give excellent yields of *relatively* stable monomeric aldimines. Normally the reaction of aliphatic primary and secondary carbinamines with formaldehyde yields cyclic trimeric azomethines [*Tertiary-Alkyl Primary Amines*, Rohm & Haas Co., Technical Publication No. SP-33, p. 24 (1955)].

(9) All melting points and boiling points are uncorrected.

tube which could be constricted by means of a pinch clamp. The apparatus was adjusted to deliver formalin solution at the prescribed rate and provided a very convenient method of accurately controlling the rate of addition.

The reaction mixture was stirred by means of the magnetic stirrer and held at the specified temperature for the required time. During the entire experiment the evolution of carbon dioxide was followed volumetrically using a "wet-test meter". The reaction mixture was then treated with 50 ml. of concentrated hydrochloric acid and 100 ml. of liquid was distilled from the mixture. The residue was made strongly basic with a 50% solution of sodium hydroxide and this mixture was fractionally distilled through a 3-ft. bubble-cap column which was equipped with a reflux head set at a reflux ratio of ten to one. The yield of secondary and tertiary amine and the amount of recovered primary amine was determined from a plot of the boiling point and refractive index of the distillate.

t-Butyldimethylamine is obtained as an azeotrope with water (86.3% amine, 13.7% water) under these conditions. The composition of the azeotrope (b.p. 76°, d_4^{25} 0.771) was determined by titration, vapor phase chromatography (Perkin-Elmer, Column Material "F"), and density. The pure *t*-butyldimethylamine could be obtained by distillation of the azeotrope from solid sodium hydroxide.

t-Butyldimethylamine. The described general procedure was used. Optimum conditions were: a 4:1 molar ratio of formic acid to amine, a 2.5:1 molar ratio of formaldehyde, a reaction temperature of 90–100°, and a reaction time of 2 hr. These conditions gave a 95% yield of product[6,10] b.p. 89°, n_D^{25} 1.4015, d_4^{25} 0.735, MR_D calcd.: 33.86. Found: 33.49. The melting point of the quaternary ammonium salt, *t*-butyltrimethylammonium iodide, m.p. 225–226° (with decomposition) agrees with the value previously reported.[10]

t-Butylmethylamine. The described general procedure was followed. Experimental conditions which gave the best yield were: A 3:1 molar ratio of formic acid to amine, a 1.25:1 molar ratio of formaldehyde, a reaction temperature of 50°, and a reaction time of 6 hr. The product[10] was obtained in 60% yield and 46% conversion; b.p. 69°, n_D^{25} 1.393, d_4^{25} 0.727, MR_D calcd.: 28.89%. Found: 28.61.

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(10) N. Bortnick, L. S. Luskin, M. D. Hurwitz, W. E. Craig, L. J. Exner, and J. Mirza, *J. Am. Chem. Soc.*, 78, 4039 (1956).

[CONTRIBUTION FROM INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Studies in Dieckmann Cyclization. I. Cyclization of Triethyl Pentane-1,2,5-tricarboxylate[1]

KALYANMAY SEN AND P. BAGCHI

Received January 10, 1958

Dieckmann cyclization of triethyl pentane-1,2,5-tricarboxylate has been shown to give diethyl cyclohexanone-2,3-dicarboxylate.

In connection with a research project on the synthesis of diterpenoid resin acids, in progress in this laboratory for some years, it became necessary to undertake the study of the Dieckmann cyclization of triethyl pentane-1,2,5-tricarboxylate (I).

Dieckmann cyclization of triethyl pentane-1,2,5-tricarboxylate was studied by Perkin and coworkers.[2] It was proved by them that a six-membered ring was formed in preference to a five-membered one, since the product of cyclization on hydrolysis furnished cyclohexanone-3-carboxylic acid. They did not, however, establish whether the intermediate β-keto ester had structure IIa or IIb representing the two possible modes of cyclization.

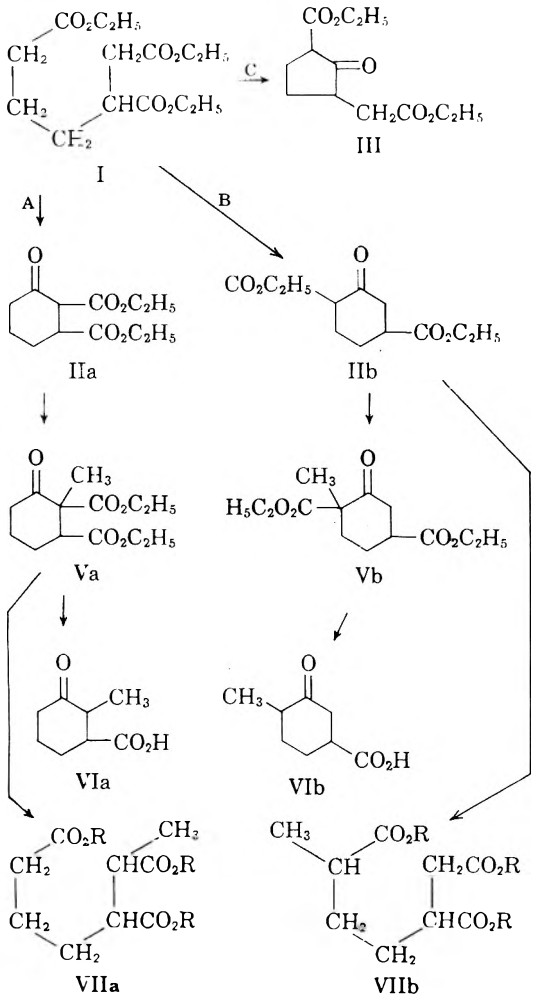
From a consideration of the inductive effect of substituents in the β-position on an α-methylene group Chakravarti[3] predicted that the cyclization of I should predominantly proceed *via* the route A rather than *via* B or C, resulting in the product IIa. Our results corroborate this view.

Triethyl pentane-1,2,5-tricarboxylate employed in these studies was prepared by two different methods. In the first method ethyl cyclopentanone-2-carboxylate was condensed with ethyl chloroacetate in benzene to produce diethyl cyclopentanone-2-acetate-2-carboxylate which, on being subjected to ring fission with catalytic amount of sodium ethoxide in ethanol, furnished the tri-ester (I). In the second method ethyl chloroacetate was condensed with diethyl sodiomalonate resulting in the formation of diethyl 1-carbethoxysuccinate. The succinic ester derivative was further condensed with ethyl γ-bromobutyrate to yield tetraethyl pentane-1,2,2,5-tetracarboxylate (IV). The tetra-

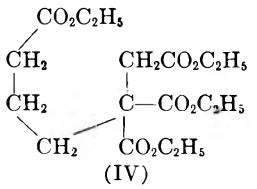
(1) Taken from the thesis submitted by Kalyanmay Sen for the degree of Doctor of Philosophy (Science) of the University of Calcutta, April 1957. A preliminary communication on this subject appeared in *Science and Culture*, 19, 312 (1953).

(2) M. E. Dobson, J. Ferns, and W. H. Perkin, *J. Chem. Soc.*, 95, 2010 (1909).

(3) R. N. Chakravarti, *J. Chem. Soc.*, 1316 (1953).



ester (IV) on hydrolysis with concentrated hydrochloric acid and subsequent esterification furnished I.



(IV)

Diekmann cyclization of I was conducted in benzene solution using 1.2 atoms of pulverized sodium. The course of cyclization was deduced from the following experiments.

The Dieckmann product was methylated *in situ* with methyl iodide. A portion of the methylated product was hydrolyzed directly with 25% hydrochloric acid whereupon an acid of m.p. 97° was formed[4] which was found to be identical with an authentic specimen of 2-methylcyclohexanone-3-carboxylic acid (VIa) through mixed m.p. determination and comparison of derivatives. Alternative method of cyclization of I would have led to the formation of 2-methylcyclohexanone-5-carboxylic acid (VIb).

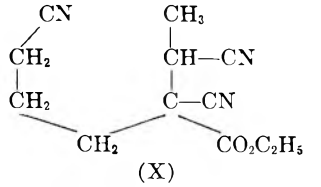
(4) O. Baudisch and W. H. Perkin, *J. Chem. Soc.*, **95**, 1886 (1909).

The above results indicate that the cyclization of I proceeded through the route A. Further confirmation of this fact was obtained by subjecting the methylated product to ring fission with a catalytic amount of sodium ethoxide in ethanol. The triester so obtained on being hydrolyzed with concentrated hydrochloric acid furnished a gum which on trituration with dioxane gave crystals melting at 145° after two crystallizations from ethyl acetate. This acid was found to be identical with 1-methylpentane-1,2,5-tricarboxylic acid (VIIa, R = H), synthesized by an unambiguous method. 1-Methylpentane-1,4,5-tricarboxylic acid (VIIb, R = H) which should have resulted had the cyclization proceeded along route B was also synthesized for comparison and was found to possess quite different properties.

Our results clearly show that the cyclization of triethyl pentane-1,2,5-tricarboxylate in benzene proceeded predominantly *via* route A and that the by-product, if any, is formed only in minor amounts.

Certain compounds were synthesized and employed for comparison purposes. 2-Methylcyclohexanone-3-carboxylic acid (VIa) was prepared by converting 2-methylcyclohexanone to 2-methyl-2-cyclohexenone (VIII)[5] *via* pyridine-catalyzed dehydrochlorination of 2-methyl-2-chlorocyclohexanone, the addition of hydrogen cyanide to VIII, and hydrolysis of the keto nitrile.

1-Methylpentane-1,2,5-tricarboxylic acid (VIIa, R = H) was prepared in the following way. Ethyl α,β-dicyanobutyrate, synthesized by a convenient procedure developed in this laboratory,[6] was con-



densed with γ-bromobutyronitrile. The resulting ethyl 1-methyl-1,2,5-tricyanopentane-2-carboxylate (X) was hydrolyzed with concentrated hydrochloric acid. The triacid formed was purified through the triester (VIIa, R = C_2H_5).

1-Methylpentane-1,4,5-tricarboxylic acid (VIIb, R = H) was prepared as follows. Ethyl 2-methylcyclopentanone-2-carboxylate was subjected to ring fission by treatment with a catalytic amount of sodium ethoxide in ethanol to give diethyl 1-methylbutane-1,4-dicarboxylate. The latter was cyclized with sodium dust in benzene and the product was condensed *in situ* with ethyl bromoacetate giving diethyl 5-methylcyclopentanone-2-acetate-2-carboxylate.[7] This on being subjected to

(5) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953).

(6) K. Sen and P. Bagchi, *J. Org. Chem.*, **20**, 845 (1955).

(7) A. E. Bradfield, E. M. Frances, A. R. Penfold, and J. L. Simonsen, *J. Chem. Soc.*, 1619 (1936).

ring fission with catalytic amount of sodium ethoxide in ethanol furnished triethyl 1-methylpentane-1,4,5-tricarboxylate (VII,R= C_2H_5) which gave 1-methylpentane-1,4,5-tricarboxylic acid (VIIb,R = H) on hydrolysis with the concentrated hydrochloric acid.

EXPERIMENTAL

(All melting points and boiling points are uncorrected).

Triethyl pentane-1,2,5-tricarboxylate (I). *A. From diethyl cyclopentanone-2-carboxylate-2-acetate.* To a solution of sodium ethoxide (0.53 g. sodium and 15 ml. ethanol) was added the diester (55 g.). The mixture at once became deep wine red and heat was evolved. It was heated on a water bath for 2 hr. To the cooled solution was added glacial acetic acid (1 ml.) and water. A nearly colorless oil separated which gave a color reaction with ethanolic ferric chloride indicating the presence of a trace of β-ketoester. It was extracted with benzene and the benzene layer was washed thoroughly with 5% sodium hydroxide solution and then with water. After removing benzene an oil was obtained which distilled at 162–163°/5 mm. (54.2 g., 82.8%), n_D^{28} 1.4373. The product did not show a ferric chloride test.

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.33; H, 8.33. Found: C, 58.56; H, 8.45.

B. Unambiguous synthesis. To a solution of sodium ethoxide (2.3 g. sodium and 40 ml. ethanol) was added diethyl α-carbethoxysuccinate (24.6 g., b.p. 140°/7 mm., prepared in 65% yield from diethyl sodiomalonate and ethyl chloroacetate) followed immediately by ethyl γ-bromobutyrate (23 g., prepared in almost quantitative yield from γ-butyrolactone by the action of hydrogen bromide in ethanol solution). After refluxing until neutral (18 hr.) water was added and the precipitated oil was taken up in ether. The ether extract was washed and dried. After removal of ether and distillation of the residual oil, tetraethyl pentane-1,2,2,5-tetracarboxylate (IV) (19 g., 50.4%) b.p. 155°/0.4 mm. was obtained.

Anal. Calcd. for $C_{17}H_{28}O_8$: C, 56.66; H, 7.77. Found: C, 56.29; H, 7.62.

The above ester (16.4 g.) and concentrated hydrochloric acid (60 ml.) were refluxed over an oil bath for 18 hr. The resulting clear solution was evaporated, dried, and subjected to esterification with 5% ethanolic sulfuric acid (75 ml.). After addition of water the oil was extracted with ether, washed successively with water, saturated sodium bicarbonate solution, and finally with water. After drying and removal of solvent the product triethyl pentane-1,2,5-tricarboxylate distilled at 162–163°/5 mm. (9.4 g., 72%).

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.33; H, 8.33. Found: C, 58.42; H, 8.32.

Cyclization of triethyl pentane-1,2,5-tricarboxylate (I). The triester (52 g.) was heated with sodium dust (5 g.) in benzene (170 ml.) in a nitrogen atmosphere for 3 hr. The contents became wine red colored, sodium being completely dissolved. The product was decomposed with ice cold hydrochloric acid (1:1, 60 ml.). The water layer was extracted once with benzene and the total benzene solution was washed thrice with water. The solvent was removed and the product (IIa) distilled at 130–135°/3 mm. (31.7 g., 72.5%), n_D^{29} 1.4637.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.5; H, 7.4. Found: C, 59.8; H, 7.2.

Methylation of the ester (IIa). To a well cooled suspension of sodium dust (3 g.) in benzene (175 ml.) was added the above cyclized ester (28.7 g.) dropwise in 10 min. and the mixture was refluxed. A deep red solution of the sodiosalt was formed. Methyl iodide (12 ml.) was added to the solution and slow heating was continued. Sodium iodide appeared within 5 min. Refluxing was continued until the solution became neutral. Water was added and the benzene layer was separated and washed thoroughly with water and the solvent was removed. The product (Va) distilled at 142–144°/3.5 mm. (24.6 g., 81%), n_D^{31} 1.4567.

Anal. Calcd. for $C_{13}H_{20}O_6$: C, 60.94; H, 7.81. Found: C, 61.28; H, 7.84.

Hydrolysis of the ester (Va). The above ester (3 g.) was boiled with 25% hydrochloric acid (75 ml.) for 21 hr. over an oil bath. The contents were filtered and the filtrate evaporated. The residue was subjected to evaporative distillation at 165–170°/1.5 mm. An oil was deposited which solidified to a hygroscopic solid m.p. 97°. Mixed melting point with an authentic sample of 2-methylcyclohexanone-3-carboxylic acid gave no depression. Semicarbazone m.p. 204° (lit.[4] 204°). The 2,4-dinitrophenylhydrazone, m.p. 209°, was crystallized twice from alcohol.

Anal. Calcd. for $C_{14}H_{16}O_6N_4$: N, 16.66. Found: N, 16.48.

Ring fission of the ester (Va). The ester (24.1 g.) was treated with an ice cold solution of sodium ethoxide (0.216 g. sodium and 7 ml. ethanol). The product was isolated in the usual way and distilled at 146°/0.6 mm. (27.7 g., 97.5%), n_D^{31} 1.4358.

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.60; H, 8.61. Found: C, 59.60; H, 8.24.

The above ester (5 g.) was hydrolyzed with concentrated hydrochloric acid (30 ml.) for 40 hr. The oily acid initially obtained on trituration with dioxane gave a solid which crystallized from ethyl acetate, m.p. 145°. Mixed m.p. with authentic 1-methylpentane-1,2,5-tricarboxylic acid (VIIa, R = H) showed no depression.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.42. Found: C, 49.61; H, 6.91.

Triethyl 1-methylpentane-1,4,5-tricarboxylate (VIIb, R = C_2H_5). Diethyl 5-methylcyclopentanone-2-acetate-2-carboxylate (23 g.) was treated with ice cold sodium ethoxide (0.21 g. sodium and 8.2 ml. ethanol) and the product was isolated in the usual manner. It distilled at 166–168°/2 mm. (21.2 g., 78.1%), n_D^{31} 1.4348.

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.60; H, 8.61. Found: C, 59.94; H, 8.20.

The above ester (5 g.) was hydrolyzed with concentrated hydrochloric acid (50 ml.) for 25 hr. 1-Methylpentane-1,4,5-tricarboxylic acid (VIIb, R = H) was crystallized from glacial acetic acid m.p. 97°.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.42. Found: C, 49.64; H, 6.65.

Ethyl 1-methyl-1,2,5-tricyanopentane-2-carboxylate (X). To an ice cold solution of sodium ethoxide prepared from sodium (2.73 g.) and ethanol (42 ml.) was added ethyl α,β-dicyanobutyrate (18.6 g.). Instantaneously a thick reddish solution was formed and the mixture was kept in ice cold water for 10 min. γ-Bromobutyronitrile (18.3 g.) was added and the mixture was refluxed for 22 hr. until it became neutral to litmus. Water was then added and the separated oil was taken up in benzene. After washing the benzene solution with water the solvent was removed and the residual oil was distilled at 224–228°/4 mm. (17.9 g., 68.9%), n_D^{31} 1.4593.

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.43. Found: C, 61.48; H, 6.50.

Triethyl 1-methylpentane-1,2,5-tricarboxylate (VIIa, R = C_2H_5). The trinitrile (X, 20 g.) was refluxed with concentrated hydrochloric acid (150 ml.) for 24 hr. The solution was evaporated over a water bath and extracted with ether. The ether solution was dried and the solvent was removed. The crude residual oil was dried carefully under vacuum and was refluxed with a mixture of ethanol (60 ml.) and concentrated sulfuric acid (8 ml.) for 34 hr. Water was added and the precipitated oil was extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, dried, and evaporated. The residual oil distilled at 162–164°/3.5 mm. (15.1 g., 58.2%), n_D^{31} 1.4358.

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.60; H, 8.61. Found: C, 59.59; H, 8.34.

The above ester (5 g.) was hydrolyzed to 1-methylpentane-1,2,5-tricarboxylic acid (VIIa, R = H) by boiling with 60 ml. concentrated hydrochloric acid for 30 hr. The solution on evaporation produced an oil which solidified on keeping for some days and was finally crystallized twice from ethyl acetate, m.p. 145°.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.42. Found: C, 49.61; H, 6.91.

2-Methyl-3-cyanocyclohexanone (IX). To an ethanolic solution of 2-methyl-2-cyclohexenone (16.7 g.) in a three necked flask fitted with a stirrer, a solution of sodium cyanide (6.4 g.) in water (20 ml.) was added with stirring. A reddish color developed which gradually intensified to wine red coloration. A slight rise in temperature was observed. After about 0.5 hr. a mixture of concentrated hydrochloric acid (6.9 ml.) and water (15 ml.) was added to this solution during 40 min., whereupon a light yellow oil separated. It was poured into a mixture of concd. hydrochloric acid (15 ml.) and water (200 ml.) and the oil was extracted with ether. The ether solution was dried and evaporated and the residual oil was distilled at 120°/3.5 mm. (5.2 g., 25%), n_D^{32} 1.4669.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.07; H, 8.03. Found: C, 69.55; H, 8.36.

2-Methylcyclohexanone-3-carboxylic acid (VIa). The above nitrile (IX, 2.5 g.) was boiled first with concd. hydrochloric acid and then with a 20% solution of potassium hydroxide at 150–160° for 20 hr. The resultant solution was acidified and then extracted with ether. The ethereal solution after drying and evaporation gave an oil which on sublimation at 167°/0.2 mm. produced a solid acid, m.p. 97° (lit.[4] m.p. 97°).

The dinitrophenylhydrazone, crystallized from ethanol, m.p. 210°.

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: N, 16.66. Found: N, 16.48.

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CALCUTTA 32, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Reaction of *N*-Bromosuccinimide with Dihydropyran

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Products identified from the reaction of *N*-bromosuccinimide with dihydropyran were 3-bromo-5,6-dihydro-4*H*-pyran, 2,3-dibromotetrahydropyran, and both geometrical isomers of 2-succinimidyl-3-bromotetrahydropyran. A polar mechanism is indicated in which a positive bromine from *N*-bromosuccinimide first adds at the 3-position of dihydropyran to form a reactive intermediate which can either lose a proton or add a negative group to give the observed products. A small acceleration of rate in the presence of oxygen or peroxide suggests that a free-radical reaction is also involved to some extent. No product of direct alpha methylenic substitution on dihydropyran was obtained. The polarizing effect of the oxygen alpha to the double bond is considered to increase the nucleophilic character and thus favor a polar mechanism.

N-Bromosuccinimide can undergo either a homolytic dissociation to free radicals or a heterolytic dissociation to give a positive halogen. The reaction most often observed with this reagent and simple olefins[1] is an alpha substitution of bromine by a free-radical mechanism. In addition to these allylic brominations, there have been a number of examples of addition to the double bond. In some cases[2] where reactions were accelerated by peroxides, the addition would appear to proceed by a free-radical mechanism. Other examples are reported where addition leading to the corresponding dibromide is promoted by the presence of inorganic salts[3,4] and alkyl ammonium salts.[4] Bailey and Bello[3] report that whereas *N*-bromosuccinimide brominates crotonitrile in the allylic position, allylic bromination is inhibited by an electron-withdrawing group attached directly to the alpha carbon.

The presence of an electron-releasing group adjacent to a double bond should increase the tendency toward reaction by a polar mechanism with an electrophyllic reagent such as a positive halogen. Dihydropyran was selected for study as an example of such a compound which also contains an alpha methylene group. The object of the investigation was thus to see whether *N*-bromosuccinimide would react with this compound to give allylic bromination by a free-radical mechanism or attack on the double bond by a polar mechanism.

Previous studies of the reaction of *N*-bromosuccinimide with dihydropyran (I) have been reported to yield tars[5] and an addition product, 2-succinimidyl-3-bromotetrahydropyran VI.[6]

Discussion. *N*-Bromosuccinimide reacted with I to give a mixture of products which appeared as a very viscous, clear residue when solvent was removed. Attempts to distil the products gave only small amounts of I and a mixture of 3-bromo-5,6-dihydro-4*H*-pyran (II) and 2,3-dibromotetrahy-

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(2) P. L. Southwick, L. A. Pursglove, and P. Numerof, *J. Am. Chem. Soc.*, **72**, 1600, 1604 (1950).

(3) W. J. Bailey and J. Bello, *J. Org. Chem.*, **20**, 525 (1955).

(4) E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 116 (1952).

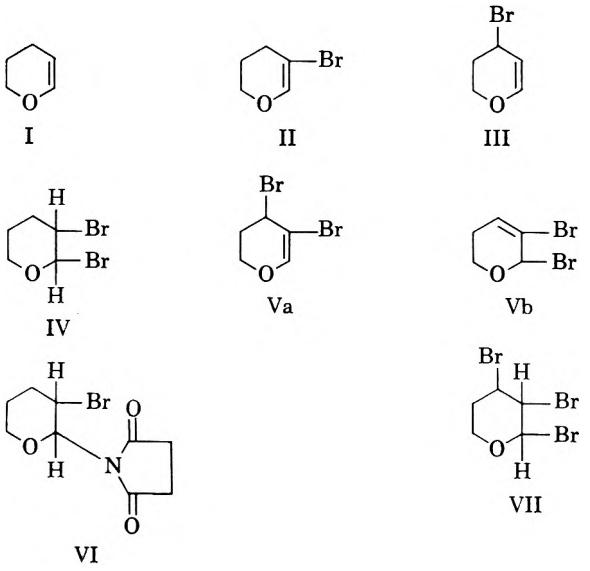
(5) C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

(6) R. Paul and S. Tchelitcheff, *Compt. rend.*, **236**, 1968 (1953).

dropyran (IV), before rapid decomposition of the residue set in. Chromatographic separation of the reaction mixture resulted in the isolation of the addition product (VI).

It appeared desirable at this point to devise an analytical scheme for quantitatively measuring some of the products obtained. It was of particular interest to determine whether any allylic bromination leading to the formation of the unknown 4-bromodihydropyran (III) was obtained, and if so in what yield.

It was found that if solutions of known concentration of I were titrated with bromine and the resulting dibromide treated with silver nitrate, silver bromide formed corresponding to 96–100% replacement of the bromine atom alpha to the oxygen.



Based on this observation a method of analysis was employed which involved treating reaction mixtures of *N*-bromosuccinimide and I as follows:

A. Titration with bromine, and then
B. Reaction with silver nitrate
C. Reaction of a second but identical run with silver nitrate, without prior titration with bromine

In order for this scheme to be applicable to any system, any of the products that react must do so quantitatively or at least nearly so. As was previously mentioned, I and IV were tested and found to meet this requirement. When II, prepared independently by dehydrohalogenation of IV, was tested, it was found neither to add bromine nor react with silver nitrate. The behavior of III (as predicted by analogy with I and IV) should include both addition of bromine and, as a vinylogous α-bromoether, reaction with silver nitrate. The analytical procedure thus gives no information about II and involves only compounds I, III, IV, and a dibromodihydropyran (V) which was included on the basis of the report by Paul and Tchelitcheff[6] that *N*-bromosuccinimide reacts with II to give V. The reaction presumably involves allylic attack on II to give Va, and by rearrangement of the intermediate free radical (or rearrangement of Va) to form Vb. Since II was isolated in this study, some conversion of II to V was considered probable. By analogy with the observed behavior of II and IV, it was expected that V would not add bromine, but would react with silver nitrate and would accordingly be indistinguishable in the analysis from IV. For this reason the results given in Table I and Table II have compounds IV and V grouped together as dibromides.

TABLE I

Effect of Benzoyl Peroxide			
Benzoyl peroxide (wt. %)[a]	0	1.0	3.0
Reaction time (min.)[b]	25.8	21.0	17.7
Dihydropyran (I)[c]			
Millimoles[d]	0.97	1.21	1.10
% yield[a]	9.7	12.1	11.0
4-Bromodihydropyran (III)			
Millimoles	0.03	−0.03	0.03
% yield	0.3	−0.3	0.3
Dibromides (IV + V)			
Millimoles	0.83	1.11	1.28
% yield	17	22.2	25.6
Effect of Oxygen			
Atmosphere	N_2	Air	O_2
Reaction time (min.)[e]	38.4	33.0	31.5
Dihydropyran (I)			
Millimoles[d]	0.97	1.20	1.23
% yield[a]	9.7	12.0	12.3
4-Bromodihydropyran (III)			
Millimoles	0.13	0.04	0.00
% yield	1.3	0.4	0.0
Dibromides (IV + V)			
Millimoles	0.57	0.76	0.87
% yield	11	15	17

[a] Based on *N*-bromosuccinimide. [b] Average of 4 runs (±1.5 min.); time required for disappearance of the last particles of NBS. [c] Unreacted I, corrected for excess initially present. [d] Ten millimoles of *N*-bromosuccinimide was used in all reactions. [e] Average of 2 runs (±1.7 min.); time required for disappearance of last particles of NBS.

The method of calculation follows:

(*a*) The equivalents of bromine (*A*) which added to the reaction mixture correspond to the equivalents of I and III, *i.e.*,

$$A = \text{I} + \text{III} \qquad (1)$$

(*b*) The equivalents of silver bromide (*B*) formed by subsequent reaction of the mixture with silver nitrate correspond to the sum of the equivalents of I, III, IV, and V. (I and III are included since addition of bromine converts them to the α-bromoethers IV and VII.)

$$B = \text{I} + \text{III} + \text{IV} + \text{V} \qquad (2)$$

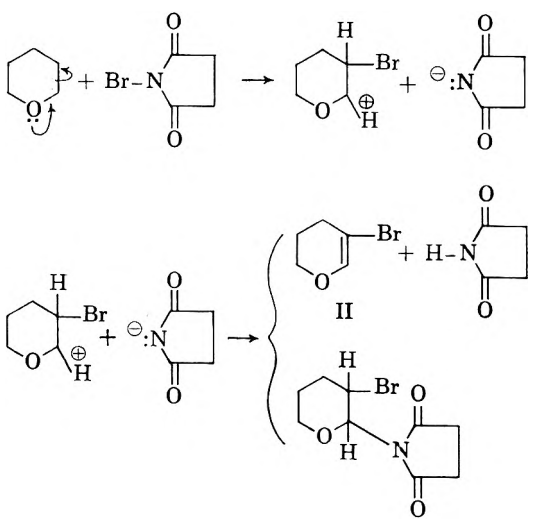
(*c*) The equivalents of silver bromide (*C*) formed by reaction of a second reaction mixture with silver nitrate correspond to the sum of the equivalents of III, IV, and V.

$$C = \text{III} + \text{IV} + \text{V} \qquad (3)$$

By grouping IV and V together as dibromides, simultaneous solutions of equations (1), (2), and (3) gave the results shown in Table I for a series of reactions intended to investigate the possible effect of peroxide and of oxygen on the reaction. In all these reactions a 25% excess of I was employed; however, this was subtracted from the calculated amount of unreacted I. The results in Table I show that in the absence of peroxide 0.83 mM. of dibromide was obtained and that 0.97 mM. of I was left in excess. Since the formation of a dibromide requires two moles of *N*-bromosuccinimide to react with one mole of I, then for every mole of dibromide formed there should be one mole of unreacted dihydropyran. The close agreement between the yield of dibromide obtained by analysis and amount of unreacted I may be considered as supporting evidence for the validity of the method of analysis. In all cases the calculated yield of III was essentially zero, but there was a small acceleration of the reaction rate in the presence of peroxide. The increased rate of formation of dibromide in the presence of peroxide could have resulted in part from radical attack on II to form Vb.

Similar results were observed with oxygen as shown in Table I. In the absence of oxygen an 11% yield of dibromide was obtained which was increased to 17% in an oxygen atmosphere. There appears to be little tendency toward allylic bromination of I to form III even in the presence of oxygen or peroxides.

The major products obtained from the reaction of *N*-bromosuccinimide with I, as demonstrated by actual isolation and identification, are the substitution product II (8% based on *N*-bromosuccinimide) and the addition product VI (7%). The dibromide IV was isolated in lesser amount (2.5%) and isolation of succinimide formed in the reaction accounted for 12.5% of the *N*-bromosuccinimide used. The following reaction scheme accounts for the formation of the major products by a polar mechanism:

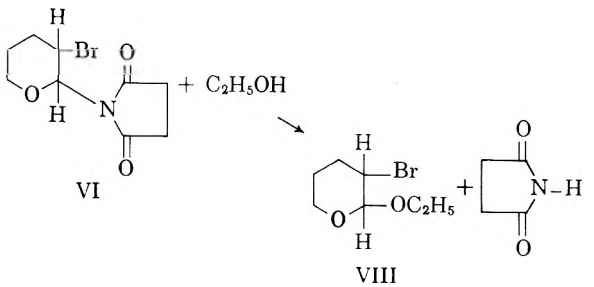


VI

The formation of dibromide IV by a polar mechanism is more difficult to explain although a mechanism has been proposed by Braude and Waight.[4] The by-product positive and negative succinimide groups are considered to unite, followed by homolytic cleavage and abstraction of hydrogen from solvent or reactants to form succinimide.

The formation of II at least in part by the dehydrohalogenation of IV in the process of isolation must be recognized as a possibility, even though the distillation was carried out at reduced pressure and undecomposed IV was obtained in the same distillate. Even if the formation of II could be accounted for in this way, the formation of VI as a coproduct would still provide strong support for a mechanism in which initial attack involves addition of a positive halogen at the double bond.

Paul and Tchelitcheff[6] presented evidence which indicated that the reaction of *N*-bromosuccinimide with I resulted in addition to give VI. Their evidence was based on the fact that refluxing the reaction mixture with absolute ethanol led to 2-ethoxy-3-bromotetrahydropyran and succinimide, and accordingly they formulated the reaction as:



VI VIII

In the present investigation the product of the initial reaction of I with *N*-bromosuccinimide was filtered to remove succinimide formed in the reaction, stripped of solvent, and then refluxed with ethanol to give a 17% yield of VIII and 13% of succinimide. When pure VI was similarly refluxed with ethanol, it was recovered unchanged with no evidence of any formation of succinimide. The observed difference in behavior between the crude mixture and pure VI has not been explained. It may be that some polar component of the reaction mixture catalyzes the reaction with VI.

The isolation of VI was accomplished by chromatographic separation of the reaction mixture. The first crystals were isolated when one of the fractions, which deposited a gummy residue on removal of eluent, formed crude crystals on standing for several days. Recrystallization from water gave VIa melting at 84.5–86.0°. When the procedure was repeated on a larger sample, a higher melting (m.p.130–130.5°) product (VIb) was obtained (in addition to VIa) which appeared to be the geometrical isomer of the lower melting product. No determination of absolute configuration was attempted. The identification of these products as

isomers was based on the similarity of their infrared spectra, elemental analysis, and conversion to the same 2,4-dinitrophenylosazone.

Woods and Temin[7] found that 2-ethoxy-3-bromo-Δ^3-dihydropyran gave a 2,4 dinitrophenylhydrazone derivative of 2-bromo-5-hydroxy-2-pentenal. The formation of this derivative involves ring cleavage of the dihydropyran ring with elimination of the ethoxyl group. It was found in the present work that under similar conditions 2-ethoxy-3-bromotetrahydropyran (VIII) lost both the ethoxyl group and bromine to form the 2,4-dinitrophenylosazone of 2,5-dihydroxypentanal. Hurd and Kelso[8] obtained the same osazone from tetrahydropyran-2,3-diol.

The conversion of both VIa and VIb to this same osazone established the positions of the succinimidyl group and bromine in the 2- and 3-positions, since the formation of this osazone from VI resulted in displacement of both the succinimidyl group and bromine. It was further found that VI did not react with silver nitrate, whereas 2,3-dibromotetrahydropyran (IV) as an α-bromoether forms silver bromide with silver nitrate. The bromine in VI must, therefore, be in the 3-position and the succinimidyl group must be in the 2-position, rather than the reverse.

It was of interest, in connection with this work, to learn that Hurd, Moffat, and Rosnati[5] on treating *N*-bromophthalimide with I isolated an 83.5% yield of 1:1 addition product. They proposed the product to be either 2-bromo-3-phthalimidotetrahydropyran formed by free-radical attack, or 2-phthalimido-3-bromotetrahydropyran, resulting from an ionic reaction. The fact that they obtained no replacement of bromine on shaking the product with silver acetate in acetic acid for one week seems inconsistent with a structure including an α-bromoether, even though the product dissolved slowly in hot dilute alkali with liberation of halide. By analogy to the results of the present study the product they isolated probably was 3-bromo-2-phthalimidotetrahydropyran formed by an ionic mechanism.

Reaction of *N*-bromosuccinimide with I in absolute ethanol proceeded rapidly and smoothly to give a 58% yield of 2-ethoxy-3-bromotetrahydropyran (VIII). Similarly, when the reaction was conducted in glacial acetic acid, a 76% yield of 2-acetoxy-3-bromotetrahydropyran (IX) was obtained. Other examples of this general type have been reported in the literature, *e.g.*, *N*-bromosuccinimide and 1-ethoxybutadiene have been reported[9] as leading to 64% α-bromocrotonaldehyde diethyl acetal. These reactions of *N*-bromosuccinimide apparently proceed by an ionic mechanism involving heterolytic cleavage of *N*-bromosuccinimide to give positive bromine.[9]

It is evident that *N*-bromosuccinimide can react by either a polar or a free-radical mechanism depending upon reaction conditions and the nature of the other reactant. Dihydropyran has an alpha methylene available for allylic bromination, but the polarizing effect of the oxygen alpha to the double bond apparently increases the nucleophilic character so that a polar reaction with the positive bromine available from *N*-bromosuccinimide predominates. The reaction appears to proceed by initial attachment of the positive halogen at the 3-position of dihydropyran with subsequent loss of hydrogen or combination with a negative group.

EXPERIMENTAL

2,3-Dibromotetrahydropyran (IV). To a solution of I (16.8 g., 0.2 mole) in 50 ml. of carbon tetrachloride, immersed in an ice bath, was added dropwise and with stirring 10 ml. of bromine in 50 ml. of carbon tetrachloride. Bromine addition was stopped when the bromine color persisted and then one drop of I was added to react with the excess bromine. A sample of this solution was used to record the infrared spectrum of IV in carbon tetrachloride solution. The remaining solution was used to prepare II.

3-Bromo-5,6-dihydro-4H-pyran (II). To the above solution was added 150 ml. of pyridine (a highly exothermic reaction resulted) and most of the carbon tetrachloride was then removed by distillation. When the temperature of the distillate reached 90°, the distillation was stopped and the residue refluxed overnight (16 hr.). After cooling, the solution was decanted into a separatory funnel with 200 ml. of water. The organic layer was separated and washed with several portions of 0.5*M* hydrochloric acid until all the pyridine was removed, and then with a solution of sodium bicarbonate and finally with water until neutral to litmus. The organic layer was separated, dried over anhydrous magnesium sulfate and distilled through a short packed column to give 2.1 g. (16%) of II b_{60} 83.5–84°, n_D^{25} 1.5068, d_4 1.533. The literature[10] gives b_{22} 63°, n_D^{16} 1.51194, d_{15}^{6} 1.54.

Anal. Calcd. for C_5H_7OBr: C, 36.84; H, 4.33; Br, 49.0. Found: C, 36.73; H, 4.92; Br, 48.3.

To test the reactivity of II with bromine and silver nitrate, a sample (153.5 mg.) of II was accurately weighed out and washed into an iodine flask with 50 ml. of carbon tetrachloride. One drop (0.02 ml.) of 0.493*M* bromine solution added to the solution of I was not decolorized. One drop of I was added to decolorize the solution which was then shaken with silver nitrate solution to give 6.9 mg. of silver bromide. Correcting for the bromine that was added, this corresponded to 0.03 meq. of silver bromide or 3% replacement of the bromine of II.

Standardization of bromine solution. An 0.5*M* solution of bromine was prepared by diluting 13 ml. of bromine to one liter with carbon tetrachloride. This solution was standardized against an exactly 0.2500*M* solution of I in carbon tetrachloride.

For the titration, an aliquot sample (5–20 ml.) of the solution of I was pipetted into a 125-ml. iodine flask and diluted to a total volume of 50–60 ml. with carbon tetrachloride. The end point was taken as the point at which the bromine color persisted for 1 min.

(7) G. Woods and S. Temin, *J. Am. Chem. Soc.*, **72**, 139 (1950).

(8) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **70**, 1484 (1948).

(9) W. Flaig, Report No. 52025, Office of the Publication Board, U. S. Dept. of Commerce; *Chem. Abstr.*, **41**, 6189 (1947).

(10) R. Paul, *Compt. rend.*, **198**, 275 (1934).

Reactions with silver nitrate. To the resultant solution from the above reaction was added 25 ml. of an aqueous alcoholic solution of 0.25*M* silver nitrate and the resultant mixture immediately placed on a wrist action shaker for 20 min. The precipitated silver bromide was filtered through a medium grade fritted glass funnel and washed with alternate portions of water and ethanol and dried in an oven at 90–100° to constant weight.

The silver bromide recovered was found to be equivalent in millimoles to 96–100% of the dihydropyran originally reacted with bromine.

Reaction of N-bromosuccinimide with I in carbon tetrachloride. Fifty ml. of an 0.2500*M* solution of I in carbon tetrachloride and 1.780 g. (0.01 mole) of *N*-bromosuccinimide were combined in a 100 ml. round-bottom flask equipped with a reflux condenser and drying tube and refluxed in a bath of boiling water. At the completion of the reaction, the flask was removed from the bath and allowed to cool to room temperature. The reaction time was measured as the interval between the falling of the first drop from the condenser and the disappearance of the last particles of *N*-bromosuccinimide.

This reaction was also conducted under a nitrogen atmosphere by passing a slow stream of nitrogen into the reaction vessel. The nitrogen was dried by bubbling through concentrated sulfuric acid followed by a drying tube filled with anhydrous calcium sulfate. The reaction was conducted under an oxygen atmosphere in a similar manner.

At the completion of the reaction a completely homogeneous, colorless to pale yellow solution was obtained. Succinimide gradually separated out as the solution was allowed to cool to room temperature.

Succinimide was identified by melting point (123–124°) mixture melting point and infrared spectrum.

Composition of the reaction mixture. Two reactions of *N*-bromosuccinimide and I were conducted simultaneously. After cooling to room temperature one of the mixtures was titrated with bromine (*A*), and then with silver nitrate (*B*). The second cooled mixture was treated directly with silver nitrate (*C*). The amount of bromine consumed (*A*) was taken as equivalent to the sum of unreacted I and of any III formed in the reaction. The silver bromide subsequently formed (*B*) was taken as equivalent to the amount of unreacted I, III, IV, and V. The amount of silver bromide (*C*) was taken as equivalent to the sum of III, IV, and V.

Isolation of reaction products. *N*-Bromosuccinimide (17.8 g., 0.100 mole) and 500 ml. of a 0.2500*M* solution of I in carbon tetrachloride were allowed to react and the cooled solution was stripped of I and carbon tetrachloride under reduced pressure. The distillate, collected in a flask immersed in an ice bath and followed by a Dry Ice–acetone trap, was titrated with bromine and found to contain 0.033 mole of I (8% unreacted I based on *N*-bromosuccinimide).

The residue taken up in carbon tetrachloride and filtered gave 1.23 g. (12.5%) succinimide. The filtrate was distilled free of solvent and then distilled at *ca.* 5-mm. pressure while gradually increasing the pot temperature (the pot was immersed in a water bath) until the residue started to darken and resinify. The distillate amounted to 1.54 g. of a clear, colorless liquid with n_D^{25} 1.5138. By infrared analysis involving comparison with known samples, the distillate was shown to be a mixture of II and IV. The amount of IV was found to be 0.29 g. (2.4% yield based on *N*-bromosuccinimide) by reaction of the mixture with silver nitrate. The amount of II was calculated, by difference, as 1.25 g. (7.6% yield). The mixture did not add bromine.

Isolation of 2-succinimidyl-3-bromotetrahydropyran (VI). *N*-Bromosuccinimide (1.78 g.) and I (1.05 g.) in 50 ml. of carbon tetrachloride were allowed to react in the usual manner. The cooled mixture was washed with water to remove succinimide, dried over magnesium sulfate, and passed through a column (50 × 2 cm.) of aluminum oxide. The column was eluted with 100 ml. of carbon tetrachloride and 100 ml. of chloroform and then three 200-ml. portions of chloroform. These last three portions extracted with hot water cooled and seeded gave 115 mg. (4.4%) of VIa m.p. 83–84°. The first seed crystals were obtained by chromatographic separation of the mixture and formed when the percolate stripped of solvent was allowed to stand for several days. Seeding was frequently, but not always, necessary to obtain crystallization.

In a subsequent experiment 9.8 g. of *N*-bromosuccinimide and 6.3 g. of I in 125 ml. of carbon tetrachloride were reacted. Succinimide (0.71 g., 13%) was filtered off and the filtrate chromatographed on an aluminum oxide column (10 × 4.5 cm.). The column was eluted with 600 ml. of carbon tetrachloride, 900 ml. of 50/50 chloroform–carbon tetrachloride and finally 150 ml. of chloroform, and collected in 10 fractions as follows: fraction 1, 175 ml.; fractions 2–8, 150 ml. each; fraction 9, 300 ml.; fraction 10, drained the column. Each fraction was stripped of solvent and extracted with hot water to give VI as follows:

Fractions 1 and 2—no crystals
Fraction 3—94 mg., m.p. 84.5–87.5°
Fraction 4—154 mg., m.p. 84.5–87°
Fraction 5—138 mg., m.p. 84–86.5°
Fraction 6—94 mg., m.p. 83–85.5°
Fraction 7—129 mg., m.p. 127.5–130°
Fractions 8 to 10—no crystals

Spectrum analysis and mixture melting points showed fractions 3–6 to be the same. The spectrum of fraction 7 indicated it to be an isomer of the preceding product. This was later confirmed by analysis and conversion to the same 2,4-dinitrophenylosazone.

The crude products from fractions 3–6 were combined and taken up in hot water, and 95% ethanol was added dropwise to the cooled solution until a clear solution was obtained. The solution on seeding deposited VIa, m.p. 84–85°. The crude product from fraction 7, recrystallized from water gave VIb, m.p. 130–130.5°.

Anal. Calcd. for $C_9H_{12}BrNO_3$: C, 41.24; H, 4.62; Br, 30.5; N, 5.35. Found (VIa): C, 41.33; H, 4.41; Br, 30.4; N, 5.30. Found (VIb): C, 41.23; H, 4.37; Br, 30.6; N, 5.35.

The residues from fractions 3–6 were again extracted with hot water to give 415 mg. of additional crude VIa, m.p. 82–83.5°. The total yield of VI amounted to 1.02 g. (7.1%) of which 0.89 g. (6.2%) was VIa and 0.13 g. (0.9%) was VIb.

Synthesis of 2-ethoxy-3-bromotetrahydropyran (VIII). To a mixture of *N*-bromosuccinimide (17.8 g., 0.1 mole) and 58 ml. of absolute ethanol, compound I (10.5 g., 0.125 mole) was added dropwise with stirring. After the *N*-bromosuccinimide was completely consumed, the succinimide was filtered off and most of the excess ethanol removed from the filtrate, under the reduced pressure of a water pump, causing the separation of more succinimide. The residue filtered and distilled gave 13.3 g. (58%) of VIII. On redistillation, the product was collected b_{18} 61–62.5°, n_D^{25} 1.4750, d_4^{25} 1.365. The literature[11] reports b_{18} 94–96°, n_D^{25} 1.4752.

Anal. Calcd. for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27; Br, 38.2. Found: C, 40.54; H, 6.42; Br, 38.7.

Synthesis of 2-acetoxy-3-bromotetrahydropyran (IX). To a mixture of *N*-bromosuccinimide (89.0 g., 0.5 mole) and 290 ml. of acetic acid in an ice bath, compound I (52.5 g., 0.625 mole) was added dropwise and with stirring. When the addition was completed a clear, colorless solution was obtained which was washed with a solution of sodium bicarbonate, extracted with ether, and washed with water until neutral to litmus. The extract, dried over magnesium sulfate and distilled free of ether, gave 84.7 g. (76% theor.) of crude IX. The crude product was twice distilled and the middle fraction, $b_{0.75}$ 82°, collected. Analysis of the product col-

(11) G. F. Woods and H. Sanders, *J. Am. Chem. Soc.*, 68, 2483 (1946).

lected indicated it was still somewhat impure. The literature[12] reports b_4 60–75°.

2,4-Dinitrophenylosazone. 2,4-Dinitrophenylhydrazine (0.1 g.), 5 ml. of 95% ethanol, 1 ml. of water and 0.5 ml. of concentrated hydrochloric acid were heated on a steam cone until complete solution was obtained and then *ca.* 0.1 g. of VIII was added. The osazone derivative started precipitating in about 5–10 min., but heating was continued until no more precipitate formed. The precipitate filtered, and recrystallized from ethanol–ethyl acetate and ethanol gave bright orange crystals, m.p. 240–241° (dec.). The literature reports m.p. 235–236° (dec.)[13] and m.p. 242°.[8]

Anal. Calcd.: C, 42.86; H, 3.39; N, 23.52. Found: C, 42.94; H, 3.25; N, 22.76.

The same procedure repeated with IV, VI, and IX gave the same derivative as shown by melting point and mixture melting point.

Reaction of ethanol with products of reaction of N-bromosuccinimide with I. *N*-Bromosuccinimide was treated with I (1.05 g.) in 50 ml. of carbon tetrachloride as previously described. The reaction mixture was cooled and 134 mg. of succinimide (13.5 %) filtered off. The filtrate was stripped of solvent and the residue refluxed overnight with 25 ml. of absolute ethanol. Ethanol was removed by distillation and the residue extracted with carbon tetrachloride and water. The carbon tetrachloride layer dried over magnesium sulfate and distilled gave 0.36 g. (17%) of VIII, $b_{1.2}$ 51–54°, n_D^{25} 1.4710. The product was confirmed as VIII by comparison of its infrared spectrum with the product obtained from the reaction of *N*-bromosuccinimide with I in ethanol.

The water extract, distilled free of water and crystallized from 95% ethanol gave 121 mg. (13%) succinimide.

Reaction of ethanol with VI. Five ml. of absolute ethanol and 6.3 mg. of VIb were combined and refluxed overnight. The mixture was distilled free of most of solvent and then poured into an evaporating dish. The air dried residue taken up in 95% ethanol and chilled gave VIb, m.p. 127–129°. Identification was based on the melting point and comparison of the infrared spectrum with that of the starting material.

The same procedure repeated with VIa gave similar recovery of only starting material when the residue was crystallized from aqueous ethanol.

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(12) J. G. M. Brenner and D. G. Jones, Brit. Patent 605,107 (1948).

(13) S. Swadesh and A. P. Dunlop, *J. Org. Chem.*, **14**, 692 (1949).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Selective Sulfonation of Amino Groups in Amino Alcohols

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The use of the pyridine–sulfur trioxide complex as a sulfonating reagent for amino alcohols has been investigated in an aqueous alkaline medium. Under these conditions, the reagent selectively sulfonates the amino group. The reaction is applicable to insoluble or soluble amino alcohols, and has also been applied to the hydroxyamino acid, serine.

The discovery of sulfonated amino groups in heparin,[1] a naturally occurring sulfated polysaccharide having alternating glucosamine and glucuronic acid units, has stimulated considerable interest in the preparation of synthetic compounds having similar constituents. For the preparation of such sulfated polysaccharides, one of the starting materials has been chitosan, the polyglucosamine which is readily obtained by alkaline hydrolysis of chitin, a naturally occurring polyacetylglucosamine present in crab shells.

In our earlier work with chitosan[2] we reported the sulfation of this polyglucosamine as a heterogeneous phase with liquid sulfur dioxide–sulfur trioxide. In this system the reaction of the amino groups was not complete, and the yields of product were variable because of the heterogeneous reaction medium. Doczi[3] and coworkers reported the preparation of sulfated chitosans having a high degree of sulfonation on the amino group, although the details of their procedure were not disclosed. Wolfrom[4] also obtained an *N*-sulfated-*O*-sulfated chitosan by the use of chlorosulfonic acid and pyridine in a heterogeneous system.

In attempting to obtain improved yields of sulfated chitosans having a high degree of *N*-sulfonation, we have studied a number of sulfonation systems. From these experiments, a method has been obtained for the selective sulfonation of amino groups in the presence of hydroxyl groups which now appears to be a reaction of general application. The procedure makes use of a well-known reagent, the pyridine–sulfur trioxide complex,[5] which has been previously reacted with both amines and

(1) (a) J. E. Jorpes, H. Bostrom, and V. Mutt, *J. Biol. Chem.*, **183**, 607 (1950). (b) K. H. Meyer and D. E. Schwartz, *Helv. Chim. Acta*, **33**, 1651 (1950).

(2) L. L. Coleman, L. P. McCarty, D. T. Warner, R. F. Willy, and J. H. Flokstra, presented before the Division of Medicinal Chemistry of the American Chemical Society, Los Angeles, Calif., March 1953; see Abstracts of Papers, 123rd Meeting, p. 19 L.

(3) J. Doczi, A. Fischman, and J. A. King, *J. Am. Chem. Soc.*, **75**, 1512 (1953).

(4) M. E. Wolfrom, T. M. Shen, and C. G. Summers, *J. Am. Chem. Soc.*, **75**, 1519 (1953).

(5) P. Baumgarten, *Ber.*, **59**, 1976 (1926).

alcohols. However, when it is utilized in an aqueous medium under mild alkaline conditions (*p*H 9–10), pyridine–sulfur trioxide has been found to sulfonate the amino group exclusively in all of the amino alcohols we have tested.

The reaction of pyridine–sulfur trioxide in aqueous alkaline medium is useful with insoluble or soluble amino alcohols. In fact our first application of the process was to the *N*-sulfonation of the insoluble polyglucosamine, chitosan. An aqueous suspension of chitosan at *p*H 9–10 was stirred at room temperature while small portions of pyridine–sulfur trioxide were added together with dilute sodium hydroxide to maintain the alkalinity.[6] Under these mild conditions the insoluble chitosan was readily converted to the sodium salt of the soluble *N*-sulfochitosan; and as the reaction proceeded, the product dissolved in the aqueous medium so that a fresh surface for reaction was continually exposed on the remaining insoluble particles. When approximately 50% of the amino groups had reacted the solid phase had disappeared; and by continuing the addition of the pyridine–sulfur trioxide at *p*H 9–10, a nearly quantitative conversion of chitosan to *N*-sulfochitosan was obtained.

The resulting product contained one sulfamate group for each hexosamine unit, uniformly distributed throughout the polysaccharide chain; and it could be precipitated as a finely divided amorphous powder from a 1% salt solution with 2 volumes of ethanol. The *N*-sulfochitosan has no detectable *in vivo* or *in vitro* anticoagulant activity. However, the amorphous product is readily obtained in a highly reactive particulate form, which can be further sulfated with sulfur dioxide–sulfur trioxide to yield *N*-sulfated, *O*-sulfated chitosans. The latter have considerable anticoagulant activity. An example illustrating the use of the sulfur dioxide–sulfur trioxide procedure with *N*-sulfochitosan is given in the experimental section.

The selective *N*-sulfonation of diethanolamine, 3-aminopropanol, and DL-serine also has been successfully carried out with the aqueous pyridine–sulfur trioxide system. It is interesting to note that amino alcohols may be selectively *O*-sulfated with chlorosulfonic acid in carbon tetrachloride by the procedure of Reeves and Guthrie.[7] Two of the amino alcohols used by these workers were also included in our experiments for comparison purposes. Therefore, it is possible to convert amino alcohols to either *N*-sulfo or *O*-sulfo derivatives by the proper selection of reagents.

(6) Excess alkali should be avoided to prevent extensive conversion of pyridine–sulfur trioxide to the red complex described by P. Baumgarten, *Ber.*, 59, 1166 (1926). Sodium carbonate may also be used as the alkaline reagent.

(7) W. A. Reeves and J. D. Guthrie, *J. Am. Chem. Soc.*, 75, 4101 (1953).

EXPERIMENTAL

Preparation of chitosan. Chitin[8] (95 g.) was suspended in about 1.5 l. of 50% sodium hydroxide, and the suspension was refluxed for 24 hr. with stirring. After cooling, the hydrolyzate was poured into 8 l. of water, and the insoluble chitosan was allowed to settle overnight. The supernatant liquid was discarded, and the residual solid was washed four times by decantation with water (5-l. portions) and four times with ethanol (500-ml. portions). The chitosan was then washed once with benzene and dried in a vacuum oven at 50°. The product weighed 62.8 g. (84%).

Anal. Calcd. for $(C_6H_{11}O_4N)_x$: C, 44.7; H, 6.88; N, 8.69; N as $—NH_2$, 8.69; acetyl, 0.0. Found: C, 47.1; H, 7.05; N, 7.97; N, as $—NH_2$, 8.01; acetyl, 1.31 (equivalent to about 6% of the amino groups present).

N-Sulfochitosan. A suspension of 54 g. of chitosan in 1000 ml. of water was dissolved by the addition of 30 ml. of concentrated hydrochloric acid. The chitosan hydrochloride was then converted to a flocculent precipitate of free chitosan by the gradual addition of 48 ml. of 30% sodium hydroxide with stirring. The suspension was stirred thoroughly at room temperature, and pyridine–sulfur trioxide was added to the aqueous medium in small portions. As the pyridine–sulfur trioxide reacted, the *p*H of the reaction medium was maintained in the range 9–10 by the continuous slow addition of a 30% sodium hydroxide solution. In this way a total of about 280 g. of pyridine–sulfur trioxide and about 465 ml. of 30% aqueous sodium hydroxide were added over a period of about 20 hr. During the course of the additions, the chitosan reacted completely and a clear, light brown solution resulted. This solution was concentrated *in vacuo* to about 1.5 l., and the concentrate was dialyzed in cellulose casings against deionized water to remove the sodium sulfate, pyridine, and other lower molecular weight materials. The brown solution in the dialysis bag was concentrated *in vacuo* to 1260 ml. and adjusted to a *p*H of 9–10. Sodium chloride (12.6 g.) was dissolved in the clear solution, and the product was precipitated as a light tan solid by the addition of 2.5 l. of absolute ethanol. The mixture was refrigerated overnight; and the solid was then removed by filtration, and washed with two portions of absolute ethanol and three portions of acetone on the filter. After drying *in vacuo* at 50°, the product weighed 81.1 g. (92% yield).

Anal. Calcd. for $[(C_6H_{10}O_4N)SO_3Na]_x$: C, 27.37; H, 3.82; N, 5.32; N as $—NH_2$, 0.0; S, 12.18. Found: C, 27.78; H, 4.05; N, 5.66, N as $—NH_2$, 0.18, S, 12.35.

Sodium N-bis(2-hydroxyethyl)sulfamate. Diethanolamine (10.5 g.) was dissolved in 125 ml. of water (*p*H 10.8). This solution was stirred at room temperature and pyridine–sulfur trioxide was added in small portions together with dilute sodium hydroxide to maintain the *p*H in the range of 9–10. A total of 17.7 g. of pyridine–sulfur trioxide and 52 ml. of 10% sodium hydroxide were added over a period of 1.5 hr.

The reaction mixture was then concentrated *in vacuo* to 100 ml. to remove excess pyridine. Sodium chloride (1 g.) was dissolved in the clear solution, and 500 ml. of absolute ethanol was added. After refrigerating the mixture overnight, 3.3 g. of solid was removed. This solid contained considerable inorganic material. The filtrate was mixed with 400 ml. of acetone, and crystals began to separate. After refrigerating the solution overnight 9.05 g. of solid was removed by filtration. The silvery leaflets melted at 218–220° on a Fisher block. The yield of pure product was 44%.

Anal. Calcd. for $C_4H_{10}O_5NSNa$: C, 23.19; H, 4.86, N, 6.76; Na, 11.10. Found: C, 23.23; H, 5.04; N, 7.10; Na, 11.10.

DL-N-Sulfoserine. DL-Serine (10.2 g.) was suspended in 100 ml. of water and dissolved by the addition of 36 ml. of

(8) The chitin was obtained from Bioproducts, Ltd., Warrenton, Ore., and was ground in a Wiley mill using a 100-mesh sieve before the deacetylation.

10% sodium hydroxide solution to yield a clear solution with *p*H 10.05. This clear solution was then reacted with 18.1 g. of pyridine–sulfur trioxide which was added in portions over about 3.75 hr. During this addition the *p*H was regulated in the range of about 9 to 10 by the continuous addition of 10% sodium hydroxide solution. At the end of this reaction time, the light yellow solution was concentrated *in vacuo* to 225 ml., and 525 ml. of absolute ethanol was added to yield a slightly milky supernatant liquid and an oily layer. The supernatant liquid was decanted and discarded, and the oily layer was thoroughly mixed with acetone and refrigerated overnight to yield 23.3 g. of solid product. Ten grams of this solid product was heated to boiling with 100 ml. of absolute ethanol and the milky supernatant liquid was decanted and discarded. The residual solid was then extracted twice with 150-ml. portions of aqueous ethanol (60 parts ethanol and 40 parts water by volume). These two extracts were combined, and treated with acetone to incipient turbidity at room temperature. After about 1 hr., a small quantity of solid material was removed by filtration, and the clear filtrate was mixed with an equal volume of acetone. Fluffy needle crystals separated from the solution, and after being refrigerated overnight, 5.5 g. (57% yield) of product was removed by filtration. This material was recrystallized from an alcohol-water mixture by the addition of acetone to incipient turbidity at 30°. The product was obtained as white needle crystals by refrigeration, 2.63 g., m.p. 205.8–206.8° (with dec.).

Anal. Calcd. for the disodium salt of DL-*N*-Sulfoserine, $C_3H_5O_6NSNa_2$: C, 15.73; H, 2.20; N, 6.11; N as $—NH_2$, 0.0; S, 13.99; Na, 20.08. Found: C, 15.51; H, 2.89; N, 6.27; N as $—NH_2$, 0.08; S, 13.82; Na, 19.45.

Sodium N-(3-hydroxypropyl)sulfamate. 3-Aminopropanol (7.5 g.) was dissolved in 130 ml. of water to yield a solution of *p*H 11.8. This solution was reacted with 12.6 g. of pyridine–sulfur trioxide added in portions over a period of 2.5 hr., with sufficient 10% NaOH added gradually to maintain a *p*H of about 11.3. At the end of the reaction time, the clear straw-colored solution was concentrated *in vacuo* to 80 ml., and the inorganic salts were precipitated by the addition of 250 ml. of absolute ethanol. After refrigeration, the finely divided inorganic material was removed by filtration. The filtrate yielded no further precipitate with another 50 ml. of alcohol. The reaction product, 4.46 g. (25%), was then precipitated by the addition of 1000 ml. of acetone. The solid was recrystallized once from hot 95% ethanol by the addition of acetone and a second time from absolute ethanol.

Anal. Calcd. for $C_3H_8O_4NSNa$: C, 20.34; H, 4.55; N, 7.91; N as $—NH_2$, 0.0; S, 18.09; Na, 12.98. Found: C, 21.2; H, 4.9; H, 7.89; N as $—NH_2$, 0.06; S, 17.88; Na, 13.5.

O-Sulfation of N-sulfochitosan. The sodium salt of *N*-sulfochitosan was prepared for the reaction with sulfur dioxide–sulfur trioxide by sifting it through a 100-mesh screen and allowing the solid to air-dry several days (10–12% adsorbed moisture). The air-dried material (32.5 g., 0.12 mole, dry basis) was placed in a flask equipped with a stirrer, dropping funnel, and dry ice condenser, and protected from moisture with a slow stream of dry nitrogen passing through a sulfuric acid exit bottle. The flask was cooled in an acetone–Dry Ice bath and dry sulfur dioxide was condensed in the flask to a total volume of about 250 ml. Liquid sulfur trioxide (40 g., 0.5 mole) was distilled into the dropping funnel under anhydrous conditions. The reaction vessel was well insulated with Vermiculite and the suspension of sodium *N*-sulfochitosan in liquid sulfur dioxide was allowed to warm to gentle reflux with continuous stirring. To the resulting stirred suspension in liquid sulfur dioxide, the sulfur trioxide was added slowly over a 20-min. period; and the reaction was then allowed to proceed under reflux with stirring for a total time of about 8 hr. The reaction product was filtered rapidly by suction with a sintered glass funnel, and washed 4 times on the filter by suspending the solid in 200-ml. portions of carbon tetrachloride. The washed solid was added to 1.5 l. of ice-water mixture containing 25 g. of sodium bicarbonate, and the resulting cold solution was adjusted to *p*H 9 with 20% sodium hydroxide solution. Inorganic salts were removed by dialysis in Visking cellulose casing until the solution in the casing gave a negative test for sulfate ion.[9] The sulfate-free solution was concentrated under reduced pressure to 875 ml. About 8.7 g. of sodium chloride was dissolved in the solution and the product was precipitated as a pasty solid by the addition of 2 l. of acetone. After refrigerating overnight, the supernatant liquid was decanted, and the pasty solid was macerated with two portions of absolute ethanol and two portions of acetone. After drying in a vacuum oven at 55°, the granular product weighed 52.4 g. (83% yield). *In vitro* activity = 60 units (Toronto)/mg. The *in vivo* activity was greater than 100% of heparin.[10] The analyses indicated that about 75% of the hydroxyl groups were sulfated.

Anal. Calcd. for $[C_{12}H_{17}O_8N_2(SO_3Na)_5]_x$ or 3 *O*-sulfate and 2 *N*-sulfate groups per anhydrodisaccharide unit: C, 17.31; H, 2.06; N-total, 3.36; N as $—NH_2$, 0.0; S, 19.25; Na, 13.8. Found: C, 17.74; H, 2.42; N-total, 3.19; N as $—NH_2$, 0.38 (Van Slyke) and 0.1 (titration); S, 18.32; Na, 13.9.

Acknowledgment. We wish to thank Mr. W. A. Struck and his associates for the microanalyses and Mr. R. F. Willy for the *in vitro* and *in vivo* anticoagulant activities.

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(9) In some instances the addition of barium chloride to the test portion yielded a precipitate of the barium salt of the sulfated chitosan. However, this precipitate readily dissolved in dilute sodium hydroxide, in contrast with barium sulfate.

(10) The procedure of M. H. Kuizenga, J. W. Nelson and G. F. Cartland, *Am. J. Physiol.*, 139, 612 (1943) was used for *in vitro* assay. *In vivo* assay was made by intravenous injection in rabbits. The chitosan derivative and heparin were compared on an equal weight basis as to duration of clotting time above the twice normal level following administration.

[CONTRIBUTION FROM CENTRAL EXPERIMENT STATION, BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR]

The Lithium-Ethylenediamine System. II. Isomerization of Olefins and Dehydrogenation of Cyclic Dienes[1,2]

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The solution formed from the reaction of lithium with ethylenediamine, which probably contains $H_2NCH_2CH_2NHLi$, is capable of rapidly and quantitatively isomerizing a terminal olefin to an internal olefin. A cyclic diene (such as 4-vinylcyclohexene) is converted to the corresponding aromatic hydrocarbon, with evolution of hydrogen gas; this reaction takes place slowly even at room temperature. The corresponding sodium compound, $H_2NCH_2CH_2NHNa$, isomerizes olefinic double bonds at a very slow rate; however it will rapidly aromatize a cyclic diene in which the double bonds are already conjugated and in the ring.

Recent work has shown[2] that lithium in ethylenediamine is a powerful reducing system. Many substances, including olefins, phenols, and even coal,[3] which are difficult to reduce by chemical means, are hydrogenated by lithium in ethylenediamine. It has also been observed[2] that incomplete reduction of a terminal olefin by the lithium-ethylenediamine system leads to a mixture of alkane and internal olefin. The present work was therefore initiated to study the isomerization of olefins; it has led to the discovery of an unusual low-temperature, base-catalyzed dehydrogenation reaction.[1]

Isomerization of olefins. When metallic lithium is added to ethylenediamine at a temperature of 80–115°, there is a rapid reaction, with evolution of hydrogen.[4] A dark blue material forms at the surface of the metal; when the solution is stirred, the color quickly spreads throughout the liquid. On continued heating, the blue color gradually fades and disappears, leaving a colorless or pale yellow solution which may contain a small amount of white solid in suspension. It seems reasonable to write:

$$Li + H_2NCH_2CH_2NH_2 \longrightarrow {}^1/_2H_2 + H_2NCH_2CH_2NHLi \quad (I)$$

N-Lithioethylenediamine, $H_2NCH_2CH_2NHLi$ (I), which is formed in this manner, functions as a catalyst for the isomerization of olefins. When 1-octene is heated with a solution of I in ethylenediamine, the material which is recovered (in 90% yield) consists entirely of internal olefins. Neither 1-octene nor octane can be detected; the absence of octane is evidence that metallic lithium is not present in the medium, since both terminal and internal olefins are readily reduced by lithium in ethylenediamine.[2,5] In a similar manner, 4-methylcyclohexene is isomerized to 1-methylcyclohexene.

Dehydrogenation of cyclic dienes. In view of these results, it seemed of interest to investigate the isomerization of a cyclic diene, in the thought that hydrogen transfer might lead to a disproportionation.[6] Accordingly, 4-vinylcyclohexene was added to a solution of *N*-lithioethylenediamine (I). There was a rapid evolution of hydrogen; the product, obtained in 87% yield, consisted entirely of ethylbenzene. This dehydrogenation reaction is apparently general; *d*-limonene (1-methyl-4-isopropenylcyclohexene) and α-phellandrene (2-methyl-5 - isopropyl - 1,3 - cyclohexadiene) both yield *p*-cymene. The dehydrogenation reaction with (I) is essentially quantitative in a few minutes at 100°; at room temperature it is much slower, but dehydrogenation does take place (3.6% yield of *p*-cymene from *d*-limonene after 1.5 hr.[7]

The reaction of sodium with ethylenediamine is much slower than that of lithium. The final solution of *N*-sodioethylenediamine, $H_2NCH_2CH_2NHNa$ (II) is dark brown and quite viscous. It might be expected that II would have properties similar to those of I. However, there are striking differences. When 1-octene is treated with this solution of II for 6 hr., the yield of internal olefins is 2.2%; under similar conditions, I effects complete isomerization in an hour or less. II will not catalyze the conversion of *d*-limonene (unconjugated double bonds) to *p*-cymene; however, it will de-

(1) Presented before the Division of Organic Chemistry at the 129th Meeting, American Chemical Society, Dallas, Tex., April 1956.

(2) The paper by L. Reggel, R. A. Friedel, and I. Wender, *J. Org. Chem.*, 22, 891 (1957), is regarded as Part I of this series.

(3) L. Reggel, R. Raymond, S. Friedman, R. A. Friedel, and I. Wender, *Fuel*, 37, 126 (1958).

(4) It has recently been observed that with some samples of ethylenediamine, the reaction of lithium is very slow at first. Since ethylenediamine is notoriously difficult to purify, the difference in reaction rate may be due to some impurity. Addition of a drop of water did not increase the rate of the slow-reacting material. However, the solutions ultimately obtained seem to have the same properties.

(5) The reaction depends in some manner upon the concentration of I; 1-octene is completely isomerized by a solution which is 1.06 molar in I, but is unchanged by a solution which is 0.33 molar in I.

(6) Compare the conversion of *d*-limonene to a mixture of *p*-cymene and *p*-menthane by palladium and platinum catalysts; Zelinski, *Ber.*, 57, 2058 (1924); Linstead, Michaelis, and Thomas, *J. Chem. Soc.*, 1139 (1940).

(7) The dehydrogenation, like the isomerization, depends upon concentration; *d*-limonene is completely converted to *p*-cymene by a solution 3.2 Molar in I, but is recovered unchanged from a solution 0.67 Molar in I.

hydrogenate α-phellandrene (conjugated double bonds) to *p*-cymene in the same yield as does I.

Mechanism of the reactions. Although migration of double bonds usually occurs under the influence of acids, there are examples of base-catalyzed rearrangements which are similar to those reactions reported here.[8] By analogy with the work of Pines, Veseley, and Ipatieff,[8a] the mechanism of the isomerization in the present case may be written:

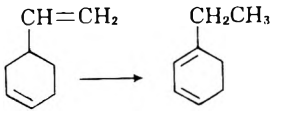
$$R{-}CH_2{-}CH{=}CH_2 + (H_2NCH_2CH_2\bar{N}H) \rightleftharpoons (R{-}\bar{C}H{-}CH{=}CH_2) + H_2NCH_2CH_2NH_2$$

$$(R{-}\bar{C}H{-}CH{=}CH_2) \longleftrightarrow (R{-}CH{=}CH{-}\bar{C}H_2)$$

$$(R{-}CH{=}CH{-}\bar{C}H_2) + H_2NCH_2CH_2NH_2 \longrightarrow R{-}CH{=}CH{-}CH_3 + (H_2NCH_2CH_2\bar{N}H)$$

This mechanism is inadequate, however, in failing to consider any role of the metal ion. It does not seem likely that the structures of the lithium and sodium compounds are very different, or that the high viscosity of the solution of II would have so great an effect upon the rate of isomerization. Nor is it likely that an essential similarity between the two is masked by solvation effects.[9] It should be pointed out, however, that certain reactions in which the anion is usually regarded as the active reagent may actually be greatly influenced by the cation present. Brady and Jakobovitz have discussed this problem in some detail,[10] and have offered explanations for several instances where the cation affects the course of the reaction. In the present work, no explanation can as yet be offered, so that the reactions must be discussed from the admittedly incomplete viewpoint which considers only the anion.

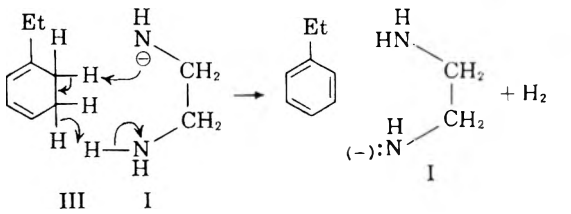
It seems reasonable that the first step in the dehydrogenation of 4-vinylcyclohexene is isomerization to the conjugated diene (III or isomer). This



III

is suggested by the fact that II will not dehydrogenate *d*-limonene (where the bonds must first be isomerized to a conjugated system), but will dehydrogenate α-phellandrene (where the double bonds are already conjugated). Since the first step in either isomerization or dehydrogenation is the removal of a proton from a carbon atom adjacent to a double bond, the reactions depend partly upon the relative acidity of the active hydrogens of the hydrocarbons (or upon the basicity of the resulting carbanion). Both I and II readily remove protons from cyclic conjugated dienes, but the removal of a less acidic proton from an unconjugated diene by II must be a slow process.

The path from III to ethylbenzene remains to be elucidated. In analogy with the isomerization mechanism, the first step may be the formation of a carbanion, which is then transformed to ethylbenzene by loss of a hydride ion. This may take place by elimination of a hydride ion as such, which would then react rapidly with either ethylenediamine or with hydrocarbon III or another molecule of 4-vinylcyclohexene, with formation of the corresponding anion and hydrogen. The bidentate character of ethylenediamine makes it possible to visualize a concerted reaction in which III and I form a cyclic intermediate.



III I

As this mechanism is written, the hydride ion is never free in solution. If it were free, it might be expected to react with other substrates present. When a mixture of *d*-limonene and 4-methylcyclohexene is treated with I, the products are *p*-cymene and 1-methylcyclohexene. No methylcyclohexane is present; thus, hydride ion has not been transferred intermolecularly. This lends some support to the idea of the cyclic intermediate, with no formation of free hydride ion. It should be noted, however, that *N*-lithiotrimethylenediamine, $H_2NCH_2CH_2CH_2NHLi$, is also capable of isomerizing a terminal olefin and dehydrogenating α-phellandrene. Thus, if the dehydrogenation does proceed *via* a cyclic intermediate, the size of the ring formed in the transition state is not critical.

This reaction is of considerable interest in that it is a low temperature, base-catalyzed, homogeneous chemical dehydrogenation which proceeds in very high yield. Pines and co-workers[8a,11] dehydrogenated *d*-limonene to *p*-cymene by sodium with a promoter such as *o*-chlorotoluene; this reaction is much slower than the lithium-ethylenediamine re-

(8) (*a*) H. Pines, J. A. Veseley, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **77**, 347 (1955); (*b*) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **20**, 839 (1955); (*c*) T. L. Jacobs, R. Akawie, and R. G. Cooper, *J. Am. Chem. Soc.*, **73**, 1273 (1951).

(9) The initial step in the isomerization as written above involves attack of the amine anion, $(H_2NCH_2CH_2NH)^-$, on the α-carbon of the olefin, with removal of a proton. It is probable that the lithium cation, because of its small size, can be solvated by only one or two solvent molecules; with sodium, the cation is larger, so that it can coordinate several solvent molecules. This difference may, in some manner, decrease the concentration or availability of the $(H_2NCH_2CH_2NH)^-$ ion when sodium is the cation present.

(10) O. L. Brady and J. Jakobovitz, *J. Chem. Soc.*, 767 (1950). See also H. Morita and A. V. Tobolsky, *J. Am. Chem. Soc.*, **79**, 5853 (1957); H. F. Herbrandson and D. S. Mooney, *J. Am. Chem. Soc.*, **79**, 5809 (1957), and references cited therein.

(11) H. Pines and H. E. Eschinazi, *J. Am. Chem. Soc.*, **77**, 6314 (1955).

action and is carried out at a considerably higher temperature. 2,5-Dihydrotoluene is partly converted to toluene by sodium amide or potassium amide in liquid ammonia[12]; however, this conversion of dihydrotoluene to toluene may take place by a hydrogen transfer (disproportionation) rather than by loss of molecular hydrogen. Furthermore, *d*-limonene is not isomerized or dehydrogenated by these reagents. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone can dehydrogenate tetralin, acenaphthene, and dibenzyl at room temperature[13]; here again, the reaction is a hydrogen transfer. In general, most nonbiological dehydrogenation reactions take place at temperatures above 200°. The dehydrogenation reaction in ethylenediamine, which produces molecular hydrogen and proceeds at a measurable rate even at room temperature, is certainly unusual. It remains to be seen whether other metal derivatives of amines or of ammonia may function in a similar way.

EXPERIMENTAL

Materials. Lithium, obtained from the Lithium Corp. of America, was used in the form of 1/8 inch wire. Anhydrous ethylenediamine (Union Carbide Chemicals Co. and Eastman) was purified by heating with sodium for a day or two, followed by distillation. Trimethylenediamine (American Cyanamid Co.) was heated with sodium for a few hours and then distilled.

Apparatus and procedure. A 4-neck flask, or a 3-neck flask with a suitable adapter, was fitted with a mercury sealed double Hershberg stirrer; a thermometer dipping below the surface of the liquid; a spiral reflux condenser with a nitrogen inlet and mercury sealed outlet; and a straight reflux condenser, 6 to 8 inches long, which was stoppered at the top. The apparatus was flushed out with nitrogen, the ethylenediamine added, and the amine heated to 90–110°. The lithium was then added in portions through the straight reflux condenser; 4 to 8 pieces, each about 1.5 inches long, were added in each portion. The rate of addition of the lithium was controlled by the hydrogen evolution and by the persistence of the dark blue color; usually gas evolution was the determining factor, the metal being added during 1.5 to 3 hours without waiting for discharge of the blue color between portions, while the mixture was stirred and maintained at 90–110°. After all of the lithium had been added and the dark blue color had disappeared, the mixture was heated for 1 or 2 hr. at 90–100° in order to be certain that all of the metal had reacted. (The final solution varied from colorless to a pale yellow or tan; it usually contained a small amount of white solid in suspension. If this colorless solution were exposed to air, a blue color formed, which was slowly destroyed when the solution was heated for a time. This color, however, was much lighter than the blue of the dissolving lithium.) The compound to be isomerized was then added at a temperature of 90–100° and the mixture stirred and heated for 1 to 5 hr. (In the dehydrogenations, the hydrocarbon was added slowly, because of the vigorous gas evolution.) The flask was then cooled in ice, and water added until most of the solid which first formed had dissolved. The product was then isolated in the usual manner and analyzed, usually by infrared spectroscopy.

Isomerization experiments. 1-Octene. (*a*) To a solution of *N*-lithioethylenediamine (I), prepared from 11.10 g. (1.60 moles) of lithium and 375 ml. of ethylenediamine, there was added 44.8 g. (0.40 mole) of 1-octene. The mixture was refluxed gently for 2.25 hr. The product (90.1% yield) consisted of internal olefins. The infrared spectrum indicated that the product was mainly 2-octene, in the proportion of approximately 60% *trans* to 40% *cis;* 1-octene was absent.

(*b*) To a solution of I prepared from 0.416 g. (0.06 mole) of lithium and 180 ml. of ethylenediamine, there was added 33.6 g. (0.30 mole) of 1-octene. The mixture was refluxed gently for 4.25 hr. The product consisted entirely of 1-octene; no β-olefin was present.

(*c*) A mixture of 375 ml. of ethylenediamine and 44.8 g. (0.40 mole) of 1-octene was refluxed gently for 5.75 hr. The product consisted entirely of unchanged 1-octene.

(*d*) A solution of $H_2NCH_2CH_2NHNa$ (II) was prepared from 13.8 (0.60 mole) of sodium and 187 ml. of ethylenediamine by heating for 9 hr.; the reaction is much slower with sodium than it is with lithium. To the resulting dark brown viscous solution there was added 44.8 g. (0.40 mole) of 1-octene during 1 hr., while maintaining the solution at about 100°. The mixture was heated for 6 hr. and then worked up in the usual manner. The product consisted largely of unchanged 1-octene, but some isomerization to internal octenes had taken place. The yield of internal olefins, corrected for a small amount present in the starting material, was 2.2%. No octane was present. There was also obtained a fairly large amount of white solid, insoluble in water and insoluble in the organic layer, which was readily removed by filtration.

(*e*) To a solution of *N*-lithiotrimethylenediamine, H_2N-$CH_2CH_2CH_2NHLi$, prepared from 1.78 g. (0.26 mole) of lithium and 60 ml. of trimethylenediamine, there was added 7.17 g. (0.064 mole) of 1-octene. The mixture was stirred and heated for 2 hr. at 100–108°. The product consisted entirely of internal olefins.

4-Methylcyclohexene. To a solution of (I) prepared from 8.33 g. (1.20 moles) of lithium and 187 ml. of ethylenediamine, there was added 19.2 g. (0.20 mole) of 4-methylcyclohexene. The mixture was heated for 2 hr. The product consisted largely of 1-methylcyclohexene, but some starting material was still present. Toluene was absent.

Dehydrogenation experiments. d-Limonene. (*a*) To a solution of I prepared from 16.65 g. (2.40 moles) of lithium and 375 ml. of ethylenediamine, there was added 54.4 g. (0.40 mole) of *d*-limonene (1-methyl-4-isopropenylcyclohexene) while the solution was maintained at 100–110°. Gas was evolved vigorously during the addition. The mixture was refluxed gently for 2.5 hr. The product (48.42 g., boiling point 167–171°) was pure *p*-cymene. The yield was 90.4%.

(*b*) To a solution of I prepared from 16.65 g. (2.40 moles) of lithium and 375 ml. of ethylenediamine, there was added during 1 hr. 54.4 g. (0.40 mole) of *d*-limonene. The solution was maintained at room temperature throughout the addition. After stirring for 0.5 hr., the mixture was decomposed with water, the temperature being maintained below 20°. The yield of *p*-cymene was 3.6%; the balance of the material was mostly *d*-limonene, but some isomers of *d*-limonene may have been present.

(*c*) To a solution of I prepared from 4.17 g. (0.60 mole) of lithium and 187 ml. of ethylenediamine, there was added 27.2 g. (0.20 mole) of *d*-limonene. Gas was evolved vigorously during the addition. The mixture was heated for 4.5 hr. The product consisted of *p*-cymene; the yield was 98.1%.

(*d*) A solution of $H_2NCH_2CH_2NHNa$ was prepared by dissolving 13.8 g. (0.60 mole) of sodium (6–8 millimeter shot) in 187 ml. of ethylenediamine. *d*-Limonene (27.2 g., 0.20 mole) was then added and the mixture heated for 9 hr. No gas was evolved. The mixture was worked up in the usual way; some brown solid material which was present was not investigated. There was obtained an 87.9% recovery of *d*-limonene; no *p*-cymene was present.

(*e*) To a solution of I prepared from 13.88 g. (2.00 moles) of lithium and 375 ml. of ethylenediamine, there was added

(12) A. J. Birch, *J. Chem. Soc.*, 1642 (1947).

(13) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).

272 g. (2.00 moles) of *d*-limonene during 1.5 hr. The mixture was heated for 0.5 hr. The product (250.5 g., b.p. 170–173°) consisted entirely of *p*-cymene; the yield was 92.1%.

(*f*) To a solution of I prepared from 1.74 g. (0.25 mole) of lithium and 375 ml. of ethylenediamine, there was added 136 g. (1.00 mole) of *d*-limonene. The mixture was heated for 1 hr.; no gas was evolved. The product consisted entirely of *d*-limonene (124.8 g., b.p. 169–172°; 91.7% recovery).

4-Vinylcyclohexene. To a solution of I prepared from 8.33 g. (1.20 moles) of lithium and 187 ml. of ethylenediamine there was added during 0.5 hr. 21.6 g. (0.20 mole) of 4-vinylcyclohexene; gas was evolved vigorously. Heating was continued for another 2.75 hr.; during this time gas evolution continued at the rate of about 1 l. per hr. The product consisted entirely of ethylbenzene; yield 86.8%.

α-Phellandrene. (*a*) To a solution of I prepared from 8.33 g. (1.20 moles) of lithium and 187 ml. of ethylenediamine, there was added 27.2 g. (0.20 mole) of crude 2-methyl-5-isopropyl-1,3-cyclohexadiene (α-phellandrene, containing about 20% *p*-cymene). Gas was evolved vigorously. The mixture was heated for 1 hr. The product consisted entirely of *p*-cymene; the yield (corrected for *p*-cymene in the starting material) was 73.7%.

(*b*) To a solution of $H_2NCH_2CH_2NHNa$ prepared by dissolving 13.8 g. (0.60 mole) of sodium shot in 187 ml. of ethylenediamine, there was added 27.2 g. (0.20 mole) of crude α-phellandrene. The mixture was then heated for 4.5 hr. The product consisted entirely of *p*-cymene; the yield (corrected for *p*-cymene in the starting material) was 76.1%. There was also obtained a white solid, insoluble in both the aqueous and organic phases.

(*c*) A mixture of 27.2 g. (0.20 mole) of crude α-phellandrene and 190 ml. of ethylenediamine was heated at 100° for 1 hr. The product, obtained in 87.2% yield, consisted of unchanged α-phellandrene.

(*d*) To a solution of $H_2NCH_2CH_2CH_2NHLi$, prepared from 2.67 g. (0.39 mole) of lithium and 60 ml. of trimethylenediamine, there was added 6.73 g. (0.064 mole) of crude α-phellandrene. The mixture was stirred and heated for 2 hr. at 112°. The product (5.33 g.) contained about 80% of *p*-cymene and 7.5% of α-phellandrene. The yield of *p*-cymene (corrected for *p*-cymene in the starting material) was 40%.

Limonene and 4-methylcyclohexene. To a solution of I prepared from 8.33 g. (1.20 moles) of lithium and 375 ml. of ethylenediamine, there was added a mixture of 54.4 g. (0.40 mole) of *d*-limonene and 76.8 g. (0.80 mole) of 4-methylcyclohexene. Gas was evolved vigorously during the addition. The mixture was heated for 4 hr. The products and yields (mass spectrometric analyses) were: *d*-limonene, 2.5%; *p*-cymene, 87.8%; 4-methylcyclohexene, 24.1%; 1-methylcyclohexene, 63.4%. Methylcyclohexane was probably absent, but may have been formed in a yield not exceeding 0.1%.

Acknowledgment. We wish to thank John A. Queiser, Gorton Wood, and Janet L. Shultz for infrared and mass spectrometric analyses.

BRUCETON, PA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

Synthesis of Some Trichloromethyl-2-benzylphenylcarbinols[1,2]

FRANK A. VINGIELLO, GEORGE J. BUESE, AND PETER E. NEWALLIS

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A series of new trichloromethyl-2-benzylphenylcarbinols, which can be considered as synthetic precursors of the DDT-type molecule, have been prepared by several reaction sequences. From the toxicity data against German cockroaches it would appear that the compounds tested have little if any insecticidal activity. Many intermediates were also tested.

In connection with our studies on the mechanism of insecticidal action of DDT, 2,2,2-trichloro-1,1-bis(*p*-chlorophenyl)ethane, we have synthesized a series of trichloromethyl-2-benzylphenylcarbinols (IVa–IVd) which are synthetic precursors of the DDT-type molecule. Since many carbinols[3] of diversified structure have been synthesized and tested for insecticidal activity, we thought compounds of the type IV would be especially interesting for several reasons.

First, Fisher-Hirschfelder-Taylor models of compounds of the type IV indicate that free rotation of one phenyl group is not possible and that free rotation of the other phenyl group is severely hindered so that the trihedralized[4] configuration may be realized. Rogers, Brown, Rasmussen, and Heal[4] have pointed out the importance of a trihedralized *p,p'*-dichlorophenyl moiety in explaining the toxicity of DDT.

Second, compound IVd has other important structural features in common with DDT; namely, a trichloromethyl group and two *p*-chlorophenyl groups whose chlorine atoms are about as distant as those in DDT.

Third, compounds of the type IV are known[3] to exhibit narrow-spectrum insecticidal properties and are thus ideally suited for activity-structure studies with certain insects.

Ketones Ia and Ib are prepared in excellent yield

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

(2) This paper has been abstracted from the master's thesis of G. J. Buese and the doctorate thesis of P. E. Newallis presented to the Virginia Polytechnic Institute in 1951 and 1957, respectively.

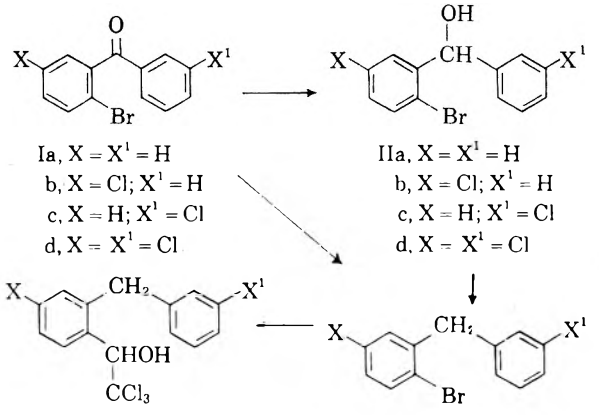
(3) R. C. Blinn, F. A. Gunther, and R. L. Metcalf, *J. Am. Chem. Soc.*, 76, 37 (1954) and references listed there.

(4) E. F. Rogers, H. D. Brown, I. M. Rasmussen, and R. E. Heal, *J. Am. Chem. Soc.*, 75, 2991 (1953). According to these authors the concept of trihedralization may be generalized as follows: "In compounds having one carbon atom two or three planar groups and a group sufficiently large to hinder the rotation of the planar groups, although capable of rotation itself, the planar groups will tend to positions corresponding to the sides of a trihedral angle."

by the aluminum chloride-catalyzed reaction of 2-bromobenzoyl chloride and 2-bromo-5-chlorobenzoyl chloride respectively on benzene. Ketones Ic and Id were prepared in good yield by allowing the cadmium reagent of 3-bromochlorobenzene to react with 2-bromobenzoyl chloride and 2-bromo-5-chlorobenzoyl chloride, respectively.

Reduction of these ketones, Ia–Id, with sodium borohydride[5] processed smoothly and in good yield to give the corresponding carbinols, IIa–IId. Carbinols IIa and IIc were also prepared in excellent yield by allowing 2-bromobenzaldehyde to react with the appropriate Grignard reagent.

The carbinols, IIa–IId, could be reduced to the corresponding diphenylmethanes using red phosphorus and iodine in glacial acetic acid. Although the ketones, Ia–Id, could be reduced directly to the diphenylmethanes using the same reagent, the results were erratic[6] and in our hands the two step reduction proved more satisfactory.



The addition of freshly distilled chloral to a Grignard reagent[7] prepared from IIIa, IIIb, IIIc, and IIId gave the corresponding trichloromethyl-2-benzylphenylcarbinols. These carbinols tend to decompose even when distilled at low pressures. Only IVa and IVb could be prepared analytically pure. By using a variety of methods all four carbinols could be converted to their acetates which could be purified to analytical purity.

Entomological testing[8] of the new compounds was undertaken by Dr. James M. Grayson and his staff at the Virginia Polytechnic Institute Entomology Department using standard methods of assay. From the toxicity data against German cockroaches it would appear that the new compounds have little if any insecticidal activity.

EXPERIMENTAL[9,10]

2-Bromo-5-chlorobenzoic acid. A mixture of 90 g. of cupric sulfate pentahydrate, 75 g. of sodium bromide, 50 g. of fine copper turnings, and 400 ml. of 48% hydrobromic acid was boiled vigorously for 3 hr. This hot solution was filtered through glass wool into a boiling solution of 150 g. of 2-amino-5-chlorobenzoic acid,[11] 600 ml. of 48% hydrobromic acid and 5000 ml. of water. The solution was stirred continuously during this addition and was kept boiling. A solution of 150 g. of sodium nitrite in 700 ml. of water was then added slowly, with stirring, to the hot acid solution. After addition was complete the solution was allowed to cool to room temperature and was finally cooled in an ice-salt bath. The solid which formed was filtered and recrystallized from water using a little charcoal. The fine white crystals were dried in a vacuum desiccator; yield 155 g. (75%), m.p. 148–149° (lit.,[12] m.p. 148–149°).

2-Bromo-5-chlorobenzoyl chloride. A mixture of 20 g. of the above acid and 19 g. of phosphorus pentachloride was heated in an oil bath maintained at 140° for 0.5 hr. The low boiling material was distilled under slightly reduced pressure and the residue was fractionated at 22 mm.; yield 20 g. (91%), b.p. 147–149°, m.p. 34–35° (lit.,[12] b.p. 146–147° (23 mm.), m.p. 34–35° no yield reported).

2-Bromo-5-chlorobenzophenone (Ib). A mixture of 25 g. of aluminum chloride and 180 ml. of dry benzene was cooled in an ice bath and stirred. A few drops of a solution of 39 g. of 2-bromo-5-chlorobenzoyl chloride in about 70 ml. of benzene was added immediately to prevent the benzene from freezing and then the remainder of the solution was added dropwise. The mixture was stirred overnight and allowed to warm to room temperature. The reaction mixture was then heated under reflux for three hours, cooled in an ice bath and decomposed with ice and 120 ml. of concentrated hydrochloric acid. The acid layer was separated and extracted with fresh benzene. The benzene layers were combined, washed with water, then sodium carbonate solution and again with water. The benzene solution was concentrated and fractionated under reduced pressure; yield 42 g. (93%), b.p., 172–173° (1 mm.). On standing the oil solidified; m.p. 100.5–102°. An analytical sample was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_8BrClO$: C, 52.82; H, 2.73. Found: C, 52.66; H, 2.80.

2-Bromo-3′-chlorobenzophenone (Ic). A Grignard reagent was prepared in ether from 44 g. (0.23 mole) of 3-bromochlorobenzene, 5.2 g. (0.23 mole) of magnesium. The solu-

(5) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, 71, 122 (1949).

(6) Difficulties in using red phosphorus and iodine have been encountered before; see for example, F. A. Vingiello, A. Borkovec, and J. Shulman, *J. Am. Chem. Soc.*, 77, 2320 (1955).

(7) H. L. Haller, P. D. Bartlett, N. L. Drake, M. S. Newman, S. J. Cristol, C. M. Eaker, R. A. Hayes, G. W. Kilmer, B. Magerlein, G. P. Mueller, A. Schneider, and W. Wheatley, *J. Am. Chem. Soc.*, 67, 1591 (1945); see also ref. (3).

(8) Dr. James M. Grayson of the Entomology Department at the Virginia Polytechnic Institute was responsible for conducting the assays. We are grateful to him for this work.

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

(10) All analyses were carried out by the Micro-Tech Laboratories, Skokie, Ill.

(11) Purchased from Distillation Products Industries, Rochester 3, N. Y.

(12) J. B. Cohen and H. S. Raper, *J. Chem. Soc.*, 85, 1267 (1904) prepared this compound by the nitric acid oxidation of the chlorobromotoluene and by a Sandmeyer reaction which gave a discolored product. In neither case was the yield given.

tion was cooled and 42 g. (0.23 mole) of dry, finely ground cadmium chloride was added. The mixture was stirred for an hour at the end of which the Gilman color test[13] was negative. The ether was replaced with benzene and 50 g. (0.23 mole) of 2-bromobenzoyl chloride in 50 ml. of benzene was added to the boiling solution as rapidly as possible. The mixture was stirred and heated for an additional 40 min. and then cooled and poured into a mixture of ice and dilute sulfuric acid. The acid layer was separated and extracted with benzene. The benzene layers were combined, washed with water, then with sodium carbonate solution, again with water, and finally concentrated. The residue was fractionated; yield 41 g. (61%) b.p., 182–183° (3 mm.). Crystallization from ethanol gave white crystals, m.p. 34.5–36°.

Anal. Calcd. for $C_{13}H_8BrClO$: C, 52.82; H, 2.73. Found: C, 52.93; H, 2.95.

2-Bromo-5,3′-dichlorobenzophenone (Id) was prepared using substantially the procedure given above for preparing Ic with 2-bromo-5-chlorobenzoyl chloride being used in place of 2-bromobenzoyl chloride. The product (73%) distilled at 203–206° (3 mm.). This oil crystallized on standing and was recrystallized from ethanol giving white crystals, m.p. 75–76°.

Anal. Calcd. for $C_{13}H_7BrCl_2O$: C, 47.31; H, 2.14. Found: C, 47.30; H, 2.27.

2-Bromo-5-chlorobenzhydrol (IIb). A solution of 1.3 g. (0.03 mole) of sodium borohydride in 15 ml. of distilled water was added dropwise to a stirred suspension of 20 g. (0.07 mole) of 2-bromo-5-chlorobenzophenone in 100 ml. of methanol. The mixture was warmed in a water bath at 60° for 30 min. and allowed to stand at room temperature for an additional 30 min. The mixture was then decomposed with 10% hydrochloric acid and extracted with ether. The ether solutions were combined, washed with water, dried, and concentrated. The residue was fractionated; yield 16 g. (79%) b.p. 144–147° (1 mm.). Crystallization from 30–60° petroleum ether gave white crystals, m.p. 49–49.5°.

Anal. Calcd. for $C_{13}H_{10}BrClO$: C, 52.46; H, 3.39. Found: C, 52.36; H, 3.70.

2-Bromo-3′-chlorobenzhydrol (IIc). *A. Via* $NaBH_4$ reduction of ketone. IIc was prepared using substantially the same procedure given above for IIb. There was obtained from 2-bromo-3′-chlorobenzophenone 77% of product distilling at 144–146° (0.5 mm.).

B. Via Grignard reagent. A Grignard reagent was prepared in ether from 76 g. (0.39 mole) of 3-bromochlorobenzene and 9.5 g. (0.39 mole) of magnesium. A solution of 47 g. (0.26 mole) of 2-bromobenzaldehyde[14] in 100 ml. of ether was added dropwise with stirring in the usual way, this gave 59 g. (82%) of a clear viscous oil which distilled at 178–180° (2 mm.).

Anal. Calcd. for $C_{13}H_{10}BrClO$: C, 52.46; H, 3.39. Found: C, 52.56; H, 3.64.

2-Bromo-5,3′-dichlorobenzhydrol (IId). This compound was prepared by the $NaBH_4$ reduction of 2-bromo-5,3′-dichlorobenzophenone using essentially the procedure described for IIb. The product (75%) was obtained as a clear, colorless oil distilling at 166–168° (0.5 mm.). Crystallization from 30–60° petroleum ether gave white, poorly formed crystals, m.p. 92–93°. Recrystallization from a petroleum ether–methanol mixture gave crystals melting sharply at 93.5–94°.

Anal. Calcd. for $C_{13}H_9BrCl_2O$: C, 47.02; H, 2.73. Found: C, 47.00; H, 2.87.

2-Bromodiphenylmethane (IIIa).[15] Although several different methods were used[16] to prepare this compound, the method of Bradsher and Vingiello[17] proved most satisfactory.

2-Bromo-5-chlorodiphenylmethane (IIIb). A mixture of 33 g. of 2-bromo-5-chlorobenzophenone, 33 g. of red phosphorus and 33 ml. of that portion of 48% hydriodic acid which boiled over 122° (715 mm.) was stirred and heated under reflux for 44 hr. The mixture was cooled to room temperature, 50 ml. of water was added, and the phosphorus was filtered. The acid solution was neutralized with 10% sodium hydroxide solution and extracted with ether. The ether solutions were combined, washed with water, dried over anhydrous calcium sulfate, and concentrated. The residue was distilled; yield 23 g. (72%) b.p., 168–170° (3.5 mm.).

Anal. Calcd. for $C_{13}H_{10}BrCl$: C, 55.45; H, 3.58. Found: C, 55.30; H, 3.71.

2-Bromo-3′-chlorodiphenylmethane (IIIc). This compound was prepared by the reduction of 2-bromo-3′-chlorobenzophenone using substantially the procedure described for IIb. The product (64%) was obtained as an oil distilling at 144–146° (1 mm.).

Anal. Calcd. for $C_{13}H_{10}BrCl$: C, 55.45; H, 3.58. Found: C, 55.66; H, 3.85.

2-Bromo-5,3′-dichlorodiphenylmethane (IIId). This compound was prepared by the reduction of 2-bromo-5,3′-dichlorobenzophenone using substantially the procedure described for IIb. The product (63%) was obtained as an oil distilling at 151–156° (1 mm.).

Anal. Calcd. for $C_{13}H_9BrCl_2$: C, 49.40; H, 2.87. Found: C, 49.62; H, 2.91.

Trichloromethyl-2-benzylphenylcarbinol (IVa). A Grignard reagent was prepared in ether from 40 g. (0.16 mole) of 2-bromodiphenylmethane and 3.8 g. (0.16 mole) of magnesium. The solution was heated under reflux and 26 g. (0.18 mole) of freshly distilled chloral in 50 ml. of dry ether was added rapidly.[18] The solution was then cooled and decomposed with a saturated solution of ammonium chloride. The ether was separated and the "cake" was washed with ether. The combined ether solutions were washed with water, 10% sulfuric acid, again with water, dried, and concentrated. An extremely viscous oil was obtained which distilled at 174–176° (1 mm.)[19]; yield 31 g. (61%).

Anal. Calcd. for $C_{15}H_{13}Cl_3O$: C, 57.08; H, 4.15. Found: C, 57.20; H, 4.07.

Acetate of trichloromethyl-2-benzylphenylcarbinol. A mixture of 1 g. of the above carbinol (IVa), 10 ml. of acetic anhydride, and 0.5 ml. of trifluoroacetate acid was heated under reflux for 4 hr. The solution was cooled, poured into an ice-water mixture and the fine, tan solid was filtered. Recrystallization from ethanol (Norite) gave 1 g. (84%) of white plates, m.p. 120–122°. Further recrystallizations from ethanol raised the melting point to 122–123°.[20]

Anal. Calcd. for $C_{17}H_{15}Cl_3O_2$: C, 57.10; H, 4.23; Cl, 29.74. Found: C, 57.10; H, 4.29; Cl, 29.90.

Trichloromethyl-2-benzyl-4-chlorophenylcarbinol (IVb). This compound was prepared by allowing the Grignard reagent of 2-bromo-5-chlorodiphenylmethane to react with chloral

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

(14) Prepared according to R. Adams and E. Vollweiler, *J. Am. Chem. Soc.*, 40, 1737 (1918).

(15) All of the diphenylmethanes (IIIa–IIId) were also made easily by the reduction of the corresponding benzhydrols (IIa–IId) using red phosphorus and iodine in acetic acid. The yields in these experiments were as follows: IIIa (77%), IIIb (71%), IIIc (66%), IIId (64%).

(16) Huang-Minlon reduction of the ketone gave only 25% yield. The aluminum chloride catalyzed condensation of 2-bromobenzyl bromide and benzene gave only 13% yield.

(17) C. K. Bradsher and F. A. Vingiello, *J. Org. Chem.*, 13, 786 (1948).

(18) When the ether was replaced with benzene and the chloral added to the boiling benzene solution, a yield of only 22% was obtained.

(19) The distillation proceeds well if the fractionating column is warmed with an electrical heating tape.

(20) The same product was obtained in 30% yield using the Schotten-Baumann procedure and in 66% yield using the boron trifluoride method.

using substantially the procedure described for IVa. The product was obtained in 55% yield as a very viscous oil which distilled at 190–192° (1 mm.).

Anal. Calcd. for $C_{15}H_{12}Cl_4O$: C, 51.46; H, 3.46. Found: C, 51.58; H, 3.42.

Acetate of trichloromethyl-2-benzyl-4-chlorophenylcarbinol. A mixture of 2 g. of the above carbinol (IVb), 4 ml. of freshly distilled boron trifluoride etherate, and 25 ml. of glacial acetic acid was heated under reflux for 10 hr. The mixture was cooled to room temperature and poured into an ice-water mixture. A reddish yellow gum separated and was dissolved in ether. The ether solution was washed with water, a dilute sodium bicarbonate solution, and again with water. The solution was then dried and concentrated. The residue was crystallized from ethanol; yield 1.7 g. (77%), m.p. 115–116°. Several recrystallizations from ethanol raised the melting point to 116–117°.[21]

Anal. Calcd. for $C_{17}H_{14}Cl_4O_2$: C, 52.07; H, 3.60. Found: C, 52.05; H, 3.82.

Trichloromethyl-2-(3′-chlorobenzyl)phenylcarbinol (IVc). This compound was prepared by allowing the Grignard reagent of 2-bromo-3′-chlorodiphenyl-methane to react with chloral using essentially the procedure described for IVa. The product was obtained in 42% yield as a very viscous oil which distilled at 185–190° (0.1 mm.).

Acetate of trichloromethyl-2-(3′-chlorobenzyl)phenylcarbinol. This compound was prepared substantially as was the acetate of IVa using trifluoroacetic acid. Recrystallization from ethanol gave a 58% yield of white crystals; m.p. 114–115°.

Anal. Calcd. for $C_{17}H_{14}Cl_4O_2$: C, 52.07; H, 3.60. Found: C, 52.12; H, 3.56.

Trichloromethyl-2-(3′-chlorobenzyl)-4-chlorophenylcarbinol (IVd). This compound was prepared by allowing the Grignard reagent of 2-bromo-5,3′-dichlorodiphenylmethane to react with chloral using substantially the procedure described for IVa. The product was obtained in 48% yield as a very viscous oil which distilled at 185–188° (0.2 mm.).

Acetate of trichloromethyl-2-(3′-chlorobenzyl)-4-chlorophenylcarbinol. This compound was prepared substantially as was the acetate of IVa using trifluoroacetic acid. Recrystallization from ethanol gave a 53% yield of white crystals; m.p. 92–93°.

Anal. Calcd. for $C_{15}H_{13}Cl_5O_2$: C, 47.87; H, 3.07. Found: C, 47.76; H, 3.12.

BLACKSBURG, VA.

(21) The same product was obtained in 72% yield using the trifluoroacetic acid method.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

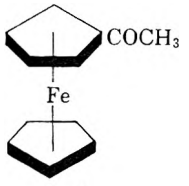
Benzoylations of Both Methyl Ketone Groups of Bisacetylferrocene with Methyl Benzoate and Alkali Amides to Form the Bis-β-diketone. Certain Derivatives[1]

CHARLES R. HAUSER AND CHARLES E. CAIN

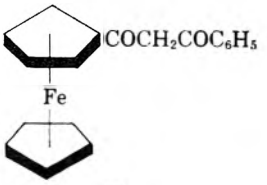
Received January 29, 1958

The benzoylations of both of the methyl ketone groups of bisacetylferrocene were effected with excess methyl benzoate and alkali amide to form the bis-β-diketone. An attempt to benzoylate only one of the methyl ketone groups was unsuccessful. The bis-β-diketone was converted to the bispyrazole, and to a copper chelate which evidently contained one molecule of the bis-β-diketone for each copper atom. Infrared data are presented for these and certain related compounds.

It has recently been shown[2] that the methyl ketone group of acetylferrocene (I) can be benzoylated with methyl benzoate by means of potassium amide to form the corresponding β-diketone (II).

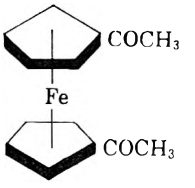


I

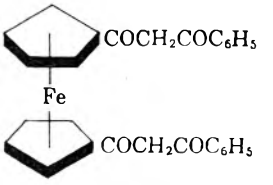


II

It has now been found that both of the methyl ketone groups of bisacetylferrocene[3] (III) can similarly be benzoylated to give the bis-β-diketone IV.[3a] For convenience these compounds are represented in the *cis*-configuration.[4]



III



IV

(1) Supported by the National Science Foundation.

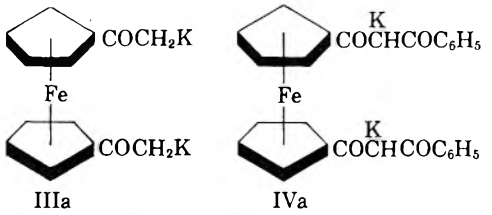
(2) Charles R. Hauser and Jacque K. Lindsay, *J. Org. Chem.*, **22**, 482 (1957).

(3) We are indebted to Linde Air Products Company, Tonawanda, N. Y., (Dr. R. L. Pruett), for a sample of this compound.

(3a) That the product was not the isomeric triacyl derivative, which might have resulted from dibenzoylation at one of the methyl ketone groups, was indicated by the absence of an infrared band at about 5.7–5.8 for the methyl ketone group which would then still be present in the molecule. Moreover, the triacyl derivative could hardly produce the bispyrazole VII and the internal copper chelate IX. Actually dibenzoylation at one of the methyl ketone groups should not be expected, since the equilibrium of similar acylations of ordinary methyl ketones with methyl benzoate is generally on the side of the anion of the β-diketone which is the monobenzoylation product (see ref. 5).

(4) Recently, D. A. Semenow and J. D. Roberts [*J. Am. Chem. Soc.*, **79**, 2741 (1957)] have presented dipole moment evidence that at least bis-*p*-chlorophenylferrocene has the *cis* configuration.

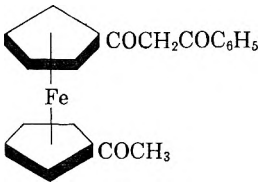
This two-fold Claisen type condensation was effected by first converting the bisacetylferrocene (III) to its dipotassio derivative IIIa by means of potassium amide in liquid ammonia and then adding methyl benzoate in ether. Almost immediately the reaction mixture became red which is the color of the bis-β-diketone and of its potassio derivative IVa, the formation of which is called for by theory.[5]



IIIa IVa

The best yield (62%) of the bis-β-diketone IV was obtained employing four equivalents each of potassium amide and methyl benzoate to one of the bisacetylferrocene (III). Under these conditions the conversion of the bis-β-diketone IV to its dipotassio derivative IVa may be considered to be effected by the two extra equivalents of the potassium amide over the two involved in the formation of the dipotassio derivative of bisacetylferrocene IIIa. Essentially the same yield (60%) was obtained with sodium amide under the similar conditions. The proportions of reactants employed with bisacetylferrocene (III) correspond to the use of two equivalents each of the alkali amide and ester to one of a monomethyl ketone, which have been recommended when the yield is to be based on the ketone.[5]

Although this two-fold condensation might be expected to involve the intermediate formation of the mono-β-diketone V or its potassio derivative, none of this intermediate was found under the above conditions or even when the dipotassio derivative of bisacetylferrocene IIIa was treated with only one equivalent of methyl benzoate. Under the latter conditions a 20% yield of the bis-β-diketone IV was obtained, and 67% of the bisacetylferrocene (III) was recovered.

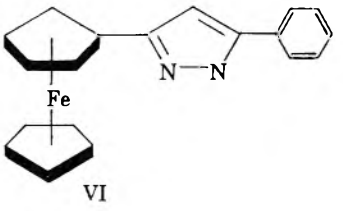


V

Moreover, when the monopotassio derivative of bisacetylferrocene was prepared by means of one equivalent of potassium amide in liquid ammonia and an equivalent of methyl benzoate then added (refluxed 5 hours in ether), none of the mono-β-diketone V was found, and 95% of the bisacetylferrocene was recovered (an infrared spectrum indicated no β-diketone present). Neither was the mono-β-diketone V isolated when bisacetylferrocene was stirred at room temperature with excess sodium methoxide and methyl benzoate in ether for 10 hours. There was obtained a black oily material, an infrared spectrum of which indicated no β-diketone present.

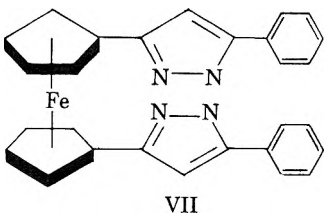
It should be mentioned that both this difficulty of preparing the mono-β-diketone by this method and the ease with which the bis-β-diketone IV was obtained were not anticipated. Apparently the second benzoyl group was introduced into the molecule much more readily than the first. The alternative possibility that the two groups were introduced simultaneously seems unlikely. The theory behind these interesting observations is being further investigated.

Derivatives and infrared data. (*A*) *Pyrazoles.* The cyclization of mono-β-diketone II with hydrazine to form the pyrazole VI has been described previously.[2]



VI

The two-fold cyclization of bis-β-diketone IV with two molecules of hydrazine to form the bis-pyrazole VII has now been effected in 82% yield employing a large excess of hydrazine. No attempt was made to prepare the mono-pyrazole of bis-β-diketone IV.



VII

In Table I are summarized some principal infrared bands of pyrazoles VI and VII and also those of the ordinary pyrazoles VIII and IX. Pyrazole VIII is well known, and its infrared spectrum has been reported previously,[6,7] but pyrazole IX appears to be new.[8]

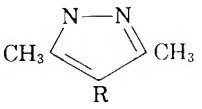
(5) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 59 (1954).

(6) C. S. Rondestvedt and P. K. Chang, *J. Am. Chem. Soc.*, 77, 6532 (1955).

(7) P. Mirone and M. Vampiri, *Atti accad. nazl. Lincei, Rend., Classe sci. fis., mat. e nat.*, 12, 583 (1952); *Chem. Abstr.*, 46, 9423 (1952).

(8) Pyrazole IX was prepared in the usual manner from 3-phenylacetylacetone by R. J. Light in this laboratory. It was obtained in 91% yield, m.p. 128.5–129.5°.

Anal. Calcd.: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.91; H, 6.89; N, 16.20.



VIII, R = H
IX, R = C_6H_5

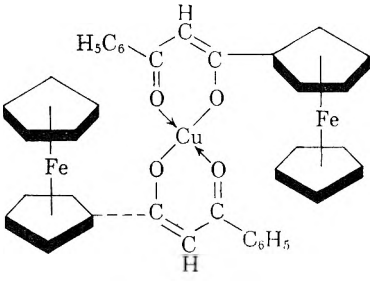
TABLE I

SPECTRA OF PYRAZOLE BANDS (μ)

Formula VIII	Formula IX	Formula VI	Formula VII
6.26	6.22	6.22	6.24
6.43	6.44	6.45	6.45
6.74	6.84	6.85	6.85
		9.02	
		9.08	

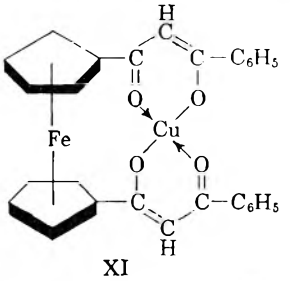
It can be seen from Table I that each of the pyrazoles listed has infrared bands at 6.28 μ, 6.44 μ, and 6.7 μ. The first two bands have been assigned[6,7] to the carbon-nitrogen double bond and to the carbon-carbon double bond respectively. The last band has apparently not been assigned but it has been considered characteristic of the pyrazole ring.[6,7] Only one of the pyrazoles listed in Table I exhibits bands at about 9 and 10 μ which are known to be characteristic of ferrocene derivatives having an unsubstituted ring.[9]

(*B*) *Copper chelates.* The reaction of mono-β-diketone II with copper acetate to form chelate X has been described previously.[2] Such chelates are known to consist of two mono-β-diketone molecules to one copper atom.[10]



X

The corresponding reaction of bis-β-diketone IV with copper acetate has now been effected to form a copper chelate which, on the basis of its molecular weight, may be represented by structure XI. Treatment of the chelate with dilute phosphoric acid regenerated bis-β-diketone IV.



XI

This conversion of bis-β-diketone IV to monomeric chelate XI is to be contrasted with that of bis-β-diketone XII to a polymeric chelate which was recently reported in a patent.[11]

XII

It should be pointed out that the *cis* relationship of the two β-diketone groups in chelate XI does not necessarily furnish evidence for the *cis* configuration of the bis-β-diketone (structure IV) since, because of the presumably low energy barrier to rotation around the iron, the bis-β-diketone might have been converted to the *cis*-chelate under the conditions employed.[9]

Such a chelate as XI involving only one bis-β-diketone molecule per copper atom might not be exactly analogous with the ordinary chelates such as X since, if the usual planar-square geometry of the copper chelate is maintained,[12] certain of the bond angles would probably have to be distorted. Actually, this distortion may be indicated by a comparison of the infrared spectrum of chelate XI with that of chelate X as discussed below.

In Table II are summarized the principal infrared bands that have been found for mono-β-diketone II and bis-β-diketone IV and their copper chelates. Also, in this table are included for comparison the bands for dibenzoylmethane which have been studied.[13]

It can be seen from Table II that in general the β-diketones and copper chelates exhibit similar infrared spectra. It is to be noted that, with the exception of chelate XI, none of the compounds listed in this table show a band at 5.7–5.9 μ which is characteristic of the free ketone carbonyl group.[14] This indicates that the β-diketones exist largely in the enol form and the copper chelates in the analogous metal enolate form.

However, certain differences are evident between the spectra of the ferrocene β-diketones and their copper chelates. In the cases of dibenzoylmethane and the two ferrocene β-diketones (II and IV) the carbonyl group band has undergone a considerable shift and reappeared in the 6.1–6.5 μ region.[13,14] With the two ferrocene β-diketones the band seems to be split into two components, one about 6.2 μ and the other about 6.35 μ.

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

(10) See J. Lecomte, *Discuss. Faraday Soc.*, 9, 125 (1950).

(11) J. P. Wilkins and E. L. Wittbecker, U. S. Patent 2,659,711, Nov. 17, 1953.

(12) See A. E. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds*, Prentice-Hall Inc., Englewood Cliffs, N. J., 1952, p. 263.

(13) See R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Am. Chem. Soc.*, 71, 1068 (1949).

(14) See L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, New York, N. Y., 1954, p. 123.

TABLE II

INFRARED SPECTRA OF BIS-β-DIKETONES AND COPPER CHELATES (μ)

Dibenzoyl-methane	Mono-β-diketone II	Mono-copper chelate X	*Bis*-β-diketone IV	*Bis*-copper chelate XI
				5.82
6.1–6.5	6.22, 6.35	6.28, 6.5[a]	6.24, 6.38	6.27, 6.5[a]
6.75	6.73	6.71	6.72	6.71
—	—	6.88	—	6.88
7.14	7.07	7.12, 7.18	7.26	7.09, 7.17
—	7.25	7.26	7.40	7.25, 7.41
7.79	7.72	7.65	7.66	7.67
8.155	8.12	8.10	8.11	8.11
8.435	8.45	8.48	8.42	8.45
9.035	8.97	—	8.94	—
—	9.02[b]	9.03[b]	—	—
—	—	9.21	—	9.22
9.36	9.32	—	9.31	9.37[c]
9.72	9.69	9.60	9.60	9.64
9.98	9.80	9.78	9.80	9.77
—	9.97[b]	9.98[b]	—	—
10.24	—	—	—	—
10.765	10.74	10.55	10.71	10.54
—	12.14	12.11	—	12.05

[a] Broad. [b] Peak assigned to ferrocene substituted on one ring. [c] Weak.

In the case of the ferrocene copper chelates (X and XI) the carbonyl group band also appears to be split into two bands, but they are about 6.3μ (a sharp band) and about 6.5 μ (a broad band). Recent work on the infrared spectra of metal chelates of certain other β-diketones has ascribed this split band which was observed by Lecomte[10] in 1950 to the conjugated enol structure of such chelates. In particular, the 6.3 μ band has been ascribed to the chelated carbonyl bond, and the 6.5 μ band to the carbon-carbon double bond.[15] There is also a characteristic band at 12.15 μ which has been assigned to a carbon-carbon double bond with one hydrogen attached; such is the case with the double bond resulting from the formation of the enolic metal chelate X or XI.

It is of interest that, in the infrared spectrum of bis-β-diketone copper chelate XI, there reappeared a band in the 5.7–5.9 μ region in which ordinary ketone carbonyls usually absorb. This weak peak at 5.82 μ was in addition to the uniformly observed shifted β-diketone carbonyl band and was not evident in the spectrum of any other of the compounds compared. That this band was not due to some impurity is indicated by the lack of such a band in the spectrum of the bis-β-diketone from which the chelate was prepared and by the lack of this band in the spectrum of the bis-β-diketone recovered from the phosphoric acid hydrolysis of the chelate. This band in the region for an unconjugated simple ketone may arise from some incomplete bonding (because of steric strain) in the chelation of the metal with four oxygens.

(15) D. P. Dryden and A. Winston, paper at Southeastern Regional Meeting, ACS, Nov. 15, 1957.

EXPERIMENTAL[16]

Bis-β-diketone IV from bisacetylferrocene. To a stirred solution of 0.2 mole of potassium amide[17] in 250 ml. of liquid ammonia was added in small portions 13.6 g. (0.05 mole) of solid bisacetylferrocene III to produce a yellow-brown suspension. After stirring for 20 min., a solution of 27.2 g. (0.2 mole) of methyl benzoate in 100 ml. of dry ether was added dropwise. The color of the suspension changed almost immediately to a dull red. The liquid ammonia was evaporated (steam bath) as 250 ml. of dry ether was added, and the resulting suspension (still red) was stirred at room temperature for 4 hr. The mixture was then filtered rapidly, and the red solid washed with dry ether until the washings were colorless. This solid (presumably the potassium salt of the bis-β-diketone) was added with stirring to about 400 ml. of *N* hydrochloric acid. The resulting red suspension was collected in a funnel and washed with water and then ether. The crude red powder, which was insoluble in ether and water and only slightly soluble in acetone, melted at 198–201°. It was recrystallized from acetone to give 15 g. (62%) of bis-β-diketone IV (purple needles) m.p. 213.5–214°. An analytical sample was prepared through the copper chelate (see below).

Anal. Calcd. for $C_{28}H_{22}O_4Fe$: C, 70.31; H, 4.64; Fe, 11.68. Found: C, 70.22; H, 4.40; Fe, 11.50.

There was recovered from the ether washings 2.8 g. (20%) of bisacetylferrocene III. Taking this into account, the conversion yield of the bis-β-diketone IV was 78%.

The experiment was repeated employing sodium amide instead of potassium amide and stirring the ether suspension of the reaction mixture for 12 hr. There was obtained 14 g. (60%) of bis-β-diketone IV, m.p. 213–214°. Since 3.5 g. (26%) of bisacetylferrocene was recovered, the conversion yield of IV was 81%. In this experiment, a sample of the solid obtained before acidification was heated in a melting point tube. Since it did not melt at 300°, it was presumably the disodium salt of the bis-β-diketone and sodium methoxide. After acidification, the crude red solid melted at 201–

(16) Analyses are by Galbraith Laboratories, Knoxville, Tenn.

(17) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, 69, 2325 (1947).

203°, and at 212.5–213.5° after recrystallization from acetone.

When the reaction was carried out with 0.1 mole each of potassium amide and methyl benzoate and 0.05 mole of bisacetylferrocene (III) (ether suspension stirred for 6 hr.), there was obtained 11 g. (46%) of bis-β-diketone IV, m.p. 213–214°. Since 6 g. (45%) of the bisacetylferrocene (III) was recovered the conversion yield was 84%.

When the reaction was carried out with 0.05 mole of potassium amide and 0.025 mole each of bisacetylferrocene (III) and methyl benzoate (ether suspension stirred for 8 hr.), there was obtained 1.8 g. (20%, 40% based on the ester) of bis-β-diketone IV, m.p. 212.5–214°. Since 4.5 g. (67%) of *bis*-acetylferrocene (III) was recovered, the conversion yield of IV based on III was 61%.

Cyclization of bis-β-diketone IV with hydrazine to form bispyrazole VII. To a solution of 5 g. (0.01 mole) of bis-β-diketone IV in 1.5 l. of absolute ethanol was added 20 g. (0.6 mole) of 95% hydrazine in 20 ml. of absolute ethanol. The resulting deep red solution was refluxed for 1 hr., during which time the color changed to a deep orange. After cooling to room temperature and standing overnight in a refrigerator, the reaction mixture was filtered (cold) to yield 3.1 g. of bispyrazole VII (orange crystalline solid), m.p. >300° dec. Reduction of the volume of the filtrate under vacuum gave an additional 0.9 g. of an orange powder, m.p. >300° dec.; total yield 4.0 g. (82%). This compound failed to dissolve appreciably (as would be indicated by color) in various refluxing solvents including benzene, acetone, hexane, ethanol, chloroform, and dioxane. However, unrecrystallized samples from both fractions gave satisfactory analytical values.

Anal. Calcd. for $C_{28}H_{22}N_4Fe$: C, 71.49; H, 4.71; N, 11.91; Fe, 11.90. Found for orange crystals: C, 71.43; H, 4.90; N, 11.88; Fe, 11.73. Found for orange powder: C, 71.37; H, 4.88; N, 11.79; Fe, 12.14.

Formation of the copper-chelate XI of bis-β-diketone IV. To a solution of 1 g. of the bis-β-diketone IV in 500 ml. of refluxing acetone was added 20 ml. of a saturated solution (large excess) of warm, aqueous copper acetate. After refluxing for 15 min., the reaction mixture was cooled and filtered. The solid was washed with water and dried. After washing with petroleum ether and recrystallizing from benzene there was obtained 1 g. (88%) of a yellow powder, m.p. >300°.

Anal. Calcd. for $C_{28}H_{20}O_4FeCu$: C, 62.08; H, 4.09. Found: C, 62.29; H, 3.99. Mol. wt. determinations[18]: Calcd. for $C_{28}H_{20}O_4FeCu$: 541.9. Found: 529, 514, 509, 521. Limit of error, ±10%.

A portion of the chelate was reconverted to the original bis-β-diketone by stirring overnight in 20% phosphoric acid. It was identified by infrared spectrum and melting point.

DURHAM, N. C.

(18) Mol. wt. determination by Laboratory of Microchemistry, Dr. Carl Tiedcke, Teaneck, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

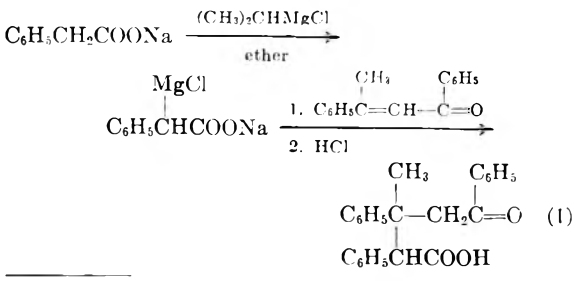
Conjugate Addition of Phenylacetic Acid and Derivatives with α,β-Unsaturated Carbonyl Compounds by Means of Sodium Amide

CHARLES R. HAUSER AND MARVIN T. TETENBAUM[1]

Received October 24, 1957

Disodio phenylacetic acid prepared by means of two equivalents of sodium amide in liquid ammonia underwent conjugate addition with benzalacetophenone and ethyl cinnamate to give excellent yields of products. Addition of cold acid to the reaction mixture from the α,β-unsaturated ester produced the corresponding di-acid instead of the intermediate mono-acid-ester. Similarly the disodium salt of phenylacetamide gave with ethyl cinnamate under these conditions the mono-acid-amide. However the monosodium salt of ethyl phenylacetate formed with this α,β-unsaturated ester the corresponding diester.

Ivanoff and co-workers[2] have effected the conjugate additions of phenylacetic acid to dypnone and phorone by means of isopropylmagnesium chloride. This Grignard reagent was employed to convert the sodium salt of phenylacetic acid to its magnesium chloride derivative which was condensed with the α,β-unsaturated ketones. The reaction may be illustrated with dypnone (Equation 1).



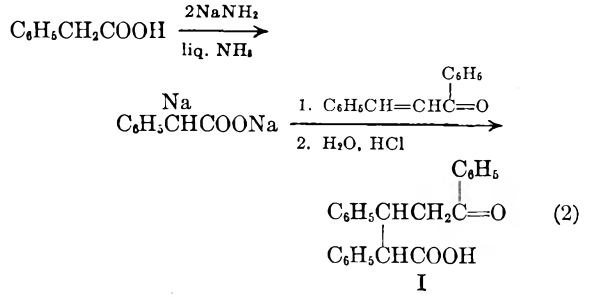
(1)

Although the yield was not given in this reaction, a 75% yield was reported for the corresponding reaction with phorone.[2]

In the present investigation the conjugate additions of phenylacetic acid and certain of its derivatives to benzalacetophenone and ethyl cinnamate were effected by means of sodium amide in liquid ammonia. Two molecular equivalents of this reagent were employed to convert the phenylacetic acid to its disodium derivative which was then condensed with the α,β-unsaturated carbonyl compound. The reaction with benzalacetophenone produced ketone-acid I in excellent yield (Equation 2).

(1) American Cyanamid Company Fellow, 1956–1957.

(2) D. Ivanoff, M. Mihova, and T. Christova, *Bull. soc. chim. France*, [4], **51**, 1321 (1932).

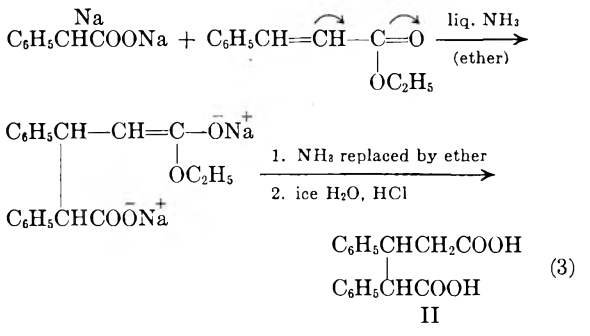


(2)

The product evidently consisted largely of the lower melting of the two possible diastereoisomers of I. In an unsuccessful attempt to effect cyclization of this isomer[3] by means of polyphosphoric acid, the recovered ketone-acid melted at the temperature reported for the higher melting isomer.

The two diastereoisomers of ketone-acid I have previously been prepared[4] by the conjugate addition of methyl phenylacetate with benzalacetophenone by means of sodium methoxide, followed by the hydrolysis of the esters and separation of the resulting isomeric ketone-acids both of which were obtained in these reactions.

The conjugate addition of disodio phenylacetic acid with ethyl cinnamate produced, on adding ice water and acid, diacid II in 95% yield (Equation 3).



(3)

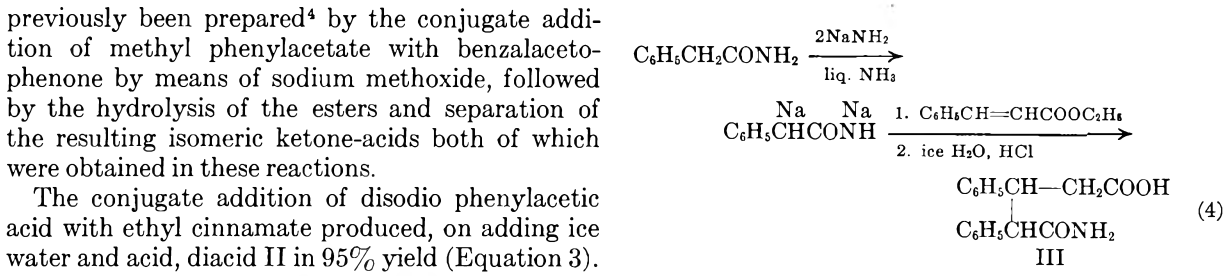
The corresponding mono-acid-ester was presumably an intermediate, but it was not isolated under the above conditions.[5]

Whereas the conjugate addition with benzalacetophenone gave largely one of the diastereoisomers of I, this reaction (Equation 3) produced a mixture of the two possible isomers of II.[6]

Like many Michael-type condensations, the present conjugate addition was realized by means of only a catalytic amount of sodium amide, although the yield of product was lower. Thus, a 46% yield of diacid II was obtained when 20 mole percent of this base was used to effect the ionization of the α-hydrogen of sodium phenylacetate. Actually 1.2 equivalents of sodium amide were employed to one equivalent each of phenylacetic acid and ethyl cinnamate, but one equivalent of this base was neutralized in converting the acid to sodium phenylacetate.

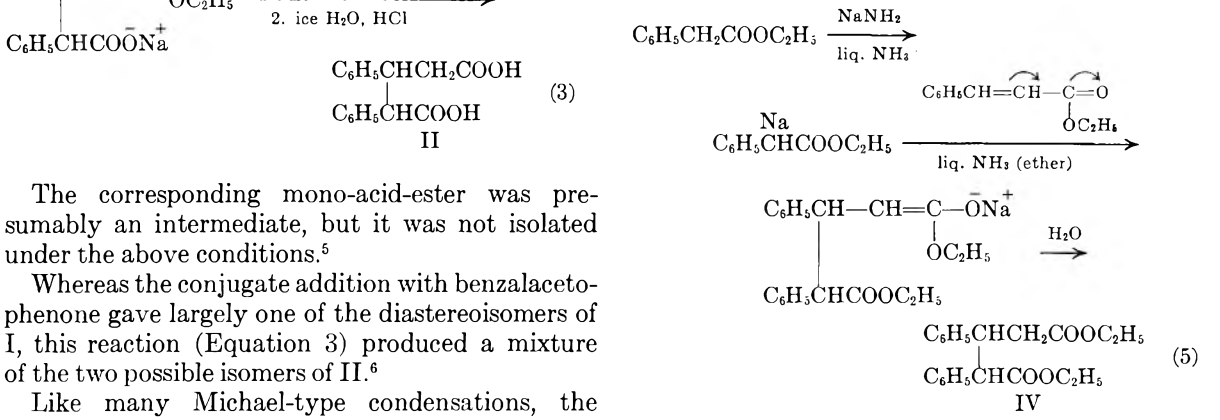
Similarly, disodio phenylacetic acid underwent conjugate addition with benzyl cinnamate to give, after treatment with cold acid, diacid II, and benzyl alcohol.

Also the disodium or dipotassium salt of phenylacetamide underwent conjugate addition with ethyl cinnamate to form the acid-amide III (71–89%) (Equation 4). None of the corresponding ester-amide, which would presumably be an intermediate, was isolated under the condition employed.[5]



(4)

On the other hand, sodio ethyl phenylacetate prepared by means of one equivalent of sodium amide was found to produce with ethyl cinnamate under similar conditions the corresponding diester IV in 65% yield (Equation 5).



(5)

The product apparently consisted largely of the lower melting diastereoisomer of IV. Saponification of this diester IV with approximately one equivalent of potassium hydroxide gave about a 50% yield of diacid II, and none of the corresponding mono-acid-ester was isolated.

The lower melting isomer of diester IV has previously been obtained in low yield from ethyl phenylacetate and ethyl cinnamate employing sodium triphenylmethide.[7] The higher melting isomer of

(3) Treatment of this compound with hydrogen fluoride at room temperature produced an orange powder (m.p. 214–215°) which was not identified.

(4) S. Avery and G. C. Jorgensen, *J. Am. Chem. Soc.*, 52, 3628 (1930).

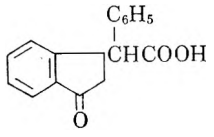
(5) The unexpected ease of hydrolysis of the ester group is being investigated.

(6) D. Lednicer of this laboratory has found, by fractional recrystallizations, that the crude conjugate addition product consists of approximately equal amounts of the two diastereoisomers.

(7) C. R. Hauser and B. Abramovitch, *J. Am. Chem. Soc.*, 62, 1763 (1940).

IV has been obtained in high yield from this conjugate addition using sodium ethoxide.[8]

It should be mentioned that diacid II (isomeric mixture) was cyclized by means of hydrogen fluoride to form apparently hydrindone V (48%).



V

This five membered ring product has previously been obtained from the anhydride of diacid II by means of aluminum chloride.[8,9] Since the anhydride has yielded the lower melting isomer[10] of diacid II on hydrolysis with alkaline carbonate, cyclic product V might have arisen from this isomer.

EXPERIMENTAL[11]

Conjugate addition of phenylacetic acid with benzalacetophenone. To a stirred suspension of 0.2 mole of sodium amide in 300 ml. of liquid ammonia[12] was added 13.6 g. (0.1 mole) of solid phenylacetic acid. After the resulting green solution of the disodium salt of the acid was stirred for 15 min., 20.8 g. (0.1 mole) of solid benzalacetophenone was added, and the stirring continued for 1 hr. The liquid ammonia was evaporated on the steam bath as an equal volume of anhydrous ether was added. The resulting ether suspension was refluxed for 1 hr., and then decomposed with ice water. The mixture, which contained a white precipitate, was filtered, and most of the solid was washed through the filter into the filtrate with dilute potassium hydroxide. The aqueous alkaline layer of the filtrate was separated from the ethereal layer, and acidified in the cold with hydrochloric acid. There was obtained an excellent yield of ketone-acid I, m.p. 185–187° and at 186–187° after two recrystallizations from methanol. This was evidently the lower melting diastereoisomer of I which has been reported to melt at 186–187°.[4] The higher melting isomer of I has been reported to melt at 260–261°,[4] and a mixture of the two isomers at 240°.[4]

When a sample of our product (m.p. 186–187°) was heated with polyphosphoric acid[13] at 125–130° for 30 min., and the reaction mixture then treated with iced hydrochloric acid, there was recovered ketone-acid I melting at 263–265° which was apparently the higher melting isomer.

Conjugate addition of phenylacetic acid with ethyl cinnamate. The disodium salt of phenylacetic acid was prepared from 0.2 mole of sodium amide and 0.1 mole of the acid in 300 ml. of liquid ammonia as described above, and a solution of 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of anhydrous ether was added with stirring. The green color of the disodium salt of the acid was discharged, and a white precipitate was produced. After stirring for 1 hr., the liquid ammonia was replaced by ether (see above), and the resulting ether suspension was refluxed for 30 min. Ice water was then added, and the aqueous alkaline layer was separated and combined with three alkaline extracts of the ether layer. After filtering to remove a small amount of tar, iced hydrochloric acid was added to produce a white precipitate which was dried overnight on the funnel. There was obtained 27 g. (95%) of α,β-diphenylglutaric acid (II) m.p. 190–233°. This mixture of isomers of diacid II was crystallized four times from a mixture of ether and petroleum ether (b.p. 30–60°) to give the higher melting isomer of II, m.p. 228–233° (reported m.p. 226–228°).[10,14]

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 71.97; H, 5.70.

Similar results were obtained when solid ammonium chloride was added to the reaction mixture in liquid ammonia within a few minutes after the ethyl cinnamate was added. The ammonia was then replaced by ether, and cold water and acid added to the resulting ether suspension.

Conjugate addition with catalytic amount of base. To a stirred suspension of 0.12 mole of sodium amide in 300 ml. of liquid ammonia was added 0.1 mole of phenylacetic acid, followed after 15 min. by 0.1 mole of ethyl cinnamate in an equal volume of ether. After 2 hr. the reaction mixture was worked up to give a 46% yield of di-acid II, m.p. 195–198°. Some (34%) ethyl cinnamate was recovered. Regenerated phenylacetic acid was detected.

Conjugate addition of phenylacetic acid with benzyl cinnamate. Benzyl cinnamate was prepared in 92% yield from one mole each of cinnamoyl chloride and benzyl alcohol, the reaction mixture being heated on the steam bath for 1 hr. and then at 200° for 30 min. The ester boiled at 183° at 3 mm. (reported boiling point 195–200° at 5 mm.).[15]

The ester (0.1 mole) in an equal volume of ether was added to a stirred solution of disodio phenylacetic acid in liquid ammonia prepared from 0.1 mole of the acid and 0.2 mole of sodium amide as described above. After 1 hr. the liquid ammonia was replaced by ether, and the resulting suspension stirred for 30 min. Ice water was added, and the layers were separated. The solvent was removed from the ether layer and the residue was distilled *in vacuo* to give a 65% yield of benzyl alcohol, b.p. 83–85° at 5 mm. (reported b.p. 92° at 10 mm.).[16] Acidification of the alkaline aqueous layer precipitated a good yield of di-acid II.

Conjugate addition of phenylacetamide with ethyl cinnamate. To a stirred suspension of 0.2 mole of sodium amide in 300 ml. of liquid ammonia was added 13.5 g. (0.1 mole) of solid phenylacetamide. The resulting bright green solution of the disodium salt of the amide was stirred for 15 min., and 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of ether was then added. The liquid ammonia was replaced by ether, and the resulting ether suspension was stirred for 1 hr. Ice water was added, and the aqueous alkaline layer (after filtering) was acidified with iced hydrochloric acid to precipitate 20 g. (71%) of mono-acid-amide III, melting at 196–197°. One recrystallization from ethanol raised the melting point to 204–205° (reported m.p. 200–205°).[10] A mixed melting point with diacid II was depressed to about 185°.

When the conjugate addition of phenylacetamide with ethyl cinnamate was similarly effected by means of potassium amide (instead of sodium amide), there was obtained an 89% yield of the mono-acid-amide III, m.p. 204–205°.

(8) G. M. Badger, J. E. Campbell, and J. W. Cook, *J. Chem. Soc.*, 1087 (1949).

(9) For another preferential five-membered ring cyclization (over the usual six-membered ring cyclization) see D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **80**, 3409 (1958).

(10) S. Avery and W. D. Maclay, *J. Am. Chem. Soc.*, **51**, 2833 (1929).

(11) Melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

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

(13) We are indebted to the Victor Chemical Works, Chicago, Ill., for a generous sample of polyphosphoric acid.

(14) The lower melting isomer of II is reported to melt at 208–210°; see Ref. 10.

(15) See Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1953, Vol. I, p. 272.

(16) J. Meisenheimer, *Ber.*, **41**, 1420 (1908).

A 2 g. sample of the mono-acid-amide III readily dissolved in cold dilute potassium hydroxide solution. On refluxing this solution for 3 hr., ammonia was evolved, and there was obtained, on acidification of the cooled solution, 1.6 g. (80%) of diacid II, m.p. 216–217°. This melting point was not depressed on admixture with diacid II prepared from the conjugate addition of phenylacetic acid and ethyl cinnamate as described above. A mixed melting point with the mono-acid-amide III was depressed to 185–190°.

Conjugate addition of ethyl phenylacetate with ethyl cinnamate. To a stirred solution of 0.1 mole of sodium amide in 300 ml. of liquid ammonia was added 16.4 g. (0.1 mole) of ethyl phenylacetate in an equal volume of ether, and the resulting solution stirred for 15 min. A solution of 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of ether was added, and the ammonia was replaced by ether. The resulting ether suspension was refluxed on the steam bath for 30 min., cooled, and decomposed with ice water. The ethereal layer (with which was combined three ether extracts of the aqueous layer) was dried over Drierite, and the solvent removed. The residue was distilled *in vacuo* to give 6.5 g. of recovered ethyl cinnamate, leaving a residue that solidified after standing at room temperature for one day. This solid was recrystallized from ethanol to give 22 g. (65%) of white diester IV, m.p. 76–77° (lit. m.p. 75–75.5°).[7] The higher melting isomer of diester IV is reported to melt at 92–93°.[17]

A 6 g. sample of diester IV was refluxed 6 hr. with an aqueous solution of potassium hydroxide containing approximately an equimolar amount of this base. After cooling and removing a small amount of gummy residue, the alkaline solution was acidified with iced hydrochloric acid. The resulting white precipitate was recrystallized from a mixture of ether and petroleum ether (b.p. 30–60°) to give 2.5 g. (50%) of diacid II, m.p. 193–196°. This melting point was not depressed on admixture with a sample of diacid II.

Cyclization of diacid II. A solution of 5 g. of diacid II in 150 g. of liquid hydrogen fluoride contained in a polyethylene bottle was allowed to stand in a hood at room temperature overnight, during which time the hydrogen fluoride had evaporated. The resulting gummy residue was dissolved in ether, and the yellow solution was poured into dilute potassium hydroxide. The two layers were separated. The orange-red aqueous alkaline layer was cooled in an ice bath and acidified with iced hydrochloric acid to precipitate 4.5 g. of a white semi-solid which was presumably hydrindone V. This product resisted crystallization from the usual organic solvents, but it readily gave a yellow-orange 2,4-dinitrophenylhydrazone in 48% over-all yield. After two recrystallizations from ethanol, this derivative melted at 262–263° (softened at 258°) in agreement with the melting point reported for it when hydrindone V was prepared by the cyclization of the anhydride of II by means of aluminum chloride.[8]

Anal. Calcd. for $C_{23}H_{18}O_6N_4$: C, 61.88; H, 4.06; N, 12.55. Found: C, 61.66; H, 4.17; N, 12.75.

(17) W. Borsche, *Ber.*, **42**, 4497 (1909).

DURHAM, N. C.

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

The Stability of Mixed Carboxylic-Carbonic Anhydrides

D. STANLEY TARBELL AND NORMAN A. LEISTER[1]

Received February 3, 1958

Preparation of a considerable number of mixed carboxylic-carbonic anhydrides shows that they are more stable than previously supposed. Some are stable crystalline solids, and many of the liquid ones can be distilled without decomposition. They have been characterized by analysis, except in the case of some liquids which could not be distilled, and by the preparation of solid derivatives.

The mixed carboxylic-carbonic anhydrides, RCOOCOOR, have been widely used for the preparation of amide and particularly of peptide linkages.[2,3] It has also been found that they can be used for numerous acylation reactions on carbon, such as acylation of malonic and acetoacetic ester,[4] the formation of ketones from organocadmium compounds,[4] and preparation of diazoketones from diazomethane.[4,5] In the recent work in which the mixed anhydrides were utilized,[2–5] generally no attempts were made to isolate them, and the impression is given that they are unstable compounds.[2,3] In early work,[6] several mixed anhydrides were prepared from the acid and ethyl chlorocarbonate; they were described as unstable oils and were not characterized suitably. More recently, the mixed anhydride has been isolated from benzylpenicillin in the form of a rather unstable gum.[7] Small yields of the mixed anhydrides III and IV have been obtained by oxidation of α-keto esters I and II by

(1) Monsanto Fellow, 1956–57.

(2) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951)

(3) *E.g.*, J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951); **74**, 676 (1952); J. R. Vaughan, Jr., and J. A. Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953); **76**, 2474 (1954); V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953); **76**, 3107 (1954); B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(4) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).

(5) B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Org. Chem.*, **18**, 161 (1953).

(6) Knoll and Co., German Patent **117,267** [*Chem. Zentr.*, **72**, 347 (1901); *Friedländer*, **VI**, 146].

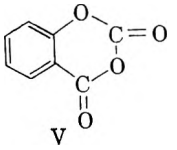
(7) R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jensen, M. E. Trevelt, and G. B. Webb, *J. Chem. Soc.*, 3733 (1953); D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3636 (1953).

peracids; the products were purified by fractional distillation, and showed satisfactory analyses.[8]

$$\text{RCOCOOEt} \xrightarrow{\text{R'CO}_3\text{H}} \text{RCOOCOOEt}$$

I, R = C_6H_5 III, R = C_6H_5
II, R = CH_3 IV, R = CH_3

Cyclic anhydrides, of the Type V, derived from salicylic or glycolic acid, have been prepared, and show reasonable stability.[9] Nevertheless, as far as we have been able to discover, there was no



V

crystalline mixed anhydride of the type III–IV known, and only the examples mentioned above appear to have been obtained pure.

We were therefore surprised to isolate[10] a stable crystalline compound, whose analysis, infrared spectrum, and conversion to the amide showed that it had the structure VI. This compound was obtained from an attempt to regenerate fumagillin methyl ester by an esterification using the mixed anhydride VI and the alcohol moiety of fumagillin.[11] The mixed anhydride VI was pre-

$$C_{16}H_{23}O_3OH + C_2H_5OC(=O)-O-C(=O)(CH{=}CH)_4COOCH_3 \longrightarrow$$

VI

$$C_{16}H_{25}O_3-O-C(=O)(CH{=}CH)_4COOCH_3 + CO_2 + C_2H_5OH$$

pared in the usual way from methyl hydrogen decatetraenedioate[12] and was used *in situ;* the mixed anhydride was isolated from the reaction mixture.

This result suggested that mixed anhydrides derived from high-melting carboxylic acids might be stable compounds. Furthermore, the availability of stable pure mixed anhydrides would permit the investigation of a number of problems of both synthetic and mechanistic character, which would increase our knowledge of the chemistry of this class. We have therefore undertaken a survey of the preparation of representative mixed anhydrides, the results of which are shown in Table I.

The assignment of the mixed carbonic-carboxylic anhydride structures to these materials is based on the elementary analysis, the typical anhydride double peaks (separated by about 60 cm.$^{-1}$) in the carbonyl region of the infrared, and, in a number of cases, the preparation of solid derivatives. The mixed anhydrides can decompose by the following paths[13]

$$RC(=O)-O-C(=O)-O-C_2H_5 \longrightarrow RC(=O)-OC_2H_5 + CO_2 \quad (A)$$

$$\longrightarrow RC(=O)-O-C(=O)R + C_2H_5OC(=O)-OC_2H_5 + CO_2 \quad (B)$$

The occurrence of either of these modes of reaction in our samples would be apparent from the elementary analysis, since both paths A and B involve elimination of carbon dioxide; furthermore, A yields the ester $RCOOC_2H_5$, and B gives the dialkyl carbonate $C_2H_5O-COOC_2H_5$. These types have normal ester carbonyl absorption in the infrared, and their absence in the mixed anhydride samples is clear from the infrared spectra of these samples.

The method of preparation of the mixed anhydrides involved washing with aqueous bicarbonate solution, and it is apparent that this treatment does not decompose the anhydrides. The mixed anhydrides can therefore be made at room temperature and without particular regard to the exclusion of water. This was demonstrtaed by the preparation of the propionic anhydride, in refluxing ether and with undried undistilled reagents. The product prepared under these conditions gave the same yield of propionanilide as the product prepared at 0° under anhydrous conditions.

It is possible, of course, that mixed anhydrides derived from acylaminoacids, which are the ones most carefully investigated heretofore,[2,3] are more unstable than the unaminated types described here.

EXPERIMENTAL[14]

Preparation and isolation of carboxylic-carbonic anhydrides. A dry ethereal solution of equimolar quantities of the

(8) P. Karrer and F. Haab, *Helv. Chim. Acta,* **32,** 950 (1949).

(9) L. A. Dupont, French Patent **771,653** [*Chem. Abstr.,* **29,** 816 (1935)]; A. E. Chichibabin, *Compt. rend.,* **213,** 355 (1941); W. H. Davies, *J. Chem. Soc.,* 1357 (1951). A cyclic anhydride similar to V has been obtained by D. Burn and W. Rigby, *J. Chem. Soc.,* 2967 (1957) by degradation of marrubiin.

(10) We are indebted to Dr. John A. Price for this experiment.

(11) For studies on the structure of fumagillin, see J. R. Schenck, M. P. Hargie, and A. Isarasena, *J. Am. Chem. Soc.,* **77,** 5606 (1955); D. S. Tarbell, P. Hoffman, H. R. Al-Kazimi, G. A. Page, J. M. Ross, H. R. Vogt and B. Wargotz, *J. Am. Chem. Soc.,* **77,** 5610 (1955); J. M. Ross, D. S. Tarbell, W. E. Lovett and A. D. Cross, *J. Am. Chem. Soc.,* **78,** 4675 (1956).

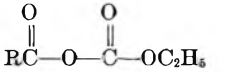
(12) C. J. Brown and J. K. Landquist, *Chem. and Ind. (London),* 973 (1953).

(13) J. Herzog, *Ber.,* **42,** 2557 (1909); A. Einhorn, *Ber.,* **42,** p. 2772; T. Wieland and H. Bernhard, *Ann.,* **572,** 190 (1951).

(14) Melting points are uncorrected. Microanalyses are by Miss Annette Smith and Microtech Laboratories. Yields are based on starting materials taken and do not take into account any recovered starting material.

TABLE I

MIXED CARBOXYLIC-CARBONIC ANHYDRIDES



R	M.P. or B.P., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Infrared Bands, Cm.$^{-1}$	Stability[a]	Derivative, RCONHR^1 R^1
$CH_3OOC(CH{=}CH)_4$	120–123	$C_{14}H_{16}O_6$	59.99	59.72	5.75	5.79	1792, 1727, 1701	+++	H[b]
$CH_3OOC(CH{=}CH)_2$	66–67.5	$C_{10}H_{12}O_6$	52.63	53.08	5.30	5.37	1808, 1732, 1712	+++	
$CH_3(CH{=}CH)_2$	148 (20 mm.) n_D^{20} 1.4980	$C_9H_{12}O_4$	58.69	59.34	6.57	6.93	1792, 1727	++	C_6H_5, m.p. 154–156°[c]
$C_6H_5CH{=}CH$	n_D^{25} 1.5529[d]	$C_{12}H_{12}O_4$	65.44	66.32	5.49	5.56	1797, 1730	+	C_6H_5, m.p. 152–154°[e]
$C_2H_5OOCCH{=}CH$ (*trans*)	n_D^{26} 1.4465	$C_9H_{12}O_6$	50.00	51.75[f]	5.60	5.69	1810, 1755, 1722	++	C_6H_5, m.p. 107.5–109°[g]
$CH_3OOCCH{=}CH$ (*cis*)	n_D^{26} 1.4481	$C_8H_{10}O_6$	47.53	48.31[f]	4.99	4.93	1812, 1733	++	[h]
$CH_3CH{=}CH$ (*trans*)	55–56 (0.5 mm.) n_D^{26} 1.4392	$C_7H_{10}O_4$	53.16	53.49	6.37	6.40	1798, 1730	++	C_6H_5, m.p. 112.5–114.5°[i]
$C_6H_4NO_2$ (*p*)	56–57	$C_{10}H_9NO_6$	50.21	50.30	3.79	3.94	1802, 1735	+++	
1-Naphthyl	[j]	$C_{14}H_{12}O_4$	68.84	68.86[f]	4.95	5.14	1795, 1735	++	[k]
$C_6H_4COOCH_3$(*p*)	48–50	$C_{12}H_{12}O_6$	57.14	57.10	4.80	5.10	1798, 1732, 1716	+++	
$C_6H_4COOC_4H_9$(*o*)	n_D^{25} 1.4915	$C_{15}H_{18}O_6$	61.21	61.13	6.17	6.39	1815, 1754, 1721	++	C_6H_5, m.p. 105–107°[l]
$(CH_3)_2CHCH_2$	44–54 (0.5 mm.) n_D^{26} 1.4053–1.4079	$C_8H_{14}O_4$	55.16	55.20	8.10	8.15	1810, 1755	++	C_6H_5, m.p. 104–106°[m]
CH_3CH_2	65–78 (20 mm.) n_D^{27} 1.3965–1.3980	$C_6H_{10}O_4$	49.31	50.37	6.90	7.13	1815, 1750	++	C_6H_5, m.p. 102–104°
CH_3	64–67 (20 mm.) n_D^{26} 1.3911	$C_5H_8O_4$	45.45	45.51	6.10	6.25	1827, 1755	++	C_6H_5, m.p. 112–114°[n]

[a] +, noticeable decomposition in a few days; ++, noticeable decomposition in a few weeks; +++, stable, all referring to room temperature. [b] See Experimental. [c] Reported by O. Doebner and A. Wolff, *Ber.*, **34**, 2222 (1901), as 153°. [d] Sample decomposed on attempted distillation; after standing several days, cinnamic anhydride, m.p. 131–134°, was deposited. Analysis was on undistilled material. [e] Reported by W. Autentrieth, *Ber.*, **34**, 186 (1901) as 150°. [f] Undistilled sample; distillation caused decomposition. [g] Calcd. for $C_{12}H_{13}NO_3$; C, 65.74; H, 5.98. Found: C, 65.76; H, 6.00. [h] Attempted preparation of the anilide gave a mixture. [i] Reported by W. Autentrieth and P. Spiess, *Ber.*, **34**, 189 (1901) as 115°. [j] Attempted distillation gave ethyl carbonate and 1-naphthoic anhydride. [k] Treatment with aniline gave a mixture of 1-naphthoic anilide, m.p. 161–163° and ethyl *N*-phenylcarbamate, m.p. 48.5–50°. [l] Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44. Found: C, 72.59; H, 6.47. [m] Reported by A. Crossley and W. Perkin, *J. Chem. Soc.*, **73**, 16 (1898) as 109–111°. [n] P. Karrer and F. Haab, *Helv. Chim. Acta*, **32**, 957 (1949), give the b.p. as 44–52° (9 mm.).

pure acid and freshly distilled triethylamine was cooled to 0° in an ice bath. With stirring, an equivalent amount of ethyl chlorocarbonate was slowly added so that the temperature remained near 0°. The mixture was stirred an additional 1.5 hr. during which time it slowly warmed to room temperature. The amine salt was filtered (nearly quantitative yield in every case) and washed with ether. The combined filtrate was washed with sodium bicarbonate solution and water, and after drying over magnesium sulfate was evaporated under vacuum at room temperature. The crystalline mixed anhydrides were recrystallized for analysis from ether–petroleum ether or benzene–petroleum ether.

Methyl hydrogen decatetraene-dioate was prepared[12] by the action of methanolic sodium hydroxide on fumagillin and melted at 209–210°; the reported[12] value is 217–218°.

Methyl hydrogen decatetraene-dioic acid chloride and amide. A mixture of 0.50 g. of methyl hydrogen decatetraenedioate, 0.6 g. of phosphorus pentachloride, and 10 cc. of petroleum ether was refluxed for 1.75 hr. The solvent and phosphorus oxychloride were removed under reduced pressure, yielding 0.28 g. of product, m.p. 151–154° with decomposition.

Anal. Calcd. for $C_{11}H_{11}ClO_3$: C, 58.28; H, 4.90. Found: C, 58.32; H, 5.05.

Treatment of a chloroform solution of the ester acid chloride above with ammonia gas gave a white precipitate of the corresponding *amide*, m.p. 209–210° after recrystallization from aqueous methanol. This product gave no depression on mixed melting point with the amide prepared by action of ammonia gas on the mixed anhydride VI.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32. Found: C, 63.33; H, 6.50.

ROCHESTER, N. Y.

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

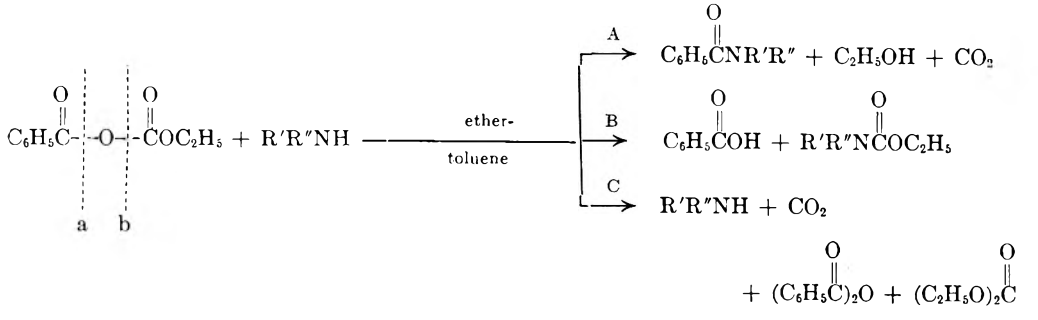
Action of Secondary Amines on Mixed Carboxylic-Carbonic Anhydrides; the Factors Favoring Urethan Formation Instead of Amide Formation[1]

NORMAN A. LEISTER[2] AND D. STANLEY TARBELL

Received February 3, 1958

The action of a series of ten secondary amines on benzoic-carbonic anhydride leads in each case to urethan formation in addition to amide formation, with urethan predominating in most cases. Increasing the steric hindrance around the amino nitrogen increases the ratio of urethan to amide. A series of mixed anhydrides in which the carboxylic acid component was varied was treated with *N*-methylaniline. Pivalic acid and aromatic acids gave more urethan than amide; other acids, without alkyl or aryl substitution on the α-carbon, gave more amide than urethan. The results are discussed in the light of other work on reactions of unsymmetrical anhydrides.

It has been shown that mixed carboxylic-carbonic anhydrides are very useful for acylation of primary amines to form amides,[1] and for formation of phthalimides from phthalamic acids,[3] as well as for various acylations on carbon.[1,4] We were therefore surprised to find that an attempt to prepare the bisamide from *N*-methylaniline and a phthalic acid derivative gave a very unsatisfactory result. A study of the action of *N*-methylaniline on benzoic-carbonic anhydride showed that the main product was *N*-methyl-*N*-phenylcarbamate, instead of the expected *N*-methylanilide. The action of a series of representative secondary amines on this mixed anhydride was therefore studied, as well as the action of *N*-methylaniline on a series of mixed anhydrides in which the carboxylic acid component was varied. The results show that secondary amines usually react with mixed carbonic anhydrides to form a mixture of urethan and amide; the former may predominate, depending on the compounds involved. These results may be useful in considering the mixed carbonic anhydrides for synthetic operations.



(1) Previous papers in this field: (*a*) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957); (*b*) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958). Reference 1*b* contains adequate references to the earlier literature.

(2) Monsanto Fellow, 1956–1957.

(3) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(4) J. A. Price and D. S. Tarbell, *Org. Syntheses*, **37**, 20 (1957).

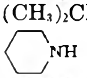
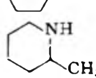
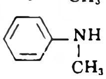
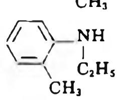
The possible reactions between a secondary amine and benzoic-carbonic anhydride are indicated above.[5]

Path A involves attack of the amine nitrogen on the carboxylic carbonyl, with splitting at "a" to give the amide. In path B, the carbonate carbonyl is attacked by the amine, and the bond at "b" is broken, resulting in urethan formation and regeneration of benzoic acid. Path C corresponds to no reaction with the amine, but instead, disproportionation of the mixed anhydride leads to benzoic anhydride, diethyl carbonate, and carbon dioxide.

A series of secondary amines was allowed to react with the anhydride under standard conditions, the products were separated and purified by ordinary methods, and percentage yields were determined. The results are shown in Table I. All of the products obtained corresponded to those expected from paths A, B, and C.

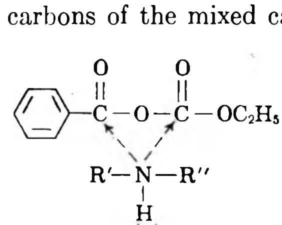
TABLE I

REACTIONS OF SECONDARY AMINES WITH BENZOIC-CARBONIC ANHYDRIDE

	Products				
		% B		% C	
Amine	% A (Amide)	(Urethan)	(Acid)	(Unreacted amine)	%A/%B
$(CH_3)_2NH$	28[a]	19[a]	43	—[b]	Ca. 1.0
$(C_2H_5)_2NH$	29	49	58	—	0.59
$(CH_3)_2CH_2NH$	4	44	40[c]	40[c]	0.09
	50	34	39	—	1.5
	15	67	67	10	0.22
	16	66	68	4	0.24
	9	63	54	24	0.14
$C_2H_5OOCCH_2N(CH_3)H$	9.5	72	80	—	0.13
$(C_6H_5)_2NH$	4	0(1)	0(1)	86	4

[a] These yields are lower than the actual amount of material generated in the reaction. Losses were due to the relatively high volatility and water solubility of these compounds. [b] The dash (—) signifies that the yield was small and could not be conveniently determined. [c] Isolated as diisopropylamine benzoate.

A brief inspection of the results in Table I indicates that the reaction of secondary amines with benzoic-carbonic anhydride is not generally a good method for the preparation of amides. The particularly low yield of the amide derived from ethyl sarcosinate would perhaps indicate that the procedure is also inapplicable to the preparation of *N*-substituted peptide linkages, although mixed anhydrides other than benzoic-carbonic anhydride may give better yields. Nevertheless, most amino acids have bulky residues on the α-carbon atom and, since such substitution seems to hinder amide formation markedly, the general usefulness of the method is questionable. By analogy with the mechanisms proposed for nucleophilic attack on carboxylic anhydrides,[6,7] it is assumed that there is involved in these reactions a rate-determining nucleophilic attack of the amine nitrogen on one of the carbonyl carbons of the mixed carbonic anhy-



dride. Competition for the amine nitrogen is thereby established between the two carbonyl carbon atoms. Since paths A and B are not reversible and the products of each are not interconvertible, the relative amounts of products formed from the two cannot be thermodynamically controlled but rather must be kinetically controlled. Thus, the amide to urethan ration (A/B), as given in Table I, is a measure of the relative rates of attack of the amine on one or the other of the two carbonyl carbon atoms.

Table I shows a sharp decrease in the A/B ratios as methyl groups are added to the α-carbons of the amines in the series dimethyl-, diethyl-, diisopropyl-amine. A similar decrease is observed in the piperidine–2-methylpiperidine pair, and the *N*-methylaniline – *N*-ethyl-2-methylaniline pair. The rate of reaction according to path A is being diminished more than that according to path B. This is most plausibly attributed to the steric effect of increasing substitution around the nitrogen, and not to changes in the intrinsic nucleophilicity of the nitrogen. Path B would be expected to be less sensitive to changes in steric requirements than path A. It is known that increasing substitution in alcohols diminishes the rate of acylation by acid chlorides.[8]

Furthermore, Hall has recently shown[9] the rate of acylation of amines by ethyl chlorocarbonate to be very sensitive to increasing substitution around the amino nitrogen; the relative rates of reaction of piperidine, 2-methylpiperidine, *s*-butylamine and *t*-butylamine with this acylating agent are approximately 10^4, 10^2, 10, and 1. It has been

(5) W. H. Davies, *J. Chem. Soc.*, 1357 (1951), observed formation of a carbamate from aniline and the anhydride of *O*-carboxysalicylic acid.

(6) A. R. Emery and V. Gold, *J. Chem. Soc.*, 1456 (1950).

(7) D. B. Denney and M. A. Greenbaum, *J. Am. Chem. Soc.*, **79**, 3701 (1957).

(8) J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, **47**, 837 (1925); J. F. Norris and F. Cortese, *J. Am. Chem. Soc.*, **49**, 2640 (1927).

(9) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5439 (1957).

shown that the catalytic effect of tertiary amines on the hydrolysis of acetic anhydride is diminished by increasing substitution on the α-carbon of the amines.[10]

The behavior of diphenylamine does not follow the above pattern; it reacts only slightly, but gives exclusively amide and no urethan. This is possibly connected with its low basicity.

In order to gain some insight into the effect of changes in the carboxylic portion of the mixed anhydride in these reactions, *N*-methylaniline was treated with a series of carboxylic-carbonic anhydrides in which the carboxylic group was varied in size and conjugation. The same standard conditions and methods of product separation were employed as in the study just described, and the results are given in Table II.

TABLE II

REACTIONS OF *N*-METHYLANILINE WITH CARBOXYLIC-CARBONIC ANHYDRIDES

$$RCOOCOOC_2H_5 + C_6H_5N(CH_3)-H \xrightarrow{\text{ether}} \text{Products}$$

	Products				
R—	% A (Amide)	% B (Urethan)	% B (Acid)	(Unreacted amine)	%A/%B
iso-C_4H_9—	64	0 (<1)	0 (<1)	12	>64
$C_6H_5CH_2CH_2$—	75	8.4	15	5	8.9
C_6H_5CH=CH—	63	17	20	5	3.7
$CH_3(CH$=$CH)_2$—	49	20	29	4	2.5
tert-C_4H_9	0 (<1)	32	1[b]	65	<0.03
C_6H_5—	16	66	68	5	0.24
p-$O_2NC_6H_4$	29	39	38	11	0.74
p-$CH_3OC_6H_4$—	8[a]	47	58	41	0.17

[a] Not isolated. [b] Generated pivalic acid reacted with mixed anhydride to give 88% of pivalic anhydride.

It is immediately evident that good yields of *N*-methylanilides can indeed be obtained with certain carboxylic-carbonic anhydrides. Others, however, such as pivalic- and benzoic-carbonic anhydrides give mainly the urethan. In the first four cases listed the degree of extended conjugation is varied widely and yet the yields of amides change very slightly. On the other hand, a change in the extent of α-substitution, such as that in going from isovaleric- to pivalic-carbonic anhydride, effects an absolute reversal of reaction course. Seemingly, then, the degree of conjugated unsaturation is of relatively little importance as compared with the degree of substitution of the α-carbon atom in the carboxylate grouping. On the basis of the results given in Tables I and II it can thus be concluded that this method is most probably suitable for the preparation of tertiary amides if the secondary amine does not contain a high degree of steric bulk about the nitrogen atom and if the α-carbon of the carboxylate grouping is not highly branched.

A comparison of the results with hydrocinnamic, cinnamic, and sorbic anhydrides shows that conjugation decreases the reactivity of the carbonyl carbon, relative to the carbonate carbonyl. This is in agreement with observations[11] which show that α,β-unsaturated esters are hydrolyzed by base at a somewhat slower rate than the corresponding saturated esters.

The reactivity of the carboxyl carbonyl in the benzoic anhydride is increased by the presence of the electron-withdrawing *p*-nitro group, and is decreased by the electron-donating *p*-methoxyl group. These effects on the reactivity are similar to those shown by electron-donating and -withdrawing groups on the rate of alkaline hydrolysis of esters of substituted benzoic acids,[12] and may be taken as support for the assumption that in the present reactions, as in the alkaline hydrolysis of esters, the rate-determining step is the attack of the nucleophile on the carbonyl carbon atom.

It is apparent that in general the rates of reaction by paths A and B are of the same order of magnitude; path A can be slowed down markedly by changes in both the environment of the carboxyl carbonyl group and the nature of the attacking nucleophile. The retardation is doubtless due mainly to steric effects.

EXPERIMENTAL[13]

Reactions of secondary amines with benzoic-carbonic anhydride. A solution of 12.2 g. (0.1 mole) of benzoic acid and 10.1 g. (0.1 mole) of dry triethylamine in 150 cc. of dry toluene and 50 cc. of dry ether was cooled to −5 to 0° in an ice salt bath. With stirring, 10.8 g. (0.1 mole) of ethyl chlorocarbonate was added from a Dry Ice-cooled addition funnel at such a rate that the temperature did not exceed 0°. The mixture was stirred for 0.5 hr. at this temperature. The secondary amine (0.1 mole) was then added from the Dry Ice-cooled addition funnel (solid amines were dissolved in ether) and the mixture stirred another 0.5 hr. at 0°. After warming to room temperature overnight, the triethylamine hydrochloride was filtered, washed several times with ether and dried. An essentially quantitative yield (95–99%) was obtained in each case.

The filtrate was in general washed with dilute hydrochloric acid, then with saturated sodium bicarbonate solution, and finally with water. Acidification of the bicarbonate solution yielded the benzoic acid, which was collected and weighed. The organic solution was dried and distilled under reduced pressure. The benzamides and carbamates obtained in this way, which were known compounds, were found to agree satisfactorily in physical properties with those reported in the literature. The infrared spectra were determined in some cases, and the carbonyl frequencies agreed with the expected values. The reactions yielding new compounds are described below.

(10) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409 (1953).

(11) P. Heinänen, *Ann. Acad. Sci. Fennicae, Ser. A, II*, No. 9 (1943); *Chem. Abstr.*, **40**, 3672 (1946).

(12) C. K. Ingold and W. S. Nathan, *J. Chem. Soc.*, 222 (1936); E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

(13) See footnote 14 of reference 1b.

Diisopropylamine. The precipitated triethylamine hydrochloride was filtered at 0°, after which the diisopropylamine was added to the filtrate and the reaction mixture stirred 0.5 hr. at the low temperature. After warming to room temperature overnight, the solution had deposited 8.9 g. (40%) of diisopropylamine benzoate, m.p. 132–154°. (Recrystallization of this material from ethanol-ether did not change the melting point behavior, which was also exhibited by an authentic sample prepared by addition of diisopropylamine to benzoic acid in ether.) Washing the reaction filtrate with dilute acid and base gave no isolable unreacted amine or regenerated benzoic acid. Fractional distillation of the neutral material yielded 7.65 g. (44%) of ethyl *N,N*-diisopropylcarbamate, b.p. 83–87.5°/20 mm., n_D^{20} 1.4294.

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05. Found: C, 62.72; H, 11.02.

Further distillation produced 1.0 g. of *N,N*-diisopropylbenzamide, b.p. 164–174°/20 mm., which partially solidified on standing. After several recrystallizations from ligroin it had m.p. 69–71° (0.8 g., 4%).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.29: H, 9.63.

Further distillation afforded 4.1 g. (36%) of benzoic anhydride.

2-Methylpiperidine. Extraction of the filtered reaction solution with dilute hydrochloric acid gave about 1 g. (10%) of unreacted 2-methylpiperidine. Extraction with sodium bicarbonate solution yielded 8.15 g. (67%) of regenerated benzoic acid, m.p. 121–123°. Drying and removal of the solvent from the remaining neutral solution afforded a colorless liquid, which upon distillation produced 11.5 g. (67%) of the colorless liquid *N*-carbethoxy-2-methylpiperidine, b.p. 53–57°/0.3 mm., n_D^{25} 1.4561 to 1.4579.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.00. Found: C, 62.45; H, 9.83.

Further distillation of the residue gave rise to 3.7 g. of a viscous liquid, b.p. 127–134°/0.3 mm., which did not crystallize. Chromatography on acid-washed alumina and elution with 50% ether-ligroin gave a total of 3.0 g. (15%) of colorless prisms of *N*-benzoyl-2-methylpiperidine, m.p. 45.5–48°.[14]

Ethyl sarcosinate. Washing of the filtered reaction solution with dilute hydrochloric acid yielded only a trace (1%) of unreacted amine. Sodium bicarbonate extraction gave 6.5 g. (80% from 0.067 mole of reactants) of benzoic acid. Fractionation of the dried, neutral solution afforded 9.1 g. (72%) of product, b.p. 118–122° (20 mm.), n_D^{27} 1.4290 to 1.4295.

(14) H. Bunzel, *Ber.*, 22, 1054 (1889), reports a m.p. 44–45°.

Anal. Calcd. for $C_8H_{15}NO_4$: C, 50.78; H, 7.99. Found: C, 51.01; H, 8.47.

The residue of the above distillation was redistilled at a lower pressure to give 1.4 g. (9.5%) of ethyl *N*-benzoylsarcosinate, as a viscous oil, b.p. 130–137° (0.5 mm.) which slowly crystallized on standing (m.p. 37.5–40.5°).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 64.88; H, 6.94.

Reactions of N-methylaniline with carboxylic-carbonic anhydrides. A solution of 0.1 mole of the pure acid and 10.1 g. (0.1 mole) of freshly distilled triethylamine in 200–300 cc. of dry ether or toluene was cooled to −5 to 0° in an ice salt bath. To this stirred solution was added 10.8 g. (0.1 mole) of ethyl chlorocarbonate from an addition tube cooled with Dry Ice. The mixture was stirred 0.5 hr. after the addition was complete. Freshly distilled *N*-methylaniline (10.7 g., 0.1 mole) was then added from the cooled addition tube, and after another 0.5 hr. stirring at 0°, the mixture was allowed to warm to room temperature overnight. The precipitated triethylamine hydrochloride was filtered, washed, and dried, and weighed 12.5–13.5 g. (91–97%). The filtrate was washed three times with dilute hydrochloric acid, five times with saturated sodium bicarbonate solution and once with water. Addition of sodium hydroxide to the acid washes precipitated the unreacted amine. Acidification of the basic washes yielded the regenerated acids which were filtered and dried in the cases of the solid acids or extracted with ether in the cases of the liquid acids. Their identification was established by melting points or infrared spectra. The neutral solution was dried, and after removal of the solvent, was in most cases fractionally distilled. The products formed, the amides, ethyl *N*-methyl-*N*-phenylcarbamate and the symmetrical acid anhydrides, if present, were identified by their boiling point, refractive index, or melting point, and by their infrared spectra. In order to save space the details of separation and identification are omitted.

Sorbic-carbonic anhydride. Upon standing a few minutes, the neutral yellow oil as above, (20.5 g.) deposited 7.3 g. of colorless needles, which were recrystallized from ligroin, m.p. 87.7–88.7°. Cooling of the mother liquors in ligroin gave another 2.6 g. (total yield, 49%). The analytical sample was recrystallized from hexane and had m.p. 87–88°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.54; H, 7.76.

Distillation of the mother liquors yielded 3.5 g. (20%) of ethyl *N*-methyl-*N*-phenylcarbamate, b.p. 136–139° (20 mm.), n_D^{20} 1.5125 to 1.5143.

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[CONTRIBUTION FROM THE NORTHERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Reactions of Conjugated Fatty Acids. VII. Catalytic Cyclization and Aromatization of *cis,trans*-Octadecadienoic Acid with Selenium[1]

H. M. TEETER, E. W. BELL, AND M. J. DANZIG[2]

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When *cis,trans*-conjugated methyl linoleate was heated at 250° with selenium, the product consisted of a mixture of isomeric *cis*- and *trans*-octadecenoates and cyclized material that appeared to be a mixture of dialkylbenzene and dialkylcyclohexene and could be converted to *o*-phthalic acid in 54% yield. In the presence of hydrogen acceptors, the ratio of octadecenoate to cyclic product was decreased. Results of a kinetic study suggest that the first step in the reaction is a rapid isomerization of *cis,trans*-conjugated methyl linoleate to the *trans,trans* isomer and that it is the latter that cyclizes.

During studies[3] of the use of selenium as a catalyst in preparing Diels-Alder adducts from dienophiles and *cis,trans*-conjugated methyl linoleate, it was observed that when the *cis, trans*-conjugated ester was heated to 250° with selenium, but in the absence of a dienophile, it was converted to a material no longer containing significant amounts of diene conjugation. At first it was presumed that polymerization could account for this result, but when it was found that the reaction product left a negligible residue upon conventional vacuum distillation, it was evident that a reaction of unanticipated nature had taken place. This paper reports the results of our investigation of the effect of selenium upon *cis, trans*-conjugated methyl linoleate.

The reaction product obtained by heating *cis, trans*-conjugated methyl linoleate with selenium at 250° was separated by complexing with urea into a complex-forming fraction (A, 67%) and a non-complex-forming fraction (B, 31%). On the basis of iodine number, ultraviolet and infrared spectra, fractional crystallization of its component fatty acids, and the dibasic acids resulting from oxidation with permanganate-periodate,[4] Fraction A appears to be a mixture of isomeric methyl *cis*- and *trans*-octadecenoates having unsaturation in positions 7 through 14, with little or no stearate present.

Since Fraction B did not complex with urea, it was presumably some type of cyclized fatty acid derivative. If cyclization and aromatization of the *cis,trans*-conjugated methyl linoleate had taken place, the product would be a dialkylbenzene that would show characteristic absorptions in its ultraviolet and infrared spectra. In the ultraviolet, an absorption peak was observed at 272 mμ and a shoulder at 242.5 mμ. A very strong absorption was found at 752 cm.$^{-1}$ in the infrared and a weaker absorption at about 700 cm.$^{-1}$ A band in the range of 735 to 770 cm.$^{-1}$ would be expected for a dialkylbenzene.[5] Infrared absorption for isolated *trans* bonds was not present.

Fraction B was aromatized by successive treatment with *N*-bromosuccinimide and *N,N*-dimethylaniline and then oxidized with potassium permanganate. *o*-Phthalic acid was obtained in 54% yield.

The strong infrared absorption at 752 cm.$^{-1}$ shown by Fraction B, its ultraviolet spectrum, low iodine number (approx. 22), and conversion in good yield to *o*-phthalic acid, are consistent with the interpretation that this fraction is a mixture of aromatic and hydroaromatic compounds, specifically a dialkyl benzene and a dialkyl cyclohexene. From the iodine number, about 25% of Fraction B appears to be dialkylcyclohexene.

A recent paper by Floyd *et al.*[6] describes the aromatization of nonconjugated linoleic acid with palladium as a catalyst. Stearate (18%), monoolefins (40%), aromatic compounds (30%), and polymers (7%) were obtained. Dialkyl cyclohexene-type products were not reported. The aromatic fractions obtained by these workers had infrared spectra similar to those of the noncomplexing fraction of the present report. Absorption near 273 mμ was prominent in all aromatic fractions.

A brief study was made of the kinetics of the reaction of selenium with *cis,trans*-conjugated methyl linoleate. It was found that total conjugation is lost during the reaction at essentially the same rate as *trans,trans* conjugation whereas *cis,trans* conjugation is lost at a considerably more rapid rate (Figure 1). These results suggest that the first step in the reaction is a rapid isomerization of the *cis,trans* isomer to the *trans,trans* and that it is the latter that cyclizes. Construction of molecular models shows that cyclization by joining the two α-positions of a diene should occur readily with the *trans,trans* configuration but not with the *cis,trans*.

(1) Presented at the fall meeting of the American Oil Chemists' Society, Cincinnati, Ohio, Sept. 30–Oct. 2, 1957.

(2) Present address, Lord Manufacturing Co., Erie, Pa.

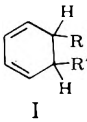
(3) H. M. Teeter, E. W. Bell, J. L. O'Donnell, M. J. Danzig, and J. C. Cowan, *J. Am. Oil Chemists' Soc.*, **35**, 238 (1958).

(4) E. P. Jones and J. A. Stolp, *J. Am. Oil Chemists' Soc.*, **35**, 71 (1958).

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, 1954, p. 55.

(6) D. E. Floyd, R. F. Paschke, D. H. Wheeler, and W. S. Baldwin, *J. Am. Oil Chemists' Soc.*, **33**, 609 (1956).

The detailed mechanism whereby selenium brings about ring closure of *trans,trans*-conjugated methyl linoleate is not known. However, the over-all effect must be abstraction of a hydrogen atom from each of the methylene groups adjacent to the diene system to produce a cyclohexadiene derivative such as I. The hydrogen abstracted is presumably



I

transferred to another molecule of conjugated linoleate, reducing it to an octadecenoate. The cyclohexadiene I could then be further dehydrogenated by another conjugated linoleate to yield the dialkylbenzene and a second octadecenoate molecule. Alternatively, I could disproportionate to dialkyl benzene plus dialkyl cyclohexene. This disproportionation appears to be the only way in which the latter could be formed.

The molecular ratio of octadecenoate to cyclized product would be 2:1 if aromatization were complete and no dialkylcyclohexene were formed. This ratio would be 1:1 if aromatic and cyclohexene derivatives were formed only by disproportionation of the cyclohexadiene I. Intermediate ratios would be expected if both routes to aromatic were followed. The ratio observed in our experiments is about 2.2:1. If one stearate is considered equivalent to two oleate molecules, the results of Floyd[6] indicate a ratio of about 2.5:1. The ratio of octadecenoate to the cyclized product observed in our work, together with the iodine number and spectral properties of the cyclized material, suggest that aromatic substances were probably produced by both routes.

If a hydrogen transfer process is involved in the cyclization and aromatization of conjugated methyl linoleate, the ratio of octadecenoate to cyclized product would be expected to change if the reaction were carried out in the presence of a hydrogen acceptor. When crotonic acid was used as a hydrogen acceptor, a ratio of about 1.3:1 was observed. With nitrobenzene as acceptor, cyclized product was obtained in 29% yield, but no appreciable amount of octadecenoate was recovered. However, this reaction appeared to be very complex, and considerable amounts of unidentified tarry by-products were obtained. Cyclic material found in this reaction showed a strong band at 273 mμ in the ultraviolet as well as strong bands at 752 and 704 cm.$^{-1}$ in the infrared. Identification of aniline in the reaction mixture shows that hydrogen transfer to nitrobenzene took place during the reaction.

EXPERIMENTAL

Methyl linoleate (n_D^{30}, 1.4578; iodine number, 172.3) was prepared by debromination of tetrabromostearic acid in methanol solution.[7] Alkali-isomerization[8] gave conjugated linoleic acid: a = 100 l.g.$^{-1}$ cm.$^{-1}$ at 233 mμ; n_D^{30} 1.4793. The methyl ester of the conjugated linoleic acid (n_D^{30} 1.4694; acid value 2.4) showed 90.5% *cis,trans* and 12.8% *trans,trans* conjugation as determined by infrared analysis.

Reaction of cis-trans-conjugated methyl linoleate with selenium. A Parr medium pressure, stainless-steel, hydrogenation apparatus was charged with 50 g. of conjugated methyl linoleate, 250 ml. of heptane, and 1 g. of selenium. The apparatus was flushed with nitrogen, and nitrogen was then introduced to 40 p.s.i. The vessel was then sealed and heated with constant stirring at 250° for 4.5 hr. After cooling, the reaction mixture was filtered, and the solvent was removed under reduced pressure. The residue (49.9 g.) had an iodine number of 67 and 0.0% conjugation as determined by ultraviolet analysis.

To remove selenium, this residue was stirred with mercury for 3 hr. and decanted from the metal; 44.4 g. of ester was recovered.

Urea separation of deselenized product. The deselenized residue was separated into an urea-complexing fraction (I, 67%) n_D^{30} 1.4523, and a nonurea-complexing fraction (II, 30.8%) n_D^{30} 1.4868, by the following procedure:

The deselenized residue (44.4 g.) was added to a warm solution of 310 g. of urea and 500 ml. of methanol. The mixture was allowed to crystallize at room temperature overnight. The precipitate containing the urea-complexing fraction was filtered with suction and washed with a saturated methanol solution of urea. The urea complex was then decomposed by mixing with about 200 ml. of 10% aqueous hydrochloric acid. The mixture was extracted four times with 50-ml. portions of ethyl ether. The combined ether extracts were washed neutral with water and dried over anhydrous sodium sulfate. An ester (29.7 g.) was recovered (Fraction A).

Urea-complexing fraction. Distillation of 28.6 g. of Fraction A *in vacuo* yielded fractions as shown in Table I.

TABLE I

FRACTIONAL DISTILLATION OF UREA-COMPLEXING FRACTION FROM SELENIUM-TREATED CONJUGATED METHYL LINOLEATE

Fraction No.	B.P., °C./Mm.	Weight, G.	Iodine Number	n_D^{30}
A-1	118–127°/0.25	8.1	86.5	1.4496
A-2	132–140°/0.1	8.0	82.3	1.4497
A-3	134–140°/0.025	10.8	86.8	1.4509
Residue	—	1.5	—	—

Because fractions A-1 to A-3 differed only slightly in properties they were combined and saponified to obtain the acids (iodine number 90; neut. equiv. 280; diene conjugation <1%). When a sample of these acids was recrystallized from ethanol, the highest melting fraction isolated had m.p. 39–44°. This fraction is presumed to be elaidic acid, since a mixed melting point with authentic elaidic acid showed no depression.

Another sample of the acids was submitted to analytical oxidation with permanganate-periodate in accordance with the procedure of Lemieux and Von Rudloff[9] as modified by Jones and Stolp.[4]

Total recovery of mono- and dibasic acids was 93%. The following dibasic acids were recovered in the mole percentages shown: C_7, 3.9%; C_8, 8.1%; C_9, 11.4%; C_{10}, 14.0%; C_{11}, 13.6%; C_{12}, 12.0%; C_{13}, 10.1%, C_{14}, 8.0%. In

(7) J. W. McCutcheon, *Org. Syntheses*, **22**, 77 (1942).

(8) J. P. Kass and G. O. Burr, *J. Am. Oil Chemists' Soc.*, **61**, 3293 (1939).

(9) R. V. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

chromatography the monobasic acid peak showed contamination with dibasic acids of still longer chain length.

The infrared spectrum of Fraction A showed the presence of *trans* bonds. Since the data obtained do not permit exclusion of the presence of *cis* isomers, this urea-complexing fraction was tentatively identified as a mixture of isomeric methyl *cis*- and *trans*-octadecenoates.

Nonurea-complexing fraction. The filtrate from the urea separation yielded 13.7 g. of nonurea-complexing ester (Fraction B). A portion of this dark brown ester (12.6 g.) was fractionally distilled (Table II).

TABLE II

FRACTIONAL DISTILLATION OF NONUREA-COMPLEXING FRACTION FROM SELENIUM-TREATED METHYL LINOLEATE

Fraction No.	B.P., °C./Mm.	Weight, G.	Iodine Number	n_D^{30}
B-1	117–130°/0.025	1.00	21.6	1.4842
B-2	130–160°/0.025–0.1	1.37	21.8	1.4849
B-3	160–192°/0.025–0.05	7.18	22.1	1.4849
B-4	192–195°/0.025	0.99	—	—
Residue	—	1.59	—	—

Fraction B-3 was treated with mercury and decolorized by passing an ethereal solution through a column packed with a mixture of carbon (10%) and activated alumina (90%). The recovered product (5.9 g.) contained no conjugation. Infrared analysis of the fraction showed very strong absorption at 752 cm.$^{-1}$ and some absorption at 700 cm.$^{-1}$ In the ultraviolet, this fraction showed a peak at 272 mμ (a, 1.45 l.g.$^{-1}$ cm.$^{-1}$) and a shoulder at 242.5 mμ (a, 2.93 l.g.$^{-1}$ cm.$^{-1}$).

Aromatization and oxidation of the nonurea-complexing fraction. The non-urea-complexing fraction (B, 1.5 g.), 30 ml. of carbon tetrachloride, and 4.45 g. of *N*-bromosuccinimide were refluxed for 3.5 hr. and allowed to cool overnight. The solids were removed by filtration, and 2.63 g. of brominated material was recovered from the filtrate.

A mixture of this product and 7 ml. of *N,N*-dimethylaniline was heated to 125° for 1 hr. Water was added to the reaction mixture, and the organic layer was taken up in ether. The ethereal solution was extracted with 10% aqueous hydrochloric acid, washed twice with water, and dried over anhydrous sodium sulfate.

After removal of solvent, the debrominated product, 4 g. of sodium hydroxide, 80 ml. of water, and 10 g. of potassium permanganate were stirred and heated to reflux for 5 hr. Additional permanganate (5 g.) was then added, and heating was continued until the permanganate was used up. The cooled reaction mixture was acidified with 50% sulfuric acid, and sulfur dioxide was added to reduce the manganese dioxide present.

The *p*H of the reaction mixture was adjusted to 7 by the addition of sodium hydroxide. The solution was then acidified with 10% hydrochloric acid and extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. There was obtained 0.45 g. (53.6%) of solid; m.p. 187–188° after sublimation *in vacuo*. Ultraviolet spectra of the product and of pure *o*-phthalic acid were identical. A sample of the product was converted to phthalic anhydride, m.p. 129–130°. Mixed melting point with pure phthalic anhydride (m.p. 130–131°) was 129–130°.

Reaction of conjugated methyl linoleate with selenium in the presence of hydrogen acceptors. (*a*) *Crotonic acid.* A Carius tube was charged with 5.0 g. of conjugated methyl linoleate, 2.9 g. of crotonic acid, 0.1 g. of selenium, 10 ml. of benzene, and 0.05 g. of hydroquinone. The tube was sealed in a nitrogen atmosphere and heated at 250° for 3 hr. When the tube was cooled, it was opened, and the contents were extracted with a saturated aqueous solution of sodium bicarbonate. The residue (iodine number 39) was recovered from the benzene layer and treated with urea as previously described. An urea-complexing fraction (53.2%) and a nonurea-complexing fraction (41.7%) were obtained. Handling loss was 3%.

(*b*) *Nitrobenzene.* A mixture of conjugated methyl linoleate (10 g.), 24 g. of nitrobenzene, and 0.25 g. of selenium was refluxed for 6.5 hr. Distillation of the nitrobenzene left 12.3 g. of viscous black residue. This residue was flash distilled, yielding a reddish brown product (3.4 g.) boiling at 116–225°/0.025 mm. This product was treated with urea as previously described. No appreciable amount of urea-complexing material was recovered.

The nonurea-complexing fraction (2.9 g.) was distilled, yielding two fractions. The first fraction (0.8 g.) showed b.p., 120–140°/0.025 mm.; n_D^{30}, 1.4954; iodine number, 23.8; 0.0% conjugation. A strong band at 273 mμ was present in the ultraviolet spectrum. Strong absorptions at 752 cm.$^{-1}$ and at 702 cm.$^{-1}$ were observed in the infrared spectrum. The second fraction (1.8 g.) showed b.p., 140–160°/0.025 mm.; n_D^{30}, 1.4922; iodine number, 16.7; 0.0% conjugation. A strong band at 273 mμ was present in the ultraviolet spectrum, and a strong absorption at 752 cm.$^{-1}$ was noted in the infrared spectrum. The residues from the distillations were very viscous black materials from which no additional fatty material could be isolated. The nitrobenzene fraction recovered from the original reaction mixture was treated with anhydrous hydrogen chloride. Crude aniline hydrochloride (1.5 g.; hot stage m.p., 178°) was recovered. This product was recrystallized twice from ethanol; m.p. 195–196°. The melting point of pure aniline hydrochloride is 198°.

Kinetic study of the reaction of selenium with conjugated methyl linoleate. A mixture of conjugated methyl linoleate (34.9 g.; 44.3% *trans,trans* and 32.7% *cis,trans* conjugation) and 0.9 g. of selenium was stirred and heated at 250° under nitrogen at atmospheric pressure. Samples were withdrawn at 5-min. intervals. Total conjugation and *cis,trans* and *trans, trans* conjugation were obtained on each sample by infrared analysis. The results are shown in Fig. 1.

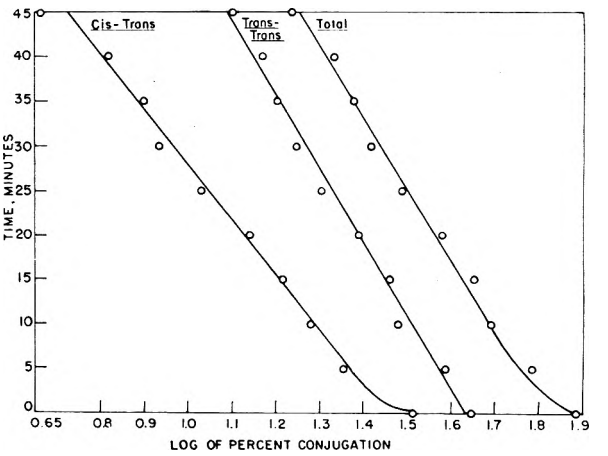


Fig. 1. Effect of selenium treatment on diene content of conjugated methyl linoleate

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PEORIA, ILL.

[CONTRIBUTION FROM THE GENERAL RESEARCH & CHEMICAL TECHNOLOGY SECTION, HARCOURT BUTLER TECHNOLOGICAL INSTITUTE]

Chalcones. Condensation of Aromatic Aldehydes with Resacetophenone. II

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Using resacetophenone as starting material, some chalcones and flavanones have been synthesized for the first time.

Since so many plant pigments have been recognized as polyhydroxychalcones, it was of some interest to synthesize compounds of this type. The present paper records the syntheses of the polyhydroxychalcones derived by the Claisen-Schmidt reaction of resacetophenone with *o*-,*m*-,*p*-tolualdehydes, 2,3-dimethoxybenzaldehyde, and vanillin in the presence of aqueous-alcoholic potassium hydroxide by either the cold or hot condensation procedure, outlined by Geissman and Clinton.[1] In all the cases reported except vanillin, it was found that some quantity of the flavanone accompanied the corresponding chalcone. The chalcones prepared above were then cyclized to flavanones with 4% aqueous-alcoholic sulfuric acid.

High temperature condensation of resacetophenone with the isomeric tolualdehydes is advantageous over the cold condensation, as the former leads to increased yield of chalcones and decreased resin formation. The quantity of 2′,4′-dihydroxy-2,3-dimethoxychalcone recovered is more when the reaction is carried out at room temperature for 48 hours than at the end of a reaction time of 7 days. The longer reaction period increases the quantity of a slowly crystallizable oil formed along with the chalcone, and from which it is readily separated owing to its greater solubility in alcohol. This oil slowly solidifies on ageing and was found to chiefly consist of the corresponding flavanone. This observation leads to the conclusion that when the reaction time is increased, the reaction does not stop with the formation of chalcone, but the latter partly undergoes gradual cyclization into flavanone. This conclusion is in agreement with that reported by Shah and his co-workers.[2]

2′,4,4′-Trihydroxy-3-methoxychalcone has previously been obtained by Russell and Todd[3] by condensation of resacetophenone dibenzoate with vanillin benzoate in the presence of dry hydrogen chloride, and saponification of the resulting 2′,4,4′-tribenzoyloxy-3-methoxychalcone into the required chalcone. We have, however, succeeded in effecting a direct synthesis of 2′,4,4′-trihydroxy-3-methoxychalcone by condensing resacetophenone with vanillin in the presence of strong alkali, in the cold, but the yield of chalcone was small (about 5%).

Owing to the reversible[4] nature of the Claisen-Schmidt reaction, it is apparent that by taking the reactants in excess of the stoichiometric proportion, the yield of the α,β-unsaturated ketone can be increased. An excess of the aldehyde component is desirable as against that of resacetophenone, since with the excess of the latter the reaction takes other than the desired course.[5] In the case of all the above condensations by taking an excess of aldehyde the yield of chalcone was found to increase.

2′,4′-Dihydroxychalcone was synthesized by the interaction of resacetophenone and benzaldehyde in the presence of 40% aqueous-ethanolic potassium hydroxide solution, at room temperature, for seven days. Besides the expected α,β-unsaturated ketone small quantities of 7-hydroxyflavanone, benzyl alcohol, and benzoic acid were identified. The isolation of the last two products indicates that some of the benzaldehyde undergoes the Cannizzaro reaction.

EXPERIMENTAL

All melting points are uncorrected. Resacetophenone,[6] *o*-tolualdehyde,[7] and *p*-tolualdehyde[8] were prepared as described previously. *m*-Tolualdehyde was prepared from *m*-tolunitrile[9] *via* the Stephen's reaction.[10] The aldehydes were characterized through their phenylhydrazones.

2′,4′-Dihydroxy-2,3-dimethoxychalcone. Resacetophenone (6.0 g.), 2,3-dimethoxybenzaldehyde (6.5 g.), and ethanol (40 cc.) were mixed at 0° and to the mixture 40% aqueous potassium hydroxide (176 cc.) was added with shaking at room temperature. The mixture was allowed to stand, out of contact with air, for 47 hr. with shaking at intervals, during which it acquired a dark red color. After dilution with cold water, it was acidified with 6*N* hydrochloric acid and the voluminous yellow precipitate was separated, filtered, washed with warm water, dissolved in about 400 cc. ether and extracted thrice with 5% aqueous sodium bicar-

(1) T. A. Geissman and R. O. Clinton, *J. Am. Chem. Soc.*, **68**, 697 (1946).

(2) G. N. Vyas and N. M. Shah, *J. Indian Chem. Soc.*, **28**, 75 (1951); C. C. Patel and N. M. Shah, *J. Indian Chem. Soc.*, **31**, 867 (1954).

(3) A. Russell and J. Todd, *J. Chem. Soc.*, 422 (1937).

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(7) J. W. Williams, C. H. Witten, and J. A. Krynitsky, *Org. Syntheses*, **Coll. Vol. III**, 818 (1955).

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(10) H. Stephen, *J. Chem. Soc.*, 1874 (1925).

bonate solution (75 cc., 75 cc., and 50 cc.). The bicarbonate washings on neutralization gave 2,3-dimethoxybenzoic acid (0.12 g.) The ethereal layer was washed with water and extracted with four 50-cc. portions of 10% aqueous potassium hydroxide solution. The alkaline solution on neutralization gave flocks of yellow mass together with an oil which crystallized during the course of several months and was identified as 7-hydroxy-2',3'-dimethoxyflavanone, m.p. 170°. From the yellow mass the chalcone crystallized in yellow stellate aggregates of squat prisms from ethanol and then from benzene in flat needles, yield, 4.9 g. (41.7% based on the resacetophenone used), m.p. 188–189°.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.98; H, 5.37. Found: C, 68.07; H, 5.30.

The chalcone is very soluble in acetone, ethyl acetate and pyridine, moderately soluble in other common organic solvents, and sparingly soluble in petroleum ether and water.

7-Hydroxy-2',3'-dimethoxyflavanone. The above chalcone (1.0 g.) in ethanol (60 cc.) water (35 cc.) and concentrated hydrochloric acid (3 cc.) was refluxed for 61 hr. on a water bath. The residue obtained after the removal of alcohol under reduced pressure was treated with water (300 cc.). The oily mass thus obtained solidified and crumbled to powder in contact with alcohol, which on repeated crystallization from alcohol and finally from benzene gave the flavanone as colorless, shiny plates with tapering ends; yield, 0.2 g., m.p. 170°.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.98; H, 5.37. Found: C, 67.60; H, 5.21.

2',4'-Dihydroxy-2,3-dimethoxychalcone 2,4-dinitrophenylhydrazone. A solution of 2,4-dinitrophenylhydrazine (0.2 g.) in concentrated sulfuric acid (2.0 cc.) and ethanol (7 cc.) was refluxed with 2',4'-dihydroxy-2,3-dimethoxychalcone (0.6 g.) in alcohol (25 cc.) for 10 hr., when the 2,4-dinitrophenylhydrazone separated as dark red microcrystalline needles; yield, 0.13 g., which on recrystallization from acetone-alcohol melted at 251–252°.

Anal. Calcd. for $C_{23}H_{20}O_8N_4$: N, 11.66. Found: N, 11.80.

Acetylation of 2',4'-dihydroxy-2,3-dimethoxychalcone. Acetylation by acetic anhydride, and fused sodium acetate at 125–130° for 5 hr. gave an oil, which partially solidified after about 2 months and the solidified mass, on crystallization from ethanol and finally from benzene, gave the monoacetate in yellow short slender needles, m.p. 123.5°. Acetylation with acetic anhydride and pyridine in the cold gave the monoacetate in good yield.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.65; H, 5.30. Found: C, 66.52; H, 5.35.

Schotten-Baumann benzoylation of 2',4'-dihydroxy-2,3-dimethoxychalcone gave an oily product which failed to crystallize.

2',4,4'-Trihydroxy-3-methoxychalcone. Aqueous potassium hydroxide (88 cc., 40%) was gradually added with shaking to a solution of resacetophenone (3.0 g.) and vanillin (3.0 g.) in ethanol (20 cc.) at 0°. The reaction mixture was then kept in a closed container at room temperature for 7 days, with occasional shaking, and on being worked up as before, gave the crude chalcone as an oil. The oil was desiccated and repeatedly washed with hot petroleum ether (b.p. 40–60°) and finally with hot benzene in order to remove most of the associated vanillin. It was finally purified by precipitation from aqueous alkaline solution. The chalcone crystallized from 40% aqueous ethanol as yellow microcrystalline powder and then from boiling benzene (sparingly soluble) in glistening yellow flakes. The yield was 0.3 g., m.p. 210° (Russell and Todd[3] record m.p. 210°).

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.92. Found: C, 67.11; H, 4.84.

This chalcone was also prepared by using different solvents as reaction medium, *viz.*, water, ethylene glycol. The use of ethanol as solvent, sometimes, produces the chalcone as an oily-resinous mass, difficult to crystallize. Attempts to prepare the chalcone by the hot condensation procedure, however, failed.

When the condensation was carried out, in the presence of aqueous-alcoholic potassium hydroxide, for a period of 6 months or 1 year, a black resinous mass was obtained.

4',7-Dihydroxy-3'-methoxyflavanone. The above chalcone was isomerized by dilute aqueous ethanolic sulfuric acid and worked up as in the previous case. The flavanone crystallized from ethanol (animal charcoal) in glistening plates, m.p. 191°.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.92. Found: C, 67.32; H, 4.91.

2',4,4'-Trihydroxy-3-methoxychalcone 2,4-dinitrophenylhydrazone. This derivative was prepared from the above chalcone in the usual way. It separated from ethyl acetate in dark red micro-needles, m.p. 235°.

Anal. Calcd. for $C_{22}H_{18}O_8N_4$: N, 12.02. Found: N, 11.74.

2',4,4' - Triacetoxy - 3 - methoxychalcone. Acetylation of 2',4,4'-trihydroxy-3-methoxychalcone (0.3 g.) by acetic anhydride (6.1 cc.) and fused sodium acetate (0.7 g.) at 125–130° for 6 hr. gave the required compound as an oil which gradually solidified and crystallized from 95% ethanol in glistening pale yellow plates, m.p. 133°, yield, 0.35 g.

Anal. Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.88. Material dried at 62° in a high vacuum. Found: C, 63.92; H, 4.81.

It is less soluble in organic solvents than the parent chalcone and gives a negative ferric chloride reaction.

2',4'-Dihydroxy-2-methylchalcone. Resacetophenone (3.0 g.) in ethanol (12 cc.) was condensed with *o*-tolualdehyde (2.28 cc.; d_4^{19} 1.0386) in presence of 40% aqueous potassium hydroxide (88 cc.) by keeping in a closed container for 7 days at room temperature and worked up as before. The crude chalcone (1.1 g.) was purified by several recrystallizations from aqueous ethanol (animal charcoal) and finally from benzene when it separated as yellow needle-like crystals, m.p. 180–181°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.57; H, 5.86.

The mother liquor left after crystallization of the chalcone gave 7-hydroxy-2'-methylflavanone in small amount as colorless plates, m.p. 212°.

7-Hydroxy-2'-methylflavanone. 2',4'-Dihydroxy-2-methylchalcone was isomerized to the flavanone as previously described. It was obtained from ethyl alcohol in mica-like plates, m.p. 212°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: 75.81; H, 5.60.

2',4'-Dihydroxy-3-methylchalcone. A mixture of resacetophenone (3.0 g.), *m*-tolualdehyde (2.31 cc., $d_4^{21.4}$ 1.0189), ethanol (25 cc.) and potassium hydroxide pellets of 85% purity (15 g. dissolved in 15 cc. water) was heated in a water bath at about 60° for 2 hr. It was worked up as usual. The crude chalcone obtained as an oil (2.1 g.) was washed with warm water, dried, and dissolved in chloroform. A little petroleum ether (b.p. 40–60°) was added to the solution. After some time a resinous deposit had formed on the sides of the container. The clear liquid was decanted and a little more petroleum ether was added, this process being repeated until no more resin precipitated. Further addition of petroleum ether brought about the separation of the chalcone as an oil. The oil was nucleated with a few seed crystals of 2',4'-dihydroxy-3-methylchalcone obtained from a previous preparation and chilled. The entire mass solidified after some time. For further purification the solid mass was dissolved in benzene and fractionally precipitated by the addition of light petroleum ether and the various fractions thus obtained were left overnight in a refrigerator; the last fraction had solidified. The supernatant layer of benzene–petroleum ether mixture was decanted, and to this solid a small quantity of ethanol was added to dissolve the associated oily impurity and the solvent was decanted from the solid immediately. The solid was then crystallized from aqueous-methanol (animal charcoal) in yellow needles, m.p. 135°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.42; H, 5.90.

7-Hydroxy-3'-methylflavanone. The above chalcone was isomerized to flavanone in the usual way. The reaction product, after the removal of alcohol under reduced pressure, on standing in contact with glacial acetic acid in a refrigerator for 12 hr. partially solidified. The adherent oily portion was centrifuged and the solid thus recovered was dissolved in ethanol and precipitated by the addition of water, filtered, and dried. The product on repeated dissolution in benzene and precipitation by light petroleum ether gave the flavanone as pinkish white microcrystalline powder, m.p. 146–147°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.74; H, 5.82.

2',4'-Dihydroxy-4-methylchalcone. A solution of resacetophenone (3.0 g.), *p*-tolualdehyde (2.36 cc., $d_4^{16.7}$ 1.0194) in ethanol (25 cc.) was treated with potassium hydroxide pellets of 85% purity (15 g. dissolved in 15 cc. water), and heated in a water bath at about 60° for 2 hr. It was worked up as before. The crude chalcone (2.6 g.) separated as a yellow oil. It was washed several times with warm water (about 70°) and dried. On nucleation with the crystals of isomeric 2',4'-dihydroxy-2-methylchalcone and cooling in a freezing mixture, with stirring, the oil suddenly solidified. An alcoholic solution of this solidified mass on standing deposited the 2',4'-dihydroxy-4-methylchalcone in needles, but the compound was not pure since the crystals occluded an appreciable quantity of resinous matter from the solution. The crystalline magma was filtered at a pump, washed with a little ethanol, and then crystallized from aqueous ethanol in yellow needles and finally from benzene in yellow, well shaped prisms, m.p. 153–154°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.41; H, 5.80.

The resulting aqueous alcoholic mother liquor deposited 7-hydroxy-4'-methylflavanone in irregular plates, m.p. 170°.

7-Hydroxy-4'-methylflavanone. The ring closure of the above chalcone (crude) by refluxing it with aqueous-alcoholic sulfuric acid gave an oily product which crystallized slowly (80 days) in contact with acetic acid. Recrystallization from alcohol (animal charcoal) furnished the flavanone in colorless rectangular plates, m.p. 170–171°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.22; H, 5.62.

The chalcones described in this paper give a yellow coloration with concentrated sulfuric acid (except 2',4,4'-trihydroxy-3-methoxychalcone-red, 2',4'-dihydroxy-2,3-dimethoxychalcone-orange), dissolve in alkali with the production of an orange color which changes to yellow, and give a dark brown coloration with ethanolic ferric chloride.

All the flavanones, described herein, on reduction with magnesium and ethanolic hydrochloric acid give a pink color, whereas 4',7-dihydroxy-3'-methoxyflavanone, gives various transitory shades of color, *viz.* bluish violet, violet, rose-violet, and finally pink.

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KANPUR, INDIA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Organometallic Compounds from Aryl Halides Containing Ether Functions[1]

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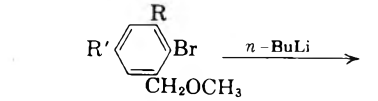
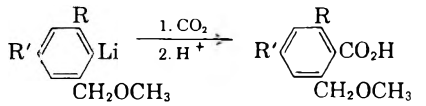
A number of *o*-methoxymethylaryl halides have been synthesized, and a study has been made of the synthesis and properties of the corresponding aryllithium and arylmagnesium compounds.

Although aryl methyl ethers which contain lithium in the nucleus have been synthesized previously, a careful study of the preparation and properties of *o*-methoxymethylphenyllithium compounds has apparently not been made. In the present study a method for the preparation of such compounds has been developed which consists of allowing an *o*-bromobenzyl methyl ether to react with *n*-butyllithium for a limited time. In this way *o*-methoxymethylbromobenzene (Ia), 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene (Ib), and 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene (Ic) were converted to the corresponding lithium derivatives, IIa, IIb, and IIc. Carbonation of these lithium compounds afforded the acids, IIIa, IIIb, and IIIc in yields of 34, 65, and 91%, respectively. In comparison, 4 - *t* - butyl - 2,6 - dimethylbromobenzene, when treated similarly, gave the corresponding acid in a 51% yield.



Ia, R = H, R' = H
Ib, R = CH_3, R' = $C(CH_3)_3$
Ic, R = CH_2OCH_3, R' = $C(CH_3)_3$



IIa IIIa
IIb IIIb
IIc IIIc

Coupling of the aryllithium with the aryl bromide may be responsible for the variation in the yields of acids; the aryllithium compound least hindered

(1) This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

sterically might couple to the greatest extent and give the acid in lowest yield.

When lithium metal was used in place of *n*-butyllithium with the above bromobenzenes, the results were much more involved. It was known, of course, that nuclear metalation of benzyl ethers by organoalkali compounds could be complicated since ethers of the type had been shown to react with these reagents in a number of ways. Among these are cleavage[2] and reactions involving metalation of the side-chain followed by elimination,[3] displacement,[4] and rearrangement.[5]

When the simplest of the aryl bromides (Ia) was treated with lithium, and the resulting mixture poured on solid carbon dioxide the only product that could be identified, in fact, was bibenzyl and that in small amount. Similar treatment of Ib produced the debrominated derivative, 3-*t*-butyl-5-methoxymethyltoluene, in a yield of 25%. The formation of this compound is best explained perhaps by hydrogen-metal interchange between IIb and the α-hydrogen atom of a benzyl methyl ether, most probably the coupling product formed from Ib. This reaction would then be analogous to similar metalations observed by interaction of benzyl ethers with phenyllithium.[4,5]

The bibenzyl could have originated in the following way. Benzyl methyl ether might first be produced in a manner analogous to the formation of 3-*t*-butyl-5-methoxymethyltoluene just indicated. Cleavage of benzyl methyl ether by lithium would give benzyllithium, which could then displace a methoxyl group from another molecule of the ether to yield bibenzyl. Although benzyl ethers are not normally cleaved by metals at the temperature of refluxing ether, it has been shown that a slow cleavage of benzyl phenyl ether by sodium begins at 39°.[2] The occurrence of bibenzyl as a product in the cleavage of benzyl ethers has been ascribed to nucleophilic displacement rather than free radical combination.[6]

It is noteworthy that when 4-*t*-butyl-2,6-dimethylbromobenzene was allowed to react with lithium under the conditions employed for Ia and Ib, the corresponding acid was obtained in a 30% yield. This experiment supports the hypothesis that the disappearance of the aryllithium compounds IIa and IIb is associated with attack of the ether function. Similar reaction of Ic with lithium followed by treatment with carbon dioxide failed to produce any acid; only starting material was recovered.

Although it was expected that the major products formed by the reaction between Ia and Ib with lithium might be coupling products, attempts to isolate these compounds by distillation, recrystallization, and chromatography were unsuccessful. It seemed possible that oxidation would convert the coupled ethers to carboxylic acids which could then be identified more easily. Accordingly the benzyl methyl ethers Ia and Ib were subjected to the action of potassium permanganate. Compound Ia afforded *o*-bromobenzoic acid in an 86% yield, but Ib yielded the dicarboxylic acid, 2-bromo-5-*t*-butylisophthalic acid (71%), rather than the monocarboxylic acid. Apparently the methyl group is oxidized about as easily as the methoxymethyl group. When the oxidation was carried out on the complex mixtures obtained from the reaction of Ia and Ib with lithium, no acids were formed.

Organometallic compounds which contain suitably placed ether groups offer the possibility of internal coordination between an electron pair of the ether oxygen atom and the metal atom. Such coordination has been used by Holmberg to explain the behavior of certain *o*-methoxyphenyl Grignard reagents toward carbonation.[7] Of the organomagnesium compounds studied, those which could form four- and five-membered rings gave both ketones and acids, while those which could form six-membered rings gave only acids. He ascribed the enhanced reactivity of the former Grignard reagents to strain in the rings. Investigation of *o*-bromobenzyl methyl ether revealed that the entrainment method was required for adequate conversion of this bromide to the Grignard reagent; the latter compound when carbonated afforded the corresponding acid in only a 13% yield. The apparent sluggishness of the reaction was attributed to stability of the five-membered ring formed by internal coordination.[8]

The Grignard reagent of Ib was prepared only by the use of the entrainment method. 4-*t*-Butyl-2-(β-methoxy)ethyl-6-methylbenzyl chloride, in contrast, formed the Grignard reagent in the normal manner. Although these two organomagnesium compounds are capable of internal coordination, no unusual behavior was observed; they were converted to the corresponding acids in yields of 26 and 28%, respectively. The diether bromide (Ic) failed to react with magnesium even though conditions were varied over a wide range. The diether iodide, prepared by action of iodine on the diether lithium intermediate (IIIc), was also unreactive toward magnesium.

Several interesting effects were uncovered in the synthesis of the diether bromide (Ic). Treatment of 4-*t*-butyl-2,6-dimethylbromobenzene with two equivalents of *N*-bromosuccinimide yielded a mixture of 2-bromomethyl-4-*t*-butyl-6-methylbromobenzene and 4-*t*-butyl-2,6-di(bromomethyl)-bromobenzene. Although these compounds are solids, they

(2) P. Schorigin, *Ber.*, **57B**, 1627 (1924).
(3) C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).
(4) A. Lüttringhaus, G. Wagner-v. Sääf, E. Sucker, and G. Borth, *Ann.*, **557**, 46 (1945).
(5) G. Wittig and L. Löhmann, *Ann.*, **550**, 260 (1942).
(6) R. L. Burwell, *Chem. Revs.*, **54**, 615 (1954).
(7) G. A. Holmberg, *Acta Chem. Scand.*, **9**, 555 (1955).
(8) F. G. Mann and F. H. Stewart, *J. Chem. Soc.*, 2819 (1954).

were separated from each other more easily by fractional distillation than by recrystallization. Treatment of the tribromide with sodium methoxide afforded the diether bromide in an 85% yield. The other bromoethers were prepared by similar procedures.

The first step in the synthesis of 4-*t*-butyl-2-(β-methoxy)ethyl-6-methylbenzyl chloride was treatment of 5-*t*-butyl-*m*-xylene with 1.75 equivalents of N-bromosuccinimide. This bromination yielded 3-bromomethyl-5-*t*-butyltoluene (42%) and 3,5-di(bromomethyl)-*t*-butylbenzene (13%).

The Grignard reagent from 3-bromomethyl-5-*t*-butyltoluene reacted with chloromethyl ether to give the desired 3-*t*-butyl-5-(β-methoxy) ethyltoluene (34%); products arising from hydrolysis, coupling, and rearrangement were also isolated. Although benzyl Grignard reagents undergo rearrangement when treated with chloromethyl ether,[9,10] they yield only the normal products with carbon dioxide.[8,9] In keeping with this observation, we found that carbonation of *o*-bromobenzylmagnesium bromide gave *o*-bromophenylacetic acid as the major product with smaller amounts of *o*-bromobenzyl alcohol and *bis*-(2-carboxyphenyl) ethane. Similarly, no rearrangement products were reported in the reaction between *o*-bromobenzylmagnesium bromide and ethylene oxide.[11] Chloromethylation of 3-*t*-butyl-5-(β-methoxy)ethyltoluene afforded the benzyl chloride in a 72% yield.

EXPERIMENTAL[12]

Bromination of 4-t-butyl-2,6-dimethylbromobenzene. A mixture of 65 g. (0.27 mole) of 4-*t*-butyl-2,6-dimethylbromobenzene,[13] 96.1 g. (0.54 mole) of *N*-bromosuccinimide, 0.1 g. of benzoyl peroxide, and 300 ml. of carbon tetrachloride was heated on a steam bath, with stirring. At the end of 5 min. the color changed from cream to pink; within 30 min. the color was discharged. The mixture was heated under reflux for an additional 1.5 hr., cooled to room temperature, and filtered. The amount of succinimide (52.5 g.) recovered was quantitative. The carbon tetrachloride was removed from the filtrate, and the residual yellow liquid distilled. The first fraction (b.p. 122–123°/1.2 mm.) was the crude 2-bromomethyl-4-*t*-butyl-6-methylbromobenzene, which crystallized when cooled. After two recrystallizations from 95% ethanol it melted at 38–39.5°, yield 11.4 g. (13%).

Anal. Calcd. for $C_{12}H_{16}Br_2$: C, 45.02; H, 5.04. Found: C, 45.24; H, 5.22.

The second fraction (b.p. 165–168°/1.4 mm.), which also crystallized when cooled, melted at 75–78°, yield 76.5 g. (71%). The pure 4-*t*-butyl-2,6-di(bromomethyl)bromobenzene, m.p. 89–90°, was obtained only after repeated recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_{15}Br_3$: C, 36.12; H, 3.79. Found: C, 36.26; H, 3.86.

In another experiment a mixture of 149.5 g. (0.62 mole) of 4-*t*-butyl-2,6-dimethylbromobenzene, 165.7 g. (0.92 mole) of *N*-bromosuccinimide, 750 ml. of carbon tetrachloride, and 1 g. of benzoyl peroxide was heated with stirring for 3 hr. The succinimide was collected on a filter, and the solvent removed from the filtrate. The residual liquid when distilled yielded 90.0 g. (45%) of the dibromide, b.p. 136–138°/2.5 mm. and 40.7 g. (17%) of the tribromide, b.p. 169–174°/2.5 mm.

4-t-Butyl-2,6-di(methoxymethyl)bromobenzene. To 170 ml. of reagent grade methanol, cooled by an ice bath, was added slowly 9.4 g. (0.41 g.-atom) of sodium. When the sodium had dissolved, the solution was brought to reflux and a solution of 54 g. (0.14 mole) of 4-*t*-butyl-2,6-di-(bromomethyl)bromobenzene in 170 ml. of anhydrous benzene was added dropwise during 2 hr. After the addition was complete, stirring was continued for 0.5 hr. under reflux. The mixture was then filtered to get rid of the insoluble salts, and the filtrate was distilled azeotropically to remove the methanol. The benzene solution was washed with water and dried over calcium chloride. A yellow solid formed when the benzene was evaporated under water-aspirator pressure. After one recrystallization from 95% ethanol the dimethoxy bromide melted at 80.5–81.0°, yield 34.9 g. (85%).

Anal. Calcd. for $C_{14}H_{21}BrO_2$: C, 55.81; H, 6.98. Found: C, 55.87; H, 7.24.

4-t-Butyl-2-methoxymethyl-6-methylbromobenzene. This procedure is similar to that employed for the diether bromide. A solution of sodium methoxide, prepared by the addition of 5.8 g. (0.25 g.-atom) of sodium to 100 ml. of methanol, was heated to reflux while 40.0 g. (0.125 mole) of 2-bromomethyl-4-*t*-butyl-6-methylbromobenzene in 100 ml. of benzene was added dropwise to it during 1 hr. The methanol was removed by azeotropic distillation, and the residue extracted with water. The benzene layer was dried, and the solvent evaporated. The remaining liquid afforded 29.3 g. (87%) of the monomethoxy bromide, b.p. 93.0–93.5°/0.3 mm.

Anal. Calcd. for $C_{13}H_{19}BrO$: C, 57.60; H, 7.01. Found: C, 57.67; H, 6.91.

o-Bromobenzyl methyl ether. A mixture of 158.5 g. (0.927 mole) of *o*-bromotoluene, 165 g. (0.927 mole) of *N*-bromosuccinimide, and 0.2 g. of benzoyl peroxide in 300 ml. of carbon tetrachloride was heated on the steam bath for 18 hr. Distillation of the residue left by removal of the succinimide and evaporation of the solvent gave 181.6 g. (78%) of *o*-bromobenzyl bromide, b.p. 133–134°/18.5 mm. The literature records a boiling point of 129°/19 mm.[14]

The bromide was converted to the ether by a modification of the method of Holliman and Mann.[15] To a solution of 19.0 g. (0.825 g.-atom) of sodium in 500 ml. of methanol, cooled in an ice bath, was added 181 g. (0.725 mole) of the bromide. The mixture was heated 1.5 hr., and the solvent removed by distillation. The residue was added to water in a separatory funnel, and the organic layer extracted with ether. The residual liquid left by distillation of the ether afforded 119.5 g. (82%) of the bromo ether, b.p. 111–112°/17 mm. The reported boiling point is 106–107°/16 mm.[15]

3-Bromomethyl-5-t-butyltoluene. To a mixture of 592 g. (3.33 moles) of *N*-bromosuccinimide and 308 g. (1.90 moles) of 5-*t*-butyl-*m*-xylene was added 0.5 g. of benzoyl peroxide and 1 l. of carbon tetrachloride. The mixture was stirred under reflux for 19 hr. after which the succinimide was collected on a filter and the filtrate concentrated. Distillation of the residue yielded 19.23 g. (42%) of 3-bromomethyl-5-*t*-butyltoluene, which boiled at 104–109°/2.5 mm.

(9) H. Gilman and J. E. Kirby, *J. Am. Chem. Soc.*, 54, 345 (1932).

(10) L. Malm and L. Summers, *J. Am. Chem. Soc.*, 73, 362 (1951).

(11) M. H. Beeby and F. G. Mann, *J. Chem. Soc.*, 411 (1951).

(12) All melting points are corrected; all boiling points are uncorrected.

(13) R. C. Fuson, J. Mills, T. G. Klose, and M. S. Carpenter, *J. Org. Chem.*, 12, 587 (1947).

(14) J. Kenner and J. Wilson, *J. Chem. Soc.*, 1111 (1927).

(15) F. G. Holliman and F. G. Mann, *J. Chem. Soc.*, 1634 (1947).

Anal. Calcd. for $C_{12}H_{17}Br$: C, 59.75; H, 7.05. Found: C, 59.73; H, 7.17.

The infrared spectrum of the second fraction (b.p. 128–130°/2.7 mm. has a band at 675 cm.$^{-1}$, which is consistent with a —$CHBr_2$ function.

From the remaining material, after three recrystallizations from 95% ethanol was obtained 78.8 g. (13%) of 3,5-di(bromomethyl)-*t*-butylbenzene, m.p. 115–118°.

Anal. Calcd. for $C_{12}H_{16}Br_2$: C, 45.02; H, 5.04. Found: C, 45.16; H, 4.91.

From the mother liquors was obtained a fraction which boiled at 99–101°/0.3 mm. The infrared spectrum of this liquid exhibits bands at 2720 cm.$^{-1}$ and 1705 cm.$^{-1}$ characteristic of an aromatic aldehyde, as well as a band at 115 cm.$^{-1}$ assignable to an aliphatic ether.

Reaction of 3-t-butyl-5-methylbenzylmagnesium bromide with chloromethyl ether. The benzyl Grignard reagent was prepared by adding a solution of 50 g. (0.21 mole) of 3-bromomethyl-5-*t*-butyltoluene in 400 ml. of ether to 12.6 g. (0.518 g.-atom) of magnesium. The addition, which required 6 hr., was followed by stirring for 1.5 hr. After the Grignard reagent had been allowed to stand overnight it was filtered under nitrogen and added during 3 hr. to a flask containing 16.7 g. (0.207 mole) of chloromethyl ether in 50 ml. of ethyl ether. The reaction mixture was cooled by an ice bath during the addition, then heated gently under reflux for 1 hr. Decomposition was effected with hydrochloric acid. The ether layer was washed, dried, and freed of solvent. Distillation of the residue yielded four fractions, the first of which (b.p. 65–68°/2.9 mm.) was shown to be 5-*t*-butyl-*m*-xylene by comparing its infrared spectrum and refractive index with those of a known sample, yield 6.1 g. (18%). The second fraction (b.p. 106–112°/3 mm.) was 3-*t*-butyl-5-(β-methoxy)ethyltoluene, yield 14.5 g. (34%).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.13; H, 10.60.

An absorption band (875 cm.$^{-1}$) attributed to a 1,2,3,5-tetrasubstituted benzene is present in the infrared spectrum of the third fraction (b.p. 129–132°/3.4 mm.). This spectrum also contains bands at 1120 and 1100 cm.$^{-1}$, which are assignable to a hindered aliphatic ether. This compound, tentatively identified as 5-*t*-butyl-2-methoxymethyl-*m*-xylene, weighed 5.8 g. (14%). The last fraction (b.p. 188–193°/3.6 mm.) proved to be the coupling product, 3,3′-di-*t*-butyl-5,5′-dimethylbibenzyl, yield 4.0 g. (12%).

Anal. Calcd. for $C_{24}H_{34}$: C, 89.37; H, 10.63. Found: C, 89.50; H, 10.82.

Chloromethylation of 3-t-butyl-5-(β-methoxy)ethyltoluene. A mixture of 4.2 g. (0.02 mole) of 3-*t*-butyl-5-(β-methoxy)-ethyltoluene, 1.76 g. (0.0585 mole) of paraformaldehyde, and 40 ml. of concentrated hydrochloric acid was stirred while dry hydrogen chloride was bubbled into it. The temperature was kept at 35° during the reaction, which was allowed to proceed for 3 hr. The mixture was extracted with ether, the extracts were washed and dried, and the ether was removed. Distillation of the residue afforded 3.6 g. (72%) of the chloromethyl compound, b.p. 108–110°/0.45 mm.

Anal. Calcd. for $C_{15}H_{23}OCl$: C, 70.73; H, 9.04. Found: C, 70.64; H, 8.95.

Carbonation of o-bromobenzylmagnesium bromide. To a flask containing 11.7 g. (0.48 g.-atom) of magnesium was added 30 g. (0.12 mole) of *o*-bromobenzyl bromide in 250 ml. of ether during 3.5 hr. A nitrogen atmosphere was maintained during the addition. Stirring was continued for 2 hr. after which the mixture was filtered under nitrogen on solid carbon dioxide. The carbonated mixture was decomposed with iced hydrochloric acid. The ether layer was extracted with two 100-ml. portions of 10% sodium hydroxide solution. Acidification of the extracts produced crystals, which were collected on a funnel, washed, and dried. The solid was treated with hot carbon tetrachloride, which caused part of the crystals to dissolve. The undissolved bis(2-carboxyphenyl)ethane was isolated by filtration of the hot solution. After several recrystallizations from 95% ethanol-benzene this acid melted at 233–234°, yield 0.8 g. (5%).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.27; H, 5.02.

The literature records a melting point of 231° for this compound.[16]

After the dicarboxylic acid had been removed from the mixture of acids by filtration, the carbon tetrachloride was evaporated from the resulting mother liquor. The solid residue was recrystallized several times from hot water in the presence of carbon black. The pure *o*-bromophenylacetic acid melted at 105°, yield 10.0 g. (39%). The reported melting point is 103–104°.[17]

From the ether layer which remained after basic extraction crude *o*-bromobenzyl alcohol was obtained; after two recrystallizations from high-boiling petroleum ether it melted at 79.5–80.0°, yield 0.4 g. (2%). This compound is reported to melt at 80°.[18]

Reaction of o-bromobenzyl methyl ether with n-butyllithium. In a dry flask which had been flushed with nitrogen, a mixture of 4.7 g. (0.023 mole) of *o*-bromobenzyl methyl ether in 75 ml. of ether and 114 ml. (0.093 mole) of 0.81*N* *n*-butyllithium[19] was heated, with stirring, under gentle reflux for 45 min. After the mixture had cooled, it was poured on an excess of solid carbon dioxide. The carbonated mixture, upon reaching room temperature, was extracted with two 90-ml. portions of 10% sodium hydroxide solution. Acidification of the basic extracts with concentrated hydrochloric acid precipitated 2-methoxymethylbenzoic acid, yield 1.3 g. (34%), m.p. 91–94°. The literature records a melting point of 93–94°.[20]

Reaction of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene with n-butyllithium. To a dry flask containing 100 ml. (0.035 mole) of 0.35*N* *n*-butyllithium was added all at once a solution of 3.0 g. (0.011 mole) of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene in 50 ml. of ether. The mixture was stirred under reflux for 0.5 hr. and poured on solid carbon dioxide. The carbonated material was extracted with dilute sodium hydroxide solution, and the extracts were boiled for a few minutes, filtered hot, and cooled in an ice-salt bath. Acidification of the solution with concentrated hydrochloric acid produced an oil which crystallized when allowed to stand overnight in the refrigerator. The crude 4-*t*-butyl-2-methoxymethyl-6-methylbenzoic acid was collected on a filter, washed with water, and dried, yield 2.1 g. (80%), m.p. 76–80°. After several recrystallizations from low-boiling petroleum ether–methylcyclohexane the acid melted at 80–81°, yield 1.7 g. (65%).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.19; H, 8.48. Found: C, 70.93; H, 8.43.

Reaction of 4-t-butyl-2,6-di(methoxymethyl)bromobenzene with n-butyllithium. A solution of 1.5 g. (0.0050 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene in 25 ml. of ether was added all at once to 50 ml. (0.020 mole) of 0.40*N* *n*-butyllithium in 50 ml. of ether. The mixture was heated at reflux, with stirring, for 45 min. and poured on solid carbon dioxide. After being allowed to come to room temperature the carbonated material was treated as in the preceding experiment. 4-*t*-Butyl-2,6-di(methoxymethyl)benzoic acid was isolated, m.p. 77–80°, yield 1.2 g. (91%). The pure acid melts at 79.0–79.5°.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.82; H, 8.22.

(16) C. Fischer and R. Wolffenstein, *Ber.*, **37**, 3219 (1904).

(17) P. P. Bedson, *J. Chem. Soc.*, **37**, 95 (1880).

(18) C. L. Jackson and J. F. White, *Am. Chem. J.*, **2**, 315 (1880).

(19) 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).

(20) J. v. Braun, E. Anton, and K. Weissbach, *Ber.*, **63**, 2847 (1930).

Reaction of 4-t-butyl-2,6-dimethylbromobenzene with n-butyllithium. A solution of 5.0 g. (0.021 mole) of 4-*t*-butyl-2,6-dimethylbromobenzene in 100 ml. of ether was added dropwise to a flash containing 150 ml. (0.083 mole) of 0.55*N* *n*-butyllithium during 0.5 hr. After the mixture had been heated for 0.5 hr., with stirring, it was poured on excess solid carbon dioxide. By the usual procedure was isolated 2.1 g. (48%) of 4-*t*-butyl-2,6-dimethylbenzoic acid, m.p. 164–168°. This acid has been reported to melt at 167–168°.[13]

Reaction of o-bromobenzyl methyl ether with lithium. To a flask containing 2.08 g. (0.30 g.-atom) of lithium metal cut in small pieces and 100 ml. of ether was added all at once 5 g. of *o*-bromobenzyl methyl ether in 25 ml. of ethyl ether. A stream of nitrogen was passed through the mixture, which was stirred mechanically. While the mixture was heated sufficiently to maintain gentle refluxing, 25 g. of *o*-bromobenzyl methyl ether, which made a total of 30 g. (0.15 mole), dissolved in 100 ml. of ether was added during 1 hr. Stirring was continued for 20 hr. at the end of which time most of the lithium had disappeared. The solution was filtered under nitrogen on solid carbon dioxide. The mixture was extracted with base; acidification of these extracts, however, failed to give an acid. The ether layer was washed and dried. The residual liquid left by evaporation of the solvent was distilled under vacuum. The first fraction (b.p. 46–48°/0.1 mm.) solidified when allowed to stand and melted at 45–51°. This melting point, the odor, and the infrared spectrum, which exhibits a band (695 $cm.^{-1}$) assignable to a monosubstituted benzene, suggested that the compound was bibenzyl. The melting point for bibenzyl is reported at 52°.[21]

Later fractions boiled at 52–74°/0.1 mm. and 72–75°/0.1 mm. The infrared spectra of these fractions show bands assignable to a monosubstituted benzene (698 $cm.^{-1}$), an *o*-disubstituted benzene (758 $cm.^{-1}$) and an aliphatic ether (1100 $cm.^{-1}$). An undistillable residue remained which could not be purified by chromatography or crystallization.

Reaction of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene with lithium. The reaction was initiated by the addition of a solution of 5 g. of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene in 15 ml. of ether to 0.85 g. (0.12 g.-atom) of lithium in 50 ml. of ether. When heat was applied, with stirring under nitrogen, fairly vigorous refluxing began. At this point an additional 10 g. of the ether bromide, making a total of 15 g. (0.055 mole), in 50 ml. of ether was added dropwise in 0.5 hr. The mixture was stirred under reflux overnight. Treatment with carbon dioxide gave no acid. The ether layer remaining after the basic extraction was dried. Distillation of the residue obtained by evaporation of the solvent yielded a liquid which boiled at 67–68°/0.5 mm. The yield was 2.7 g. or 25%, based on the assumption that the compound is 3-*t*-butyl-5-methoxymethyltoluene.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.34; H, 10.69.

The infrared spectrum of this compound exhibits bands assignable to an aliphatic ether (1108 $cm.^{-1}$) and a 1,3,5-trisubstituted benzene (855, 708 $cm.^{-1}$). Attempts to purify the nondistillable residue were unsuccessful.

Treatment of 4-t-butyl-2,6-di(methoxymethyl)bromobenzene with lithium. A mixture of 1.5 g. (0.005 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene and 0.076 g. (0.011 g.-atom) of lithium in 50 ml. of ether was heated to reflux, with stirring. Although the stirring was allowed to continue for 20 hr., little sign of reaction was noticed and no acid was obtained by treatment of the mixture with carbon dioxide. Only starting material was recovered from the ether layer.

Reaction of 4-t-butyl-2,6-dimethylbromobenzene with lithium. To a flask containing 0.633 g. (0.091 g.-atom) of lithium and 100 ml. of ether was added 1.0 g. of 4-*t*-butyl-2,6-dimethylbromobenzene. The flask was warmed and in a few minutes the ether became turbid, which indicated that the reaction had begun. A solution containing 9.0 g. (which made a total of 10.0 g. or 0.041 mole) of the bromide in 50 ml. of ether was then added dropwise during 0.5 hr. The mixture was heated, under gentle reflux, with stirring, for about 20 hr. After unchanged lithium had been removed by filtration through glass wool, the solution was poured on solid carbon dioxide. The carbonated material was extracted with three 50-ml. portions of 10% sodium hydroxide solution. When the basic extracts were acidified, 4-*t*-butyl-2,6-dimethylbenzoic acid precipitated as a cream colored solid. After several recrystallizations from low-boiling petroleum ether–methylcyclohexane, the acid weighed 2.6 g. (30%), m.p. 166–168°. The reported melting point is 167–168°.[13]

Oxidation of o-bromobenzyl methyl ether. A mixture of 5.0 g. (0.025 mole) of *o*-bromobenzyl methyl ether and 50 ml. of water was heated with stirring on a steam bath until the water began refluxing. A solution of 14.5 g. of potassium permanganate in 250 ml. of water was then added dropwise to the emulsion during 0.5 hr. The mixture was stirred under reflux for 3 hr. Manganese dioxide was removed by filtering the hot alkaline mixture on a Büchner funnel. The manganese dioxide was washed with two 50-ml. portions of hot water, and the resulting clear, yellow filtrate was concentrated to a volume of about 200 ml. When concentrated hydrochloric acid was added to this hot solution, a white precipitate formed immediately. After the solution had cooled, the solid was collected on a filter and washed with water until the filtrate was free of chloride ion. The dried *o*-bromobenzoic acid weighed 4.3 g. (86%), m.p. 146–147°. The literature records a melting point of 150°.[22]

Oxidation of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene. The procedure was nearly the same as that described in the preceding experiment. A mixture of 3.5 g. (0.013 mole) of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene and 30 ml. of water was heated, with stirring; to it was added a solution of 6.7 g. (0.043 mole) of potassium permanganate in 140 ml. of water during 15 min. Since permanganate ion was still present at the end of 8 hr., stirring was continued overnight. The next morning the purple color had disappeared, and the solution was alkaline. The mixture was filtered, the manganese dioxide washed, and the filtrate concentrated to a volume of about 100 ml. Acidification caused precipitation of the crude 2-bromo-5-*t*-butylisophthalic acid as a colorless solid. It was collected by filtration, washed, and air dried, m.p. 243–257°, yield 1.7 g. On the basis of the potassium permanganate used this is a yield of 71%. After one recrystallization from dioxane-benzene, the acid melted at 255–256°. An analytical sample of the acid was prepared by sublimation.

Anal. Calcd. for $C_{12}H_{13}O_4Br$: C, 47.84; H, 4.32. Found: C, 47.95; H, 4.43.

Reaction of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene with magnesium. To a flask containing 1.6 g. (0.068 g.-atom) of magnesium and a crystal of iodine was added several drops of a solution containing 8.8 g. (0.032 mole) of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene and 3.5 g. (0.032 mole) of ethyl bromide in 60 ml. of ether. The flask was warmed and, after the Grignard reaction had begun, the remaining solution was added dropwise over 1.5 hr. The mixture was then stirred under gentle reflux for 15 min. during which time almost all the magnesium was consumed. The dark brown mixture was poured on solid carbon dioxide, and the carbonated material allowed to reach room temperature. The crude 4-*t*-butyl-2-methoxymethyl-6-methylbenzoic acid isolated by usual procedures, melted at 70–76°, yield 3.0 g. Its purification was effected by recrystallization from low-boiling petroleum ether–methylcyclohexane. The pure acid weighed 2.0 g. (26%), m.p. 80–81°.

Reaction of 4-t-butyl-2-(β-methoxy)ethyl-6-methylbenzyl chloride with magnesium. A solution containing 3.5 g. (0.014

(21) R. A. Smith and S. Natelson, *J. Am. Chem. Soc.*, **53**, 3476 (1931).

(22) M. Rhalis, *Ann.*, **198**, 103 (1879).

mole) of 4-*t*-butyl-2-(β-methoxy)ethyl-6-methylbenzyl chloride in 100 ml. of ether was allowed to drop upon 0.7 g. (0.03 g.-atom) of magnesium over a period of 2 hr. The 4-*t*-butyl-2-(β-methoxy)ethyl-6-methylphenylacetic acid, isolated in the usual way, melted at 81–83°, yield 1.0 g. (28%). Further recrystallization of this compound from low-boiling petroleum ether–methylcyclohexane raised the melting point to 83–84°.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 73.01; H, 9.36.

Treatment of 4-t-butyl-2,6-di(methoxymetny')bromobenzene with magnesium. Various attempts to effect a reaction between 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene and magnesium were made. Such solvents as ether, benzene, toluene, and tetrahydrofuran as well as ether-benzene and ether-toluene solvent pairs were used. Catalysts employed were iodine, ethyl bromide, mercuric chloride, and aluminum chloride. In all cases only starting material was recovered.

4-t-Butyl-2,6-di(methoxymethyl)iodobenzene. To a flask containing a solution of 6.0 g. (0.02 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene in 100 ml. of ether was added 60 ml. of 0.68*N* (0.04 mole) *n*-butyllithium. The orange-brown mixture was heated, with stirring, for 1 hr. and then cooled in an ice bath. The addition of a solution of 15.2 g. (0.060 mole) of iodine in 75 ml. of ether to the cold mixture was begun. The mixture was stirred for an additional hour in the cold and decomposed with crushed ice. The ether layer, after separation from the water layer, was washed successively with 50 ml. of a 5% sodium sulfite solution and water and dried over magnesium sulfate. After the ether had been removed the residue crystallized readily. The iodide, recrystallized from 95% ethanol, melted at 76–77°, yield 4.8 g. (69%).

Anal. Calcd. for $C_{14}H_{21}O_2I$: C, 48.28; H, 6.03. Found: C, 48.34; H, 5.98.

Treatment of 4-t-butyl-2,6-di(methoxymethyl)iodobenzene with magnesium. A mixture of 1.5 g. (0.0043 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)iodobenzene and 0.94 g. (0.0086 mole) of ethyl bromide in 50 ml. of ether was added dropwise during 0.5 hr. to a flask containing 0.42 g. (0.017 g.-atom) of magnesium. After the addition, the mixture was stirred under reflux for 7 hr. and filtered through glass wool on solid carbon dioxide. The mixture failed to yield any acidic product.

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

Applicability of the Arndt-Eistert Reaction to Fluorinated Acids and Their Derivatives[1]

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Perfluorinated acids containing three or more carbon atoms failed to undergo the Arndt-Eistert reaction in a normal fashion. At least two methylene groups must be present in order to obtain satisfactory yields from this reaction. In all cases, it appears that the intermediate diazo ketone is formed and that it is the second stage of the reaction, the Wolff rearrangement, that fails to take place normally, resulting in the formation of α-halo ketones.

The following ketones, $C_2F_5COCH_2Cl$, $C_3F_7COCH_2Cl$, and $C_3F_7COCH_2Br$ were prepared and characterized, and the physical properties of a number of new compounds were determined and tabulated.

This investigation reports on the applicability of the Arndt-Eistert reaction[2] to perfluorinated acids and their homologs and to the preparation of ketones of the type R_FCOCH_2X (where X is any halogen and R_F is a perfluorinated group) from perfluorinated acids and diazomethane. Since perfluorinated acids are now commercially available, it seemed the easiest and most direct way of preparing the higher acids and ketones containing the perfluorinated group.

The acids, C_2F_5COOH, C_3F_7COOH, $C_3F_7CH_2COOH$, $C_3F_7CH_2CH_2COOH$, and C_4F_9COOH, were converted to their respective acid chlorides, and added to an excess of cold ethereal diazomethane to form the corresponding diazo ketone. In each case, the diazo ketone was isolated but not purified, before the attempted rearrangement. The presence of the $-COCHN_2$ group was shown by the evolution of nitrogen when the compound was treated with concentrated hydrochloric acid.

The diazo ketones derived from C_2F_5COOH, C_3F_7COOH and C_4F_9COOH failed to undergo the Wolff rearrangement and the diazo ketone from $C_3F_7CH_2COOH$ appeared to give only negligible amounts of $C_3F_7(CH_2)_2COOCH_3$. The diazo ketone derived from $C_3F_7(CH_2)_2COOH$ underwent the rearrangement in a normal fashion in good yield.

The acids, n-$C_3F_7CH_2COOH$ and $C_3F_7CH_2CH_2COOH$ were prepared from C_3F_7COOH through the following sequence of previously known reactions.

$$R_FCOOH \xrightarrow{AgOH} R_FCO_2Ag^{3} \xrightarrow{I_2} R_FI^{4} \xrightarrow{CH_2=CH_2}$$

$$R_FCH_2CH_2I^{5} \xrightarrow{Mg} R_FCH_2CH_2MgI \xrightarrow{O_2}$$

$$R_FCH_2CH_2OH^{6} \xrightarrow{[O]} R_FCH_2COOH^{6}$$

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(2) W. E. Bachmann and W. S. Struve, *Org. Reactions*, I, 38–62 (1942).

(3) Minnesota Mining and Mfg. Co., pamphlet, *Preparation of Silver Heptafluorobutyrate.*

(4) R. N. Haszeldine, *J. Chem. Soc.*, 584 (1951).

(5) R. N. Haszeldine, *J. Chem. Soc.*, 2856 (1949).

(6) A. L. Henne, R. L. Pelley, and R. M. Alm, *J. Am. Chem. Soc.*, **72**, 3370 (1950).

Musgrave and Brown[8] have recently shown that CF_3CO_2H and CCl_3CO_2H undergo the Arndt-Eistert reaction normally and in good yield when the ester of the next higher homologous acid is formed, but give unsatisfactory yields of the acid, amide, or anilide. The reaction of CF_3CO_2H to give $CF_3CH_2CO_2C_2H_5$ has been verified by us.

It is concluded that perfluorinated acids, with the exception of CF_3COOH, fail to undergo the Arndt-Eistert reaction in a normal fashion, and that at least two insulating methylene groups must be present between the R_F and COOH groups in order to obtain satisfactory yields from this reaction. In all cases it appears that the intermediate diazo ketone is formed and that it is the second stage of the reaction, the Wolff rearrangement, that fails to take place normally.

The ketones, $C_2F_5COCH_2Cl$, $C_3F_7COCH_2Cl$ and $C_3F_7COCH_2Br$, were obtained by treating the respective acid halide with diazomethane. In the case of the α-chloroketone, the yield obtained by first forming the diazo ketone and treating this with anhydrous hydrogen chloride was essentially the same as that obtained by treating the acid chloride with diazomethane directly. The α-haloketones are strongly lachrymatory.

Attempts to prepare $C_3F_7COCH_2F$ and $C_3F_7COCH_2I$ failed. In the case of $C_3F_7COCH_2I$ various attempts were made, but the reaction was uncontrollable. Attempts to prepare $C_3F_7COCH_2F$ were confined to the treatment of C_3F_7COF with diazomethane. In general, it was found that the preparation of ketones of the type R_FCOCH_2X by this means is of little practical value, except in cases where only small amounts are desired by a rapid procedure.

EXPERIMENTAL

The acids, CF_3COOH, C_3F_7COOH and C_4F_9COOH were obtained from the Minnesota Mining and Mfg. Co., St. Paul, Minn. The acid chlorides were prepared by conventional methods using PCl_5 or $SOCl_2$ and purified before use by distillation. The diazomethane[9] was prepared from *N*-nitrosomethylurea as described by Bachmann *et al.*[2]

3,3,4,4,5,5,5-Heptafluoro-1-pentanol. Method I. A dry 2-l. three-neck flask was equipped with a Herschberg stirrer, reflux condenser, dropping funnel, and a gas inlet tube for passing dry nitrogen through the system. The condenser outlet was connected to a calcium chloride drying tube and a bubbler. The nitrogen was dried by passing it through a train consisting of a concentrated sulfuric acid scrubber and a drying tube filled with potassium hydroxide pellets.

Twelve grams (0.5 mole) of reagent grade magnesium was introduced into the flask and the apparatus was flamed. A nitrogen atmosphere was maintained by passing a slow stream of dry nitrogen through the apparatus during the reaction.

Ten ml. of ethereal methyl iodide (2 g.) was added to start the reaction, and then 126 g. (0.39 mole) of n-$C_3F_7CH_2CH_2I$, dissolved in 1 l. of sodium-dried ether, was added at a rate sufficient to maintain reflux. When the addition was complete the mixture was refluxed on a steam bath for 0.5 hr.

The mixture was cooled to −78° in a Dry Ice–acetone bath and dry oxygen was passed into the reaction flask along with the nitrogen for about 10 hr., during which time a gray salt precipitated. The mixture was allowed to warm and 200 ml. of water was added dropwise, followed by the addition of 40 ml. of concentrated hydrochloric acid.

The ether layer was removed and the aqueous layer extracted with three 50-ml. portions of ether. The combined ether layers were dried over anhydrous magnesium sulfate, the ether stripped off and the residue distilled. The fraction boiling at 116–117°/630 mm., was collected. The yield of heptafluoropentanol was 64 g. (77%).

Method II. About 0.055 mole (14 g.) of $C_3F_7CH_2CH_2O$-$COCH_3$ was mixed with 10 ml. of β,β-dihydroxyethyl ether and 0.07 mole (4 g.) of potassium hydroxide in a stoppered 25-ml. flask. The mixture was allowed to stand, with occasional shaking, at room temperature for 48 hr. The alcohol was distilled directly from the reaction mixture through a 10-theoretical plate, platinum spiral Todd column, and the fraction (10.5 g., 91%) boiling at 116–117°/632 mm. was collected; n_D^{20} 1.3151; d_4^{20} 1.506.

Anal. Calcd. for $C_5H_5F_7O$: C, 28.05; H, 2.35; F, 62.12. Found: C, 28.32; H, 2.6; F, 61.9.

3,3,4,4,5,5,5-Heptafluoro-1-pentyl acetate. Fifty grams (0.17 mole) of $C_3F_7CH_2CH_2I$, 50 g. (0.3 mole) of silver acetate and 100 ml. of glacial acetic acid were placed in a 300-ml. flask fitted with a reflux condenser and a calcium chloride drying tube. The mixture was refluxed for 48 hr. with occasional shaking. The solid became yellow, almost immediately, due to the formation of silver iodide.

The reaction mixture was cooled and slowly poured into 300 g. of cracked ice. The solution was filtered and the precipitate washed with 50 ml. of ether. The filtrate was extracted three times with 50-ml. portions of ether and the combined ether layers washed with a saturated solution of sodium bicarbonate to remove any dissolved acid and dried over anhydrous sodium sulfate.

The ether was stripped off and the residue was rectified on a 10-theoretical plate, platinum spiral Todd column. The fraction boiling at 132.5–133.0°/630 mm. was collected. The yield of ester was 24.0 g. (55%); n_D^{20} 1.3283, d_4^{20} 1.4135.

Anal. Calcd. for $C_7H_7F_7O_2$: C, 32.82; H, 2.76; F, 51.93. Found: C, 32.7; H, 2.9; F, 51.71.

3,3,4,4,5,5,5-Heptafluoropentanoic acid. Twenty-one grams (0.1 mole) of n-$C_3F_7CH_2CH_2OH$ was dissolved in 140 ml. of technical grade acetone in a 250-ml. three-neck flask fitted with a mechanical stirrer, dropping funnel, condenser, and thermometer. The mixture was cooled to 0° in an ice-salt bath maintained at −5° and 14 g. (0.14 mole) of powdered chromium trioxide was added portionwise. The addition took about 0.5 hr., during which time the temperature of the mixture was not allowed to exceed 15°. The mixture was again cooled to 0° and 15 ml. (0.35 mole) of concentrated sulfuric acid was added dropwise. The addition took about 1 hr., during which the temperature was not allowed to exceed 15°. The mixture was kept at 15° for 1 hr. after the addition was completed. The ice-salt bath was removed and the temperature allowed to rise. The temperature spontaneously reached 35° and then fell to room temperature. The reaction mixture was filtered through Filter-Cel, dried over Drierite, and the acetone was stripped off. The residue was distilled in a modified Claisen distilling flask and the fraction boiling between 50–70° at 6 mm. was collected and redistilled through a 10-theoretical plate, platinum spiral Todd column. The fraction boiling at 62–63°/6 mm. was collected. The yield was 13 g. (57%); b.p. 170–172°/630 mm.; m.p. 10°, n_D^{20} 1.3202; d_4^{20} 1.604.

(7) E. T. McBee and A. Truchan, *J. Am. Chem. Soc.*, **70**, 2910 (1948).

(8) F. Brown and W. K. R. Musgrave, *J. Chem. Soc.*, 2087 (1953).

(9) F. Arndt, *Org. Syntheses*, **15**, 48 (1935).

Anal. Calcd. for $C_5H_3F_7O_2$: C, 26.34; H, 1.33; F, 58.31. Found: C, 26.5; H, 1.51; F, 58.6.

The method described by Henne *et al.*[6] for the oxidation of $CF_3CH_2CH_2OH$ resulted in only 4% yield of $C_3F_7CH_2$-COOH when applied to the alcohol $C_3F_7CH_2CH_2OH$.

Oxidation of $C_3F_7CH_2CH_2OH$ with CrO_3 in glacial acetic acid resulted in about a 10% yield of the corresponding acid. The procedure described by Powell[10] for the oxidation of $CH_2Cl—CH_2CH_2OH$ with concentrated HNO_3, when applied to this study resulted in total destruction of the alcohol.

4,4,5,5,6,6,6-Heptafluorohexanoic acid. Four grams (0.17 mole) of dry magnesium turnings were placed in a dry 500-ml. flask fitted with a reflux condenser and dropping funnel. The whole apparatus was then heated with an open flame. The reaction was started by adding 10 g. of $C_3F_7CH_2CH_2I$ and 10 ml. of sodium-dried ether, and warming on a water bath. The reaction started immediately. An additional 40 g. (to make 0.154 mole) of $C_3F_7CH_2CH_2I$ in 200 ml. of ether was added at a rate sufficient to maintain reflux. The mixture was refluxed for an additional hour after the addition was completed to insure completeness of reaction. The reaction mixture was poured slowly onto approximately 100 g. of finely crushed Dry Ice in a 1500-ml. beaker. When the excess Dry Ice had evaporated the mixture was poured into 250 g. of cracked ice in a 500-ml. beaker and 30 ml. of concentrated hydrochloric acid was added. The mixture was poured into a separatory funnel and the beaker was rinsed with 50 ml. of benzene. The water layer was removed and extracted with two 50-ml. portions of benzene. The benzene and ether layers were combined and dried for 1 hr. over anhydrous sodium sulfate. The ether and benzene solvents were distilled through an 8-inch Vigreux column. The residue was placed in a sublimation apparatus and the remaining benzene removed under vacuum. The residue was sublimed at 4 mm. pressure to yield 20 g. of acid (55%); m.p. 36–37° (literature[11] m.p. 37°).

Preparation of 3,3,4,4,5,5,5-heptafluoropentanoyl chloride and the amide. Twenty-six grams (0.114 mole) of n-$C_3F_7CH_2$-CO_2H was placed in a 35-ml. flask fitted with a reflux condenser. The top of the condenser was attached to a calcium chloride drying tube and a dilute sodium hydroxide scrubber. Fifteen ml. (0.21 mole) of thionyl chloride was added and the mixture refluxed for 15 hr.

The reflux condenser was replaced by a 4-in. metal spiral distilling column and the excess thionyl chloride was stripped off. The acid chloride was distilled under reduced pressure and the fraction (12 g., 41.5%) boiling at 52–53°/140 mm., 94–95°/630 mm. was collected. (Approximately 10 g. of the acid was recovered, some decomposition took place during distillation.)

About 1 g. of the acid chloride was treated with dilute aqueous ammonia to yield the amide. The recrystallized and sublimed amide melted at 92.5–93.0°.

Anal. Calcd. for $C_5H_4F_7ON$: C, 26.44; H, 1.77; N, 6.17. Found: C, 26.80; H, 1.72; N, 6.18.

Preparation of 4,4,5,5,6,6,6-heptafluorohexanoyl chloride and amide. Eighteen grams (0.074 mole) of n-$C_3H_7(CH_2)_2$-CO_2H was treated under conditions similar to those used to prepare n-$C_3F_7CH_2COCl$. In this case, however, the mixture was refluxed for only 2 hr. The yield of acid chloride, b.p. 125–126°/627 mm., was 14 g. (73%).

About 1 g. of the acid chloride was treated with dilute aqueous ammonia. The precipitated amide, n-$C_3H_7(CH_2)_2$-$CONH_2$, was recrystallized from water and sublimed, m.p. 96.5–97.0°.

5,5,6,6,7,7,7-Heptafluoroheptanamide. Eighteen grams (0.074 mole) of $C_3F_7(CH_2)_2CO_2H$ was placed in a 50-ml. flask fitted with a condenser, an absorbent cotton drying tube, and an aqueous sodium hydroxide scrubber. Thirteen grams (0.11 mole) of redistilled thionyl chloride (b.p. 73–74°/628 mm.) was added and the mixture refluxed for 2 hr. The mixture was distilled in a modified Claisen distilling flask and the acyl chloride, b.p. 125–127°/627 mm. was collected.

The acyl chloride (14 g.) was dissolved in 100 ml. of sodium-dried ether and was added dropwise to a vigorously stirred solution of 0.3 mole of diazomethane in 500 ml. of ether. The mixture was kept below −10° for 2 hr. after the addition was complete. The mixture was allowed to warm to room temperature and the ether was removed under vacuum. The crude diazoketone was dissolved in 100 ml. of dioxane and placed into a 500-ml. three-neck flask. The flask was fitted with a dropping funnel, stirrer, and condenser. The outlet of the condenser was connected to an air-cooled trap, a water scrubber, a dilute sulfuric acid scrubber, and a bubbler. Approximately 150 ml. of aqueous ammonia (sp. gr. 0.90) was added to the mixture and heated to 60–70° on a water bath. To the mixture 30 ml. of 10% aqueous silver nitrate was added dropwise. The mixture was then heated to reflux for 2 hr., cooled, and the amide precipitated by the addition of 250 ml. of cold water. The precipitated amide was filtered, taken up in alcohol, and refiltered to remove the silver oxide. The alcohol was evaporated and the crude amide was sublimed from the tarry residue. The yield of the amide was 6.2 g. (33%); m.p. 101.5–102°.

Anal. Calcd. for $C_7H_8F_7NO$: C, 32.9; H, 3.16; N, 5.5. Found: C, 33.1; H, 3.04; N, 5.5.

Attempted preparation of 3,3,4,4,4-pentafluorobutyric acid. About 20 g. of C_2F_5COCl (1.16 moles) in 75 ml. of anhydrous Et_2O was slowly added with stirring to a solution of approximately 0.3 mole diazomethane in 0.5 l. of ether cooled to 0° to −10°. After completion of the addition, the solution was kept cold and stirred for an hour and finally allowed to warm up to room temperature with stirring over a period of 6 to 7 hr. The excess ether was then removed under reduced pressure with a water aspirator at room temperature. A bright yellow, oily liquid was obtained which evolved nitrogen vigorously when treated with concentrated HCl, indicating the presence of the $—CHN_2$ group. This diazo ketone was dissolved in 100 ml. of dioxane and added dropwise to a solution of 2 g. of silver oxide, 3 g. of sodium thiosulfate and 5 g. of sodium carbonate in 200 ml. of H_2O at 50–60°. The mixture was stirred for an hour after completion of the addition and finally heated to reflux for an hour.

The solution was then cooled, acidified with dilute nitric acid, and extracted with ether. The dried ether solution upon distillation did not yield any of the expected product.

The attempted Wolff rearrangement carried out with the diazo ketone dissolved in alcohol or in the presence of dioxane and aqueous ammonia did not yield the expected amide or ester.

Attempted preparation of $C_4F_9CH_2COOEt$. C_4F_9COCl was treated with CH_2N_2 in a manner similar to that described for the attempted preparation of $C_2F_5CH_2COOH$. Although the corresponding diazoketone was formed, the normal Wolff rearrangement to $C_4F_9CH_2$ COOEt did not take place.

Preparation of heptafluoropropyl chloromethyl ketone. Method I. Twenty-three grams (0.1 mole) of perfluorobutyryl chloride was dissolved in 150 ml. of sodium-dried ether in a 1-l., three-neck flask fitted with a dropping funnel, stirrer, and calcium chloride drying tube. The mixture was cooled in an ice-salt bath to −15°, and ethereal diazomethane was added dropwise to the vigorously stirred solution. The addition was stopped when the solution became pale yellow showing the presence of excess diazomethane. The mixture was kept cold for an additional 2 hr. and then allowed to warm to room temperature. The ether was stripped off and the residue rectified on a micro Podbielniak glass concentric-tube column. The yield of α-chloroketone, b.p. 97–98° at 625 mm. was 7.0 g. (28.5%), n_D^{20} 1.3240 and d_4^{20} 1.580.

Anal. Calcd. for $C_5H_2ClF_7O$: C, 24.3; F, 54.0. Found: C, 24.6; F, 53.9.

(10) S. G. Powell, *J. Am. Chem. Soc.*, 46, 2879 (1924).

(11) Private communication from the Minnesota Mining & Mfg. Co., St. Paul, Minn.

TABLE I

SUMMARY OF PROPERTIES OF NEW COMPOUNDS

Compound	B.P. °C.	Mm. Hg	M.P., °C.	n_D^{20}	d_4^{20}	Molar Refraction Calcd.[a]	Found	AR_F Calcd.
n-$C_3F_7CH_2CH_2I$	112–113	628	−5	1.3771	1.918	38.10	38.89	1.21
	77.8	185						
	44.3	47						
n-$C_3F_7CH_2CH_2OCOCH_3$	132	633		1.3283	1.4135	35.49	36.8	1.24
n-$C_3F_7CH_2CH_2OH$	116–117	632		1.3151	1.506	26.83	27.81	1.24
	62–63	111						
n-$C_3F_7CH_2COOH$	170–172[b]	630	10	1.3202	1.604	26.84	28.21	1.31
	62.3	6						
n-$C_3F_7CH_2CONH_2$			92.5– 93					
n-$C_3F_7(CH_2)_2CONH_2$			96.5– 97					
n-$C_3F_7(CH_2)_3CONH_2$			102.5–103					
n-$C_3F_7COCH_2Cl$	97–98	625		1.3240	1.580	30.18	31.8	1.21
	61	178						
n-$C_3F_7COCH_2Br$	118	631		1.3436	1.818	33.08	33.88	1.22
	80.2	213						
$C_2F_5COCH_2Cl$	74	634		1.3088	1.348	26.55	27.8	1.34

[a] Calculated from the Lorenz-Lorentz formula with 1.1 as AR_f for fluorine. [b] With dec.

Method II. Twenty-three grams (0.1 mole) of C_3F_7COCl dissolved in 150 ml. of sodium-dried ether was added dropwise to 500 ml. of ethereal diazomethane (prepared from 35 g. of *N*-methylnitrosourea) contained in a 1-l. three-neck flask fitted with a dropping funnel and stirrer. The third neck was protected with a calcium chloride drying tube. The reaction mixture was kept cold (0° to −10°) during the addition of the acid chloride.

When the addition was completed the mixture was allowed to warm to room temperature and allowed to stand for 8 hr. The dropping funnel was replaced by a gas inlet tube, and a bubbler was attached to the drying tube outlet. Anhydrous hydrogen chloride, passed successively through a safety trap, a concentrated sulfuric acid scrubber, and a second safety trap, was passed slowly into the solution. When the evolution of nitrogen ceased, the flow of hydrogen chloride was discontinued. The solution was then worked up as described in Method I. The yield of $C_3F_7COCH_2Cl$ (b.p. 98.5–99.5°/632 mm.) was 7 g. (28.5%).

Preparation of heptafluoropropyl bromomethyl ketone. This reaction was carried out under conditions similar to that described for $C_3F_7COCH_2Cl$ (Method I). Twenty-eight grams (0.1 mole) of C_3F_7COBr was used. The fraction boiling at 80–81° at 213 mm. was collected. The yield of α-bromoketone was 6 g. (20%), n_D^{20} 1.3436; d_4^{20} 1.818.

Anal. Calcd. for $C_5H_2BrF_7O$: C, 20.64; H, 0.69; Br, 27.46. Found: C, 20.69; H, 0.80; Br, 27.80.

Pentafluoroethyl chloromethyl ketone was prepared in a manner similar to that used for the preparation of $C_3F_7COCH_2Cl$.

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BOULDER, COLO.

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

Action of Aluminum Chloride on Hexafluoropropene

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Aluminum chloride has been found to react with hexafluoropropene to yield $CF_3CF{=}CFCl$, $CF_3CF{=}CCl_2$, $CF_2ClCF{=}CCl_2$, $CFCl_2CF{=}CCl_2$, $CCl_3CF{=}CCl_2$ and $CCl_3CCl{=}CCl_2$. A mechanism for the reactions involving replacement as well as rearrangement is postulated.

The reaction of aluminum chloride with chlorofluoroalkanes to replace fluorine by chlorine has been reported by Henne[2,3] and Miller and his co-workers.[4–6] In the present work, the action of aluminum chloride on hexafluoropropene was studied to ascertain the order of replacement of the organically bound fluorine atoms by chlorine and the de-

(1) From the Ph.D. dissertation submitted to the University of Colorado, May 1953. E. I. du Pont de Nemours & Co., Inc., Pre-doctoral fellow; 1952–1953.

(2) A. L. Henne and H. M. Leicester, *J. Am. Chem. Soc.*, **60**, 864 (1938).

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(6) W. A. Miller, Jr., U. S. Patent Application **47,553**. *Chem. Abstr.*, **47**, 4895 (1953).

velopment of this method as a simple procedure for the synthesis of various chlorofluoropropenes.

A study of the chlorofluoroolefins isolated, $CF_3CF{=}CFCl$, $CF_3CF{=}CCl_2$, $CF_2ClCF{=}CCl_2$, $CFCl_2CF{=}CCl_2$, $CCl_3CF{=}CCl_2$ and $CCl_3CCl{=}CCl_2$, reveals that only one isomer was obtained. This seems to rule out the possibility of random substitution.

Miller[6] has shown the singular example of the rearrangement of $CFCl_2CF{=}CF_2$ to $CF_2ClCF{=}CFCl$ under the catalytic influence of aluminum chloride without reporting experimental conditions or finding the isomer $CF_3CF{=}CCl_2$ as one of the intramolecular rearrangement products.

In this study the stability of the chlorofluoro groupings toward replacement and/or rearrangement reactions with aluminum chloride in the perhalopropenes was found to be in the following order:

$$\text{F}\!\!-\!\!\text{C}\!= > CF_3\!- > CF_2Cl\!- > CFCl_2 > =\!C\!\!<\!\!\!\!\!\!\begin{matrix}F\\Cl\end{matrix} > =\!C\!\!<\!\!\!\!\!\!\begin{matrix}F\\F\end{matrix}$$

The fluorine atom on the central carbon atom showed the greatest resistance to replacement by chlorine. In contrast to this, Miller[5] found that the fluorine atom on the central carbon atom in $CF_2ClCFClCF_2Cl$ was most easily replaceable or rearranged to $CF_3CCl_2CF_2Cl$ and $CF_3CCl_2CCl_3$.

Under the conditions of our study, $CF_3CF{=}CCl_2$ and $CCl_3CF{=}CCl_2$ were obtained in the largest quantities. The olefins, $CF_3CF{=}CFCl$, $CF_2ClCF{=}CCl_2$ and $CFCl_2CF{=}CCl_2$, were found in small amounts. Since the remarkable chemical stability of the CF_3- and CCl_2-groups is well-known in these aluminum chloride reactions,[5,7] the greater yield of $CF_3CF{=}CCl_2$ (in comparison to $CF_2ClCF{=}CCl_2$ and $CFCl_2CF{=}CCl_2$) may be attributed to this factor. These results parallel the stability of the above groups toward chlorine replacement by reagents such as antimony fluoride.

EXPERIMENTAL

Hexafluoropropene was obtained from the pyrolysis of $CF_3CF_2CF_2COONa$ according to the method of Hals, Reed, and Smith.[8]

Action of $AlCl_3$ on hexafluoropropene at low temperatures. The reaction between $AlCl_3$ and $CF_3CF{=}CF_2$ was first investigated by heating the reactants in a Pyrex combustion tube at a series of temperatures ranging from 0° to 150°. The temperature range, 50–60°, gave the best conversion of $CF_3CF{=}CF_2$ to chlorofluoropropenes with the least amount of tar formation.

About 266 g. (2 moles) of anhydrous granular aluminum chloride (Baker C.P.) was first placed in a 500 ml. capacity Parr bomb and then evacuated. After cooling the bomb to −78°, about 150 g. (1 mole) of $CF_3CF{=}CF_2$ was added. The bomb and its contents were allowed to warm gradually to room temperature under agitation and the temperature gradually raised to 50°. A maximum pressure of 200–250 p.s.i.g. was obtained in the first hour which gradually decreased to 150–200 p.s.i.g. during the next 4 hours with the temperature still at 50–60°. After being cooled to room temperature, the bomb was chilled to −20°, after which the gases were vented into a trap cooled to −78°. The recovery was 47 g. of hexafluoropropene.

The bomb was opened and the liquid products decanted from the solid residue. In 3 similar runs, a total of 450 g. (3 moles) of $CF_3CF{=}CF_2$ and 798 g. (6 moles) of $AlCl_3$ were used. The recovery was 125 g. of $CF_3CF{=}CF_2$ and 131 g. of liquid products. The solid residue, which contained a considerable amount of tar, weighed 927 g. The over-all material recovery for the 3 runs was 1183 g. as against an original total charge of 1248 g. The recovery was 94.8%.

Hydrolysis of the solid residue. A 3-l. three-neck flask was equipped with a dropping funnel, a feed-tube for solids and a reflux condenser with a gas delivery outlet leading to a series of traps cooled in an ice water and a dry ice acetone bath. Dilute hydrochloric acid and the solid residue were fed into the flask and allowed to react in an excess of the acid. An oil separated from the aqueous reaction mixture along with a large amount of tar. The gases which were liberated and collected in the traps amounted to 21 g. The aqueous acid solution containing the oil-tar layer was neutralized with dilute base and after cooling extracted with Skelly Solve B and the extract dried over sodium sulfate. Distillation of the 21 g. of gaseous products combined with the 131 g. of liquid yielded the following cuts: 2.9 g. of $CF_3CF{=}CFCl$;[9] 28 g. of $CF_3CF{=}CCl_2$;[10] 4.1 g. of $CF_2ClCF{=}CCl_2$; b.p. 79.6°/627 mm.; n_D^{20} 1.4046; d_D^{20} 1.6084.

Anal. Calcd. for $C_3Cl_3F_3$: C, 18.05; Cl, 53.5. Found: C, 18.03; Cl, 53.1.

3.6 g. of $CFCl_2CF{=}CCl_2$; b.p. 121° (627 mm.); n_D^{20} 1.4891; d_4^{20} 1.6562.

Anal. Calcd. for $C_3Cl_4F_2$: C, 16.66; Cl, 65.71. Found: C, 17.05; Cl, 65.70.

Distillation of the oil obtained from the hydrolysis of the solid residue yielded only small quantities of the above olefins. The main fraction was 116 g. of $CCl_3CF{=}CCl_2$.[11]

Action of aluminum chloride on hexafluoropropene at high temperatures. The reaction of $AlCl_3$ with $CF_3CF{=}CF_2$ was also studied at 75°, 100°, 150°, and 450°. The results showed a large increase in tar formation and the isolation of only $CCl_3CF{=}CCl_2$.

The reaction of 530 g. (3.43 moles) of $CF_3CF{=}CF_2$ and 693 g. (5.21 moles) of $AlCl_3$ was studied at 450° after 6 hr. of continuous stirring, the bomb was brought to room temperature, and vented into traps. About 201 g. of $CF_3CF{=}CF_2$ was recovered. No liquid products were recovered on opening the bomb. The solid residue was hydrolyzed with dilute HCl and treated as previously described. Fractionation yielded 19.5 g. of $CCl_3CF{=}CCl_2$ and about 50 g. of $CCl_3{-}CCl_3$ along with a higher polymeric material, m.p. 222–223°, which was not characterized.

In another run, about 19.4 g. (0.084 moles) of $CCl_3CF{=}CCl_2$ and 3.99 g. (0.028 moles) of $AlCl_3$ was placed in a 50 ml. round-bottom flask equipped with a reflux condenser and allowed to reflux for 18 hr. Hydrolysis of this reaction mixture and treatment as previously described yielded 2.6 g. of $CCl_3CF{=}CCl_2$ and 11.8 g. of $CCl_3CCl{=}CCl_2$.

Proof of structure. The proofs of structure of the various olefins were obtained by comparison of the physical properties and infrared spectra of our compounds with those of known structure previously described in the literature. The works of Miller,[6] Henne *et al.*,[9] and Whaley and Davis[7] along with our studies gave stimulus for the consideration of the following mechanism.

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1. $CF_3CF{=}CF_2 + AlCl_3 \longrightarrow AlCl_3F^- + \overset{+}{C}F_2{-}CF{=}CF_2$

2. $\overset{+}{C}F_2{-}CF{=}CF_2 + AlCl_3F^- \longrightarrow CF_2Cl{-}CF{=}CF_2 + AlCl_2F$

3. $CF_2ClCF{=}CF_2 \xrightarrow{AlCl_3} CF_3CF{=}CFCl$

4. $CF_3CF{=}CFCl + AlCl_2F \longrightarrow \overset{+}{C}F_2{-}CF{=}CFCl + AlCl_2F_2^-$

5. $\overset{+}{C}F_2{-}CF{=}CFCl + AlCl_2F_2^- \longrightarrow CF_2Cl{-}CF{=}CFCl + AlClF_2$

6. $CF_2Cl{-}CF{=}CFCl \xrightarrow{AlCl_3} CF_3CF{=}CCl_2$

7. $CF_3CF{=}CCl_2 + AlCl_3 \longrightarrow AlCl_3F^- + \overset{+}{C}F_2{-}CF{=}CCl_2$

8. $\overset{+}{C}F_2{-}CF{=}CCl_2 + AlCl_3F^- \longrightarrow CF_2ClCF{=}CCl_2 + AlCl_2F$

Steps 3 and 6 involve intramolecular rearrangement. Step 8 continues stepwise until $CCl_3CF{=}CCl_2$ is ultimately formed. This latter compound, $CCl_3CF{=}CCl_2$, which resists quite strongly the action of $AlCl_3$ to convert it to $CCl_3{-}CCl{=}CCl_2$, may be partially explained on the basis of the peculiar geometry of the molecule which prevents the complexing of $AlCl_3$ with $CCl_3CF{=}CCl_2$.

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[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS, AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH]

Preparation and Properties of β-3-Indolyl Compounds Related to Tryptophan Metabolism[1]

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3-Indolylpyruvic acid was prepared from DL-tryptophan *via* the *N*-chloroacetyl derivative and 2-methyl-4-(3′-indolal)-5-oxazolone, and also from 3-formylindole *via* 2-methyl-4-(1′-acetyl-3′-indolal)-5-oxazolone. The pyruvic acid was converted to β-(3-indolyl)lactic and β-(3-indolyl)-α-oximinopropionic acids. β-(3-Indolyl)acrylic and β-(3-indolal)malonic acids were synthesized from 3-formylindole and malonic acid. 3-Indolylglyoxylic acid, amide, and methyl ester were prepared from indole and oxalyl chloride *via* 3-indolylglyoxylyl chloride. 3-Indolylglycolic acid was obtained as a stable sodium salt by reduction of the glyoxylic acid and the instability of the free glycolic acid was confirmed. 3-Indolylcarboxylic acid was prepared from 3-cyanoindole which was obtained from 3-indolylglyoxylic acid or from 3-formylindole *via* the aldoxime. 3-Indolylacetamide was synthesized from 3-indolylacetic acid *via* the acid chloride. The factors which influence the yield, stability, and purity of these compounds are considered in relation to inadequacies in earlier literature.

Only a minor portion of the tryptophan ingested by man follows the known metabolic paths, which lead to nicotinic acid or to serotonin, and the fate of the remainder is uncertain.[4] Varying small amounts of many indole compounds are present in human urine; an abnormal excretion of some of these compounds has been reported in cases of phenylketonuria,[5] malignant carcinoid tumor,[6,7] and Hartnup disease.[8] The preparation of several 3-indolyl compounds, which were required in a study of urinary indole acids and their possible significance in relation to other metabolic paths,[9] is reported in the present paper. New syntheses of indolepyruvic acid, sodium indoleglycolate, and indoleacetamide are presented, together with effective procedures for indoleacrylic, indolecarboxylic, indoleglyoxylic, and indolelactic acids. The conditions which influence the yield, stability, and purity of the compounds are considered. These factors have not been treated sufficiently in many of the earlier publications, and procedures frequently have not been described or are inadequate.

β-(3-Indolyl)pyruvic acid (I) was prepared in 43% overall yield from DL-tryptophan *via* its *N*-chloroacetyl derivative (II) and 2-methyl 4-(3′-indolal)5-oxazolone (III). Cooley and Wood[10] used this approach to make *N*-acetyldehydrotryptophan, but did not isolate I and III. I also was obtained in low yield *via* 2-methyl-4-(1′-acetyl-3′-indolal)-5-oxazolone by condensing 3-formylindole with acetylglycine. Bentley *et al.*[11] recently described the

(1) Supported by research grants from the National Institutes of Health, U. S. Public Health Service.

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(4) For recent reviews on the metabolism of tryptophan, see A. H. Meister, *Biochemistry of the Amino Acids*, Academic Press Inc., New York, 1957, pp. 333, 407, and C. E. Dalgliesh, *Advances in Protein Chemistry*, **10**, 79 (1955).

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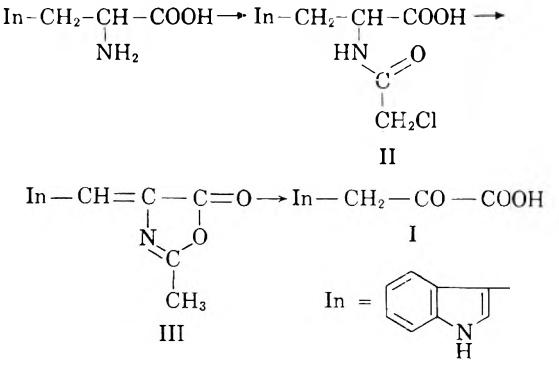


preparation of I (46% yield crude) from β-(3-indolal)hydantoin and reported that earlier syntheses, which involved the condensation of 3-formylindole with hippuric acid,[12] or with rhodanine,[13] are unsatisfactory.

The preparation of II by treating DL-tryptophan in alkaline solution with chloroacetyl chloride is well known.[14] The reported yield, however, has not exceeded 50-60%,[15] possibly because of side reactions.[16] In the present work, pure II was obtained readily in 88% yield by careful control of *p*H during acylation.

The Bergmann rearrangement[17] of II with pyridine and acetic anhydride provided crude oxazolone III in 92% and purified III in 56% yield. III reacts slowly with water or alcohols in the cold, but more rapidly on heating. Crystalline III has shown no change in properties during storage at 5° for several years.

The pyruvic acid I was prepared in 53% yield from crude oxazolone III and in 67% yield from purified III by alkaline hydrolysis. The yield and purity were impaired unless I was isolated rapidly from the aqueous hydrolyzate at a low temperature with exclusion of air. These precautions were adopted following the observation that the stability of I varies markedly with *p*H and solvent. A lower decomposition point of I and color development indicate slow deterioration in aqueous suspension, which is accelerated by mineral acids, and which also occurs to a lesser extent in alcoholic solution. The oxidative character of the breakdown is apparent from a recent report that I decomposes extensively in water on paper chromatograms,[11] where a fast reaction would be expected with a thin film exposed to air. I decomposes more rapidly at *p*H 8. Attempts to make the monosodium salt in water or absolute alcohol, analogous to the stable sodium phenylpyruvate,[18] yielded colored products of uncertain character, and the formation of 3-indoleacetic acid and 3-formylindole was observed when a sodium bicarbonate solution of I was exposed to air. Stowe[19] has mentioned recently that a rapid conversion of enolic free acid to the keto form at *p*H 8 is followed by "other unknown changes." The decomposition of I in hot alkali during synthesis is relatively slow because of exclusion of air, and possibly because of further ionization to a more stable doubly charged anion.

Solutions of I in non-reactive dry organic solvents are relatively stable; however, short crystallization periods (3–4 hr.) and avoidance of prolonged heating are advisable. I forms stable solvates with dioxane or acetic acid; the acetic acid solvate is useful in isolation and purification because of its poor solubility. The pure solvates and free I in crystalline form have shown no change in properties during storage at 5° for three years, or at room temperature for several weeks; impure preparations slowly deteriorated at room temperature.

I was converted to its oxime (IV) by a modification of the method of Holland and Nayler.[20] The high yield (88%) and stability make IV of potential interest as a means of recovering small amounts of I from biological preparations.

β-(3-Indolyl)lactic acid (V) was prepared from the pyruvic acid I in 38% yield by reduction with sodium amalgam, and in 74% yield by hydrogenation over palladium oxide. An earlier report on sodium amalgam reduction gave no procedure or yield.[21] The poor yield from this method may be attributed to instability and partial loss of sodium indolepyruvate which is present at the start of the reaction. Side reactions also occurred during catalytic hydrogenation. The reduction of I to V in 85% yield by hydrogenation over Raney nickel was indicated without details in an earlier report.[22] The preparation of V in two steps from gramine and diethyl acetoxymalonate (52% overall yield) was reported recently from this laboratory.[23] A circuitous reduction of methyl indolepyruvate with sodium borohydride also has been described.[11] The earliest synthesis of V involved basic racemization of the D-antipode[21] which was obtained by

(12) A. Ellinger and Z. Matsuoka, *Z. physiol. Chem.*, **109**, 259 (1920).

(13) C. Gränacher, M. Gerö, and V. Schelling, *Helv. Chim. Acta*, **7**, 575 (1924).

(14) E. Abderhalden and M. Kempe, *Ber.*, **40**, 2737 (1907).

(15) J. B. Gilbert, V. E. Price, and J. P. Greenstein, *J. Biol. Chem.*, **180**, 473 (1949).

(16) S. M. Birnbaum, L. Levintow, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **194**, 455 (1952).

(17) The scope of this rearrangement was extended and relevant literature reviewed recently: J. C. Sheehan and W. E. Duggins, *J. Am. Chem. Soc.*, **72**, 2475 (1950). Also see E. Baltazzi, *Quart. Revs.*, **9**, 150 (1955); R. C. Elderfield, *Heterocyclic Compounds*, J. Wiley and Sons, New York, 1957, vol. 5, p. 347.

(18) R. Hemmerle, *Ann. chim. et phys.*, **7**, 226 (1917).

(19) B. B. Stowe, *Biochem. J.*, **61**, ix (1955).

(20) D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, 280 (1953).

(21) K. Ichihara and N. Iwakura, *Z. physiol. Chem.*, **195**, 202 (1931).

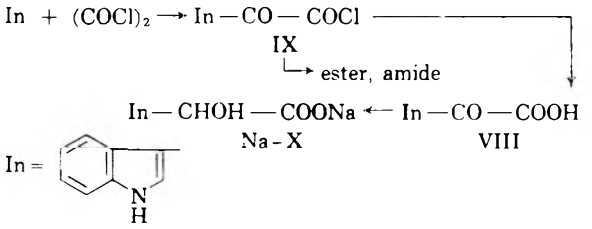
(22) L. C. Baugess and C. P. Berg, *J. Biol. Chem.*, **104**, 675 (1934).

(23) M. G. Gortatowski and M. D. Armstrong, *J. Org. Chem.*, **22**, 1217 (1957).

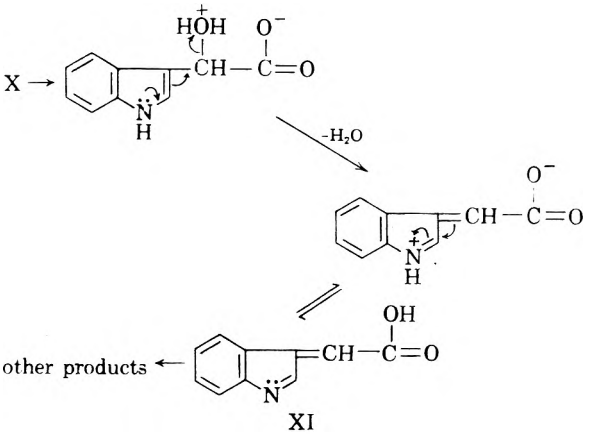
fermentation of L-tryptophan with *Oidium lactis*.[24] V is stable in crystalline form, or in organic solutions. Decomposition occurs when aqueous solutions are concentrated,[24] however, and is accelerated by mineral acids.

β-(3-Indolyl)acrylic acid (VI) was obtained in 50% yield by condensation of 3-formylindole with malonic acid. Paper chromatography was used to follow the reaction. About 77% of the 3-formylindole was converted to a crude product containing 85% VI and 15% of the intermediate indolalmalonic acid (VII), which were separated readily by extraction and fractional crystallization. In contrast, most of the VI was destroyed and the remainder was grossly contaminated with decomposition products when the procedure of Baugess and Berg[22] was followed: *i.e.* repeated precipitation of VI by acidification of an alkaline solution and final recrystallization from water. Others also have criticized the original procedure because of low variable yields.[25,26] A synthesis of VI from 1-acetyl-3-formylindole and malonic acid (48% yield) was reported recently.[26] Solutions of VI in nonreactive organic solvents are stable. Crystalline VI has shown no change in properties during storage at 5° for three years.

3-Indolylglyoxylic acid (VIII) was prepared in 87% yield by condensation of oxalyl chloride with indole and hydrolysis of the resulting indoleglyoxylyl chloride (IX). The methyl ester and amide also were obtained in high yields from IX. Giua[27] erroneously designated an impure product of this reaction as 2-indolylglyoxylic acid; its correct nature was indicated by Kharasch *et al.*[28] and confirmed recently by Specter and Anthony,[29] but sparse data were given. Other less efficient syntheses have involved the action of indolylmagnesium halides or indolylsodium on alkoxalyl chlorides or diethyl oxalate.[30–34] VIII is generally more stable than its homolog I. It decomposes slightly in hot aqueous alcohol solutions, however, and complete decomposition is observed when a hot alkaline solution is acidified.



Sodium 3-indolylglycolate (Na-X) was prepared from the glyoxylic acid VIII in 68% yield by reduction with sodium amalgam, and in 85% yield by hydrogenation over palladium oxide. Na-X also has been obtained, but without isolation, by condensation of indole with sodium glyoxylate,[35] and by reduction and saponification of esters of VIII.[11,33] Na-X is stable and readily purified; in contrast, the free acid X decomposes easily. Baker[33] observed a rapid breakdown when an aqueous solution of Na-X was acidified and concluded that X might be sensitive to atmospheric oxidation. Solutions of X in ether or methanol can be handled in air for short periods without serious loss, however, but X decomposes quickly as soon as it is precipitated from solution, even in absence of air and water. It is possible that aggregation to the solid state promotes an autocatalytic dehydration of X, with reactivity of the resulting 3-carboxymethyleneindolenine (XI) or intermediate carbonium ion leading to further changes. A similar mechanism was proposed recently to explain the behavior of 3-hydroxymethylindole.[36] In view of the instability of X, doubts may

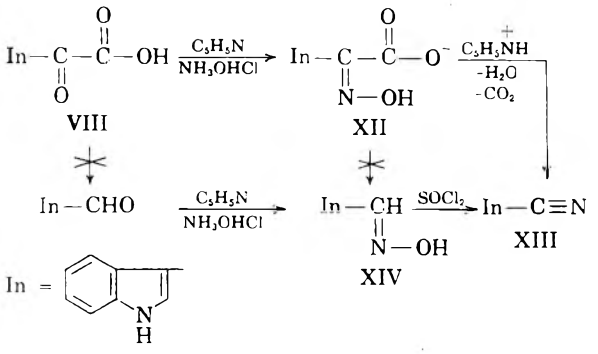


be held concerning a recently reported isolation of X from cabbage,[37] and earlier claims of synthesis by treatment of 3-dichloroacetylindole with alkali, or by oxidation of 3-chloroacetylindole.[38]

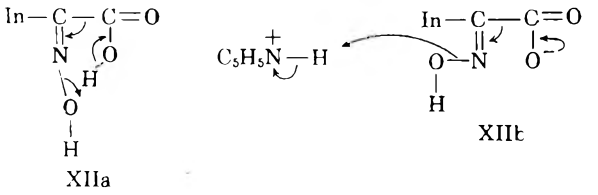
Several procedures were tested for converting the glyoxylic acid VIII to its oxime (XII) which was desired as a possible precursor for 3-indolylglycine.

(24) F. Ehrlich and K. A. Jacobsen, *Ber.*, **44**, 888 (1911).
(25) F. C. Happold and L. Hoyle, *Biochem. J.*, **29**, 1918 (1935).
(26) J. S. Moffatt, *J. Chem. Soc.*, 1442 (1957).
(27) M. Giua, *Gazz. chim. ital.*, **54**, 593 (1924).
(28) M. S. Kharasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.*, **62**, 2243 (1940).
(29) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).
(30) R. Majima and T. Shigematsu, *Ber.*, **57**, 1449 (1924).
(31) R. Majima, T. Shigamatsu, and T. Rokkaku, *Ber.*, **57**, 1453 (1924).
(32) B. Oddo and A. Albanese, *Gazz. chim. ital.*, **57**, 827 (1927) [*Chem. Abstr.*, **22**, 1775 (1928)].
(33) J. W. Baker, *J. Chem. Soc.*, 458 (1940).
(34) J. Elks, D. F. Elliott, and B. A. Hems, *J. Chem. Soc.*, 629 (1944).
(35) J. B. Greenberg, A. W. Galston, K. N. F. Shaw, and M. D. Armstrong, *Science*, **125**, 992 (1957).
(36) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).
(37) A. Fischer, *Planta*, **43**, 288 (1954); also see D. Racusen, *Arch. Biochem. Biophys.*, **58**, 508 (1955).
(38) G. Sanna, *Gazz. chim. ital.*, **59**, 838 (1929) [*Chem. Abstr.*, **24**, 2127 (1930)]; *Rend. seminario facolta sci. univ. Cagliari*, **4**, 28 (1934) [*Chem. Abstr.*, **30**, 6363 (1936)].

VIII was recovered unchanged after treatment with hydroxylamine hydrochloride in sodium bicarbonate solution at room temperature, conditions under which the homologous pyruvic acid I is transformed readily to its oxime IV. The lesser reactivity of VIII may be attributed to conjugation of the carbonyl and ring imino groups. When VIII was treated with hydroxylamine hydrochloride in boiling alcoholic pyridine, however, 3-cyanoindole (XIII) was obtained in 82% yield instead of oxime XII. An initial conversion to oxime XII probably occurs, followed by a simultaneous



dehydration and decarboxylation, which could be autocatalytic (XIIa) or catalyzed by pyridinium cation (XIIb). Simple decarboxylations of VIII or XII, which would lead to the aldoxime XIV as an



intermediate, are excluded as possible mechanisms because 3-formylindole is converted quantitatively to aldoxime XIV, and not to nitrile XIII, under conditions used for the glyoxylic acid VIII. The formation of XIII from VIII in hot potassium acetate solution was indicated without details in an earlier report.[31] XIII also has been prepared by dehydration of oxime XIV with acetic anhydride (*via* the 1-acetyl nitrile),[39] or with thionyl chloride,[40] by dehydration of 3-indolecarboxamide with phosphorus oxychloride,[40] and by the action of cyanogen chloride on indolylmagnesium iodide.[31]

The nitrile XIII is weakly acidic, and its solubility in water or aqueous alcohol increases upon addition of alkali. This property, which reflects electron withdrawal by the 3-cyano from the ring imino group, is useful in purification. XIII is stable in crystalline form or in organic solutions.

3-Indolylcarboxylic acid (XV) was prepared in 91% yield by alkaline hydrolysis of nitrile XIII. Majima *et al.*[31] mentioned without details the use of this reaction to characterize XIII. Other methods for the synthesis of XV which were tested included oxidation of 3-formylindole with alkaline permanganate,[41] reaction of indolyl magnesium iodide with carbon dioxide,[40,42] and oxidation of glyoxylic acid VIII with alkaline hydrogen peroxide. The yields from these reactions were inferior, however, and the products decomposed 12–20° lower than the product from hydrolysis of nitrile XIII, because of the presence of minor impurities which were revealed by paper chromatography.[9] The reaction of indolyl magnesium iodide with ethyl chloroformate has been used to make 3-carbethoxyindole (54–78% yield),[42,43] but hydrolysis of this ester to XV has not been reported. XV is stable in crystalline form and in alkaline solution. A partial decomposition of free XV in hot water however, has been mentioned in earlier reports.[44,45]

3-Indolylacetamide (XVI) was synthesized in 71% yield from indoleacetic acid *via* indoleacetyl chloride. The yield of acid chloride was increased from 66%[46] to 83% by use of low temperature and exclusion of moisture. The acid chloride was converted smoothly to amide XVI by the action of dry ammonia; an unsuccessful attempt to use this route was reported earlier.[47] XVI has been obtained previously in low yield by dry distillation of ammonium indoleacetate,[47] or as a byproduct in the hydrolysis of indoleacetonitrile to indoleacetic acid.[48–50]

EXPERIMENTAL

*N-Chloroacetyl-*DL*-tryptophan* (II). A solution of 102.1 g. (0.50 mole) of DL-tryptophan in 600 ml. of 0.83*N* sodium hydroxide was stirred vigorously at 5–10° while 59.3 g. (0.525 mole) of chloroacetyl chloride was added dropwise during 1 hr. The *p*H was held at 10.0–11.0 (Beckman *p*H meter) by concurrent addition of 115 ml. of 5*N* sodium hydroxide in small portions. The solution was stirred for 10 min. more, 500 ml. of ethyl acetate was added, and the mixture was acidified to *p*H 1.7 with 6*N* sulfuric acid.[51] The aqueous phase was separated and extracted with 3 more 100-ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate, treated with charcoal, and concen-

(39) R. Pschorr and G. Hoppe, *Ber.*, **43**, 2543 (1910).

(40) F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 2853 (1956).

(41) A. Ellinger, *Ber.*, **39**, 2515 (1906).

(42) R. Majima and M. Kotake, *Ber.*, **55**, 3865 (1922); **63**, 2237 (1930).

(43) R. K. Brown and R. A. Garrison, *J. Am. Chem. Soc.*, **77**, 3839 (1955).

(44) G. Ciamician and C. Zatti, *Ber.*, **21**, 1929 (1888).

(45) K. Bowden and L. Marion, *Can. J. Chem.*, **29**, 1037 (1951).

(46) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).

(47) J. W. Baker and F. C. Happold, *Biochem. J.*, **34**, 657 (1940).

(48) R. Majima and T. Hoshino, *Ber.*, **58**, 2042 (1952).

(49) H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.*, **70**, 3770 (1948).

(50) F. Poppelsdorf and S. J. Holt, *J. Chem. Soc.*, 4094 (1954).

(51) When the solution was acidified in absence of ethyl acetate, impure II precipitated as a gum which crystallized slowly.

trated at a reduced pressure to 350 ml. The solution was seeded with a rubbed aliquot during the final stage of concentration and stored at 5° for 2–3 days with occasional shaking[52]; 98.5 g. (70% yield) of cream-colored crystals was collected, m.p. 154–155° (dec.) (in bath at 150°, 1° per minute).[53] A second crop of 25.8 g. (18% yield), m.p. 152–154° (dec.), was obtained from the filtrate. A sample was recrystallized from ethyl acetate with charcoal treatment,[54] m.p. 156–157° (dec.) (lit.[10] m.p. 154–155°).

Anal.[55] Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98. Found: C, 55.89; H, 4.60; Cl, 12.35; N, 9.69.

2-Methyl-4-(3'-indolal)-5-oxazolone (III). A mixture of 112.3 g. (0.40 mole) of II, 300 ml. (3.20 moles) of acetic anhydride, and 100 ml. (1.24 mole) of anhydrous pyridine (distilled over barium oxide) was allowed to stand for 20 min. with occasional stirring. II dissolved rapidly and the temperature rose to 50°. The wine-red solution was stirred vigorously with a mixture of 1 kg. of crushed ice and 1 kg. of ice water for 30 min. The resulting mustard-yellow precipitate of III was collected on a filter, washed successively with cold water, cold 95% ethanol, and dried *in vacuo* over concentrated sulfuric acid and potassium hydroxide; 82.9 g. (92% yield), m.p. 175–182° (in bath at 160°). This material is suitable for preparation of indolepyruvic acid. A 32.0 g. portion was recrystallized from 2400 ml. of boiling benzene with charcoal treatment; brown floccules amounting to 8–10% of crude III thus were removed. III was recovered after 2 days at 5° and dried *in vacuo*[56]; 19.4 g. (56% yield), m.p. 195–197° (in bath at 190°). A second crop of 4.6 g. (13% yield), m.p. 181–190°, was obtained from the filtrate. A sample of the first crop was recrystallized 3 times from benzene (once with charcoal treatment) to give brilliant yellow needles, m.p. 200–201°.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.39. Found: C, 68.88; H, 4.46; N, 12.30.

In the optimal procedure, 3 moles of pyridine and 8 moles of acetic anhydride per mole of II react for 20 min. No effect was observed with larger proportions of pyridine or acetic anhydride. The yield of crude III decreased to 85% with 2 moles and to 60% with 1.5 moles of pyridine. The proportion of acetic anhydride was less critical; 5 moles still gave an 82% crude yield. With a 10 min. reaction period, the crude yield decreased to 83%. With reaction periods up to 24 hr., the crude yield was fairly constant; the m.p. of crude III decreased gradually, however, and its solubility in benzene increased; the recovery of purified III from benzene and its m.p. also declined progressively. Formation of an increasing proportion of the more soluble 1'-acetyl oxazolone (next section) may have been partly responsible for these changes.

2-Methyl-4-(1'-acetyl-3'-indolal)-5-oxazolone. A mixture of 5.86 g. (0.05 mole) of acetylglycine, 7.26 g. (0.05 mole) of 3-formylindole,[57] 4.10 g. (0.05 mole) of anhydrous sodium acetate, and 20 ml. (0.2 mole) of acetic anhydride was heated at 100° for 7 hr. The solution was cooled to room temperature and stirred rapidly with 50 ml. of cold water and 50 g. of ice for 30 min. The resulting brown gummy precipitate was collected on a filter, washed with cold water and several portions of cold ethanol, and dried *in vacuo* over phosphorus pentoxide and potassium hydroxide; 9.15 g., m.p. 112–175°. This material was recrystallized from benzene with charcoal treatment; 3.00 g. (23% yield), m.p. 196–199°. After 2 more recrystallizations from benzene, 1.97 g. of bright yellow needles was obtained, m.p. 204–205° (in bath at 190°); mixed with oxazolone III (m.p. 200–201°), m.p. 164–189°.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.24; H, 4.53; N, 10.00.

This oxazolone was converted to indolepyruvic acid in the same manner as oxazolone III (next section).

β-(3-Indolyl)pyruvic acid (I). A suspension of 22.62 g. (0.10 mole) of oxazolone III, m.p. 195–197°, in 300 ml. of 10*N* sodium hydroxide was refluxed for 4 hr. under a stream of nitrogen. The sodium salt of *N*-acetyldehydrotryptophan precipitated at first, but redissolved quickly. The orange solution was cooled to 5°; 1200 g. of crushed ice and 500 ml. of peroxide-free ether then were added. The mixture was stirred vigorously and acidified to *p*H 1.7 *as rapidly as possible* with 6*N* sulfuric acid at a temperature not exceeding 10°. The aqueous phase, which contained sodium sulfate crystals, was separated and extracted with 3 more 500-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, treated with charcoal, and concentrated at a reduced pressure under nitrogen until crystallization started (about 100 ml.); 500 ml. of benzene then was added and the solution was concentrated to dryness at <40°. Addition of benzene markedly curtailed darkening of the residue in the final stage of concentration. The residue was dissolved in 90 ml. of hot acetone and 90 ml. of glacial acetic acid was added. Following refrigeration, brownish-yellow crystals of I-acetic acid solvate were recovered; 16.20 g., dec. 217° (in bath at 215°, 3° per minute).[58] A further 2.52 g., dec. 216°, was recovered from the mother liquor. The combined crude crops were recrystallized from acetone-acetic acid (1:1) with charcoal treatment to give light yellow clustered blades;[59] 15.76 g., dec. 219°, and 1.86 g., dec. 218° (67% total yield). The yield decreased to 61% when the hydrolysis time was increased to 6 hr. When crude oxazolone III, m.p. 175–182°, was hydrolyzed for 4 hr., the yield was 53%.

Anal. Calcd. for $C_{11}H_9NO_3.C_2H_4O_2$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.15; H, 4.66; N, 5.21.

The solvate was recrystallized from acetone-benzene (1:3) to give free I (94% recovery, 2 crops) as pale yellow hexagonal plates, dec. 219°.[60] Free I also may be obtained by drying the solvate over potassium hydroxide *in vacuo*.[12]

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.05; H, 4.47; N, 6.89. Found: C, 64.85; H, 4.20; N, 6.67.

The dioxane solvate was obtained as a colorless powder, dec. 219°, when I was recrystallized from dioxane-benzene (1:5). Dioxane was removed from the solvate by drying at 100° and 0.1 mm. for 24 hr., or by recrystallization from acetone-benzene (1:3).

Anal. Calcd. for $2C_{11}H_9NO_3.C_4H_8O_2$: $C_4H_8O_2$, 17.8. Found: $C_4H_8O_2$, 18.1.

Stability of β-(3-indolyl)pyruvic acid (I) *in sodium bicarbonate solution.* A solution of 2.03 g. (0.01 mole) of I in 140 ml. of 1*N* sodium bicarbonate solution was allowed to stand

(52) More rapid crystallization could be promoted by adding cyclohexane, but the m.p. of II was then lower.

(53) Melting points are corrected and were taken in open capillary tubes.

(54) When II was recrystallized from boiling water,[14] an odor of indole was apparent, II acquired a violet color which was not removed by recrystallization from other solvents, and its m.p. was not improved. Crystalline II is slightly photosensitive.

(55) Analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(56) Several days were required for removal of benzene at 10 mm. and 25°; the air-dried weight, 25.9 g., corresponded to one mole of benzene of crystallization.

(57) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(58) Values reported in the literature range from 193° to 214°. Despite a recent contrary statement,[11] the decomposition point is readily reproducible and is a reliable criterion of purity under controlled heating conditions. The acetic acid and dioxane solvates decompose at the same temperature as free I, after initial decrepitation.

(59) Four more recrystallizations alternately from acetone-benzene and acetone-acetic acid yielded a colorless solvate, dec. 219°.

(60) Free I retained a pale yellow color even when a colorless solvate was recrystallized from acetone alone; the recovery in one crop was 20% or less unless benzene was added. A colorless free acid has been reported to result from repeated crystallization from acetone.[11]

at room temperature for 24 hr. with occasional shaking. The initially colorless solution darkened rapidly. The solution was extracted with four 150-ml. portions of ether; the combined ether extracts were dried over anhydrous sodium sulfate and concentrated at a reduced pressure to 0.05 g. of light brown solid in which only 3-formylindole was detected by paper chromatography.[61] The aqueous phase, after addition of 300 ml. of ether, was acidified with 6*N* sulfuric acid to *p*H 1.8 with stirring at 5°. The aqueous phase was separated and extracted with 2 more 150-ml. portions of ether. The combined *p*H 1.8 ether extracts were dried over anhydrous sodium sulfate and concentrated to dryness at a reduced pressure under nitrogen. The residue was crystallized from acetone-acetic acid (1:1) to give 1.27 g. (48% recovery) of I-acetic acid solvate in 4 crops, dec. 216–218°. The final mother liquor was concentrated to 0.90 g. of dark brown oily residue which was estimated by paper chromatography[61] to contain about 0.10 g. of I, 0.40 g. of indoleacetic acid, 0.02 g. of 3-formylindole, and other unidentified products.

β-(3-Indolyl)-α-oximinopropionic acid (IV). The procedure described in the preceding section was used with 3.47 g. (0.05 mole) of hydroxylamine hydrochloride added to the sodium bicarbonate solution before I. The neutral ether extracts were discarded. The residue from the *p*H 1.8 ether extracts was crystallized from anhydrous ether-petroleum ether (b.p. 30–60°) (1:3) to give 1.92 g. (88% yield) of IV as faintly yellow clustered blades, dec. 156° (in bath at 150°, 3° per min.). IV was recrystallized (88% recovery) from ethyl acetate-benzene (1:4) with charcoal treatment, dec. 158° (lit. dec. >175°,[22] 155°[20]).

β-(3-Indolyl)lactic acid (V). *A. Sodium amalgam reduction.* To a solution of 4.37 g. (0.021 mole) of I in 45 ml. of 1*N* sodium hydroxide was added 100 g. (0.13 g.-at.) of freshly-pulverized 3% sodium amalgam[62] in 10 equal portions at 5-min. intervals with high speed stirring. The mixture was stirred for 1 hr. more. The aqueous layer was separated, decolorized with charcoal, and extracted with ether to eliminate neutral impurities. The aqueous phase was treated with 100 ml. of ether and acidified with 6*N* hydrochloric acid to *p*H 1.6 with stirring at 5°. The aqueous phase was separated and extracted with 3 more 100-ml. portions of ether. The combined *p*H 1.6 ether extracts were dried over anhydrous sodium sulfate, treated with charcoal, and concentrated at a reduced pressure to dryness. The residue was dissolved in 240 ml. of hot 1,2-dichloroethane and the solution was treated with charcoal to remove tar. The filtrate was concentrated at a reduced pressure to 100 ml.; a small amount of purplish gum was separated by decantation. Following refrigeration, 2.06 g. of mauve-tinted powder was recovered, m.p. 140–144°. The crude V was recrystallized from 1,2-dichloroethane with charcoal treatment to give 1.66 g. (38% yield) of cream-colored powder, m.p. 144–145° (slow dec.) (lit.[11] m.p. 146–147°). Further material obtained from the mother liquors melted at a lower temperature over a wide range.

B. Catalytic Hydrogenation. To a solution of 10.53 g. (0.04 mole) of I-acetic acid solvate in 200 ml. of 95% ethanol was added 2.0 g. of palladium oxide. The mixture was hydrogenated at 50 lbs. pressure for 6 hr.; the uptake of hydrogen was not appreciable after 4 hr.[63] The catalyst was removed by filtration and the yellow filtrate, which darkened upon exposure to air, was concentrated to dryness at a reduced pressure. The residue was dissolved in 100 ml. of boiling ethyl acetate. The solution was filtered to remove 0.4 g. of brown amorphous powder, dec. 85–87°, and was treated with charcoal; the filtrate was concentrated to dryness. The residue was crystallized from ethyl acetate; 4.58 g. of V, m.p. 144–145° (dec.). The filtrate[64] was concentrated to dryness and the residue was crystallized from acetone-acetic acid (1:1); 0.52 g. of I-acetic acid solvate, dec. 217°. The filtrate was concentrated to dryness; the residue was concentrated to dryness again with benzene and with ethyl acetate, and then crystallized from ethyl acetate; 1.17 g. of V, m.p. 144–145° (dec.). The total yield of V was 74%, with allowance made for recovered I. The combined crops of V were recrystallized from ethyl acetate with charcoal treatment to give colorless crystals; 3.80 g., m.p. 146–147° (no dec.), and 0.98 g., m.p. 144–145° (dec.), (lit.[11] m.p. 146–147°).

β-(3-Indolyl)acrylic acid (VI). A solution of 14.52 g. (0.10 mole) of 3-formylindole[57] and 31.22 g. (0.30 mole) of malonic acid in a mixture of 160 ml. of pyridine (distilled over barium oxide) and 2.0 ml. of piperidine was maintained at 40° for 45 hr. The solution was concentrated at a reduced pressure and at <45° to an orange oil (68 g.). The oil was diluted with 250 ml. of water and the *p*H was adjusted to 11.0 with 2*N* sodium hydroxide. The solution was extracted with four 200-ml. portions of ethyl acetate to remove bases and neutral impurities. The aqueous phase was treated with charcoal, and the filtrate was acidified to *p*H 1.8 by dropwise addition of 6*N* hydrochloric acid with stirring at 5°. The resulting yellow precipitate was washed well with cold water and dried *in vacuo* over phosphorus pentoxide and potassium hydroxide; 14.68 g., dec. 173° (in bath at 170°, 3° per minute). The crude VI, which contained about 15% of 3-indolalmalonic acid (VII),[65] was extracted successively with 2500 and then 500 ml. of boiling anhydrous ether; 1.59 g. of VII, VI content 3%, remained undissolved as a greenish-yellow powder, dec. 178°. The combined ether extracts were concentrated at a reduced pressure to dryness. The residue was dissolved in 700 ml. of boiling ethyl acetate; the solution was treated with charcoal and the filtrate was concentrated at a reduced pressure to 175 ml. Following refrigeration, 9.33 g. (50% yield) of VI was obtained, VII content 0.1%, dec. 184° (in bath at 170°, 3° per minute), dec. 193° (in bath at 190°, 3° per minute). A sample recrystallized from ethyl acetate-cyclohexane (1:2) with charcoal treatment gave pale yellow clustered blades, VII content <0.02%, dec. 195° (in bath at 190°, 3° per minute) (lit.[26] dec. 192–3°).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.59; H, 4.85; N, 7.48. Found: C, 70.62; H, 4.87; N, 7.45.

The crude VII (1.59 g.) from the ether extraction was recrystallized twice from hot methanol with charcoal treatment; in each case, the filtrate was concentrated at a reduced pressure until crystallization commenced. VII (0.66 g.) was obtained as intense yellow needles, VI content <0.02%, dec. 209° (in bath at 205°, 3° per minute) (lit.[26] dec. 208–209°)

(61) The decomposition and paper chromatography of I under various conditions will be described in a future publication.

(62) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., New York, 1941, p. 418.

(63) Introduction of more catalyst at this point might have been helpful, since reduction was incomplete in 6 hours. Hydrogenation was slower in dioxane-95% ethanol (1:1), and did not occur at a measurable rate in dioxane, ethyl acetate, ethyl acetate-ethanol (4:1), or absolute ethanol.

(64) No further crystallization of V was induced by partial concentration. The filtrate, which was analyzed by paper chromatography, contained about 1.8 g. of V, 0.3 g. of indoleacetic acid, and 0.6 g. of I in 2.7 g. of total solutes.

(65) An appropriate series of aliquots of a tetrahydrofuran solution was chromatographed for 2 hr. on Whatman No. 1 paper with benzene-propionic acid-water (100:70:5) as the solvent together with authentic compounds (0.5–2.5 γ in 0.5 γ increments). The sheets were dried in air and sprayed with Ehrlich's *p*-dimethylaminobenzaldehyde reagent.[9] The composition of a crop was determined by visual comparison of the spots produced: 0.1 γ of VI or VII was readily detectable. The R_f's and the initial and final colors were as follows: VI, 0.73, light green → turquoise; VII, 0.14, yellow → turquoise.

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.46; H, 4.08; N, 5.96.

A suspension of 250 mg. of pure VI in 50 ml. of water was boiled gently while water (350 ml.) was added portionwise until the crystals just disappeared. The total heating time was 10 min. A white turbid mixture resulted and true solution was not observed. Following refrigeration, 147 mg. of pink powder was recovered, m.p. 93–134° (dec.); the VI content of this material was only 15%.

3-Indolylglyoxylyl chloride (IX). To a stirred solution of 29.3 g. (0.25 mole) of indole in 500 ml. of anhydrous ether at 0–5°, 25.0 ml. (0.29 mole) of oxalyl chloride was added dropwise during 30 min.; stirring and cooling were continued for 1 hr. more. The resulting yellow crystals of IX were collected on a filter, washed with anhydrous ether, and dried *in vacuo* over potassium hydroxide; 48.1 g. (92% yield), dec. 134° (in bath at 130°, 3° per minute). A sample was recrystallized from benzene, dec. 135° (lit.[28] dec. 135–136°); this material darkened to a copper color during storage at 5° for 3 years, dec. 131°.

3-Indolylglyoxylic acid (VIII). A suspension of IX in ether, prepared in the manner described above, was stirred at 0–5° and 1*N* potassium hydroxide (about 1000 ml.) was added slowly until the *p*H of the aqueous phase was 12. The fluorescent ether layer was separated and the aqueous phase was extracted with 3 more portions of ether to remove neutral impurities. The aqueous phase was treated with charcoal and 700 ml. of ethyl acetate was added to the filtrate; the mixture was stirred at 0–5° and acidified to *p*H 1.6 with 6*N* hydrochloric acid.[66] The ethyl acetate phase was separated and the aqueous phase was extracted twice more with ethyl acetate. The ethyl acetate extracts were dried over anhydrous sodium sulfate, treated with charcoal, and concentrated to dryness at a reduced pressure. The residue was dissolved in 250 ml. of boiling 95% ethanol and 1250 ml. of hot water was added. Following refrigeration, yellow crystals of VIII were recovered (a reddish-brown film suggested slight decomposition); 41.3 g. (87% yield from indole), dec. 218° (in bath at 215°, 3° per minute) (lit.[32] dec. 216°). Recrystallization from acetone-benzene (1:4) with charcoal treatment gave brilliant yellow dendrites (90–95% recovery), dec. 218°.

VIII (1.89 g., 0.01 mole) was subjected to the procedure described above for conversion of indolepyruvic acid (I) to its oxime (IV); 1.58 g. (84%) of VIII was recovered unchanged, dec. 217°, and no glyoxylic oxime (XII) was obtained.

Methyl 3-indolylglyoxylate. A mixture of 23.75 g. (0.114 mole) of crude IX, 10 ml. of pyridine and 1600 ml. of methanol was boiled gently until IX had dissolved. Following refrigeration, 21.70 g. (94% yield) of ester was obtained in two crops, m.p. 228–230° (no sintering), (lit.[33] m.p. 224°, with sintering at 210°). The crude ester was recrystallized from methanol with charcoal treatment and was recovered (88%) as pale yellow needles, m.p. 230–231°.

3-Indolylglyoxylamide. Crude IX (3.47 g., 0.0167 mole) was added slowly with stirring to 170 ml. of 1*N* ammonium hydroxide. After stirring for 30 min. more at 5°, the amide was recovered as a light brown powder; 2.89 g. (92% yield), m.p. 253–256° (dec.) (in bath at 250°, 3° per minute). Recrystallization from acetone-cyclohexane (1:1) with charcoal treatment, then absolute ethanol, gave 1.98 g. of colorless needles, m.p. 257–258° (dec.) [lit.[33] "slightly impure," m.p. 252° (dec.)].

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.9. Found: C, 63.66; H, 4.39; N, 14.7.

Sodium 3-indolylglycolate (Na-X). A. Catalytic hydrogenation. A suspension of 9.46 g. (0.05 mole) of crude VIII in 50 ml. of water was titrated to *p*H 7.5–8.0 with 2*N* carbonate-free sodium hydroxide; a small amount of insoluble material was removed by charcoal treatment. The filtrate and washings were treated with 1.0 g. of palladium oxide and hydrogenated at 50 lbs. pressure for 10 hr.; uptake of hydrogen was complete in 8 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness at a reduced pressure. The residue was concentrated to dryness again with absolute ethanol to remove water. The residue was simmered with 100 ml. of absolute ethanol, filtered, washed well with hot ethanol, then ether, and dried *in vacuo*. Na-X was obtained as a white powder; 9.32 g., dec. 306° (bath temperature 300°, 3° per minute). A solution of crude Na-X in 450 ml. of boiling methanol was treated with charcoal; an equal volume of ether was added to the filtrate. Following refrigeration, 8.91 g. (85% yield) was recovered in 2 crops. The salt was recrystallized again from methanol-ether, dec. 306°.

Anal. Calcd. for $C_{10}H_8NO_3Na$: C, 56.33; H, 3.78; N, 6.57; Na, 10.79. Found: C, 55.68; H, 4.10; N, 6.50; Na, 10.73.

The purity of Na-X was established by paper chromatography.[67] An unidentified by-product, which constituted about 10% of the residue from hydrogenation, 3% of the crude salt, and <1% after the first recrystallization, was not detectable after the second recrystallization. Similar proportions of this by-product were obtained when a hydrogenation was conducted over 4.0 g. of 5% palladium on charcoal (20 hr.); in this case, however, the yield of crude Na-X decreased to 70%, and 10% of the starting material was converted to indoleacetic acid.

B. Sodium amalgam reduction. A solution of 3.78 g. (0.02 mole) of crude VIII in 40 ml. of 0.5*N* sodium hydroxide was reduced with 61.3 g. (0.08 g.-at.) of 3% sodium amalgam[62] in the manner described above for preparation of indolelactic acid. The mixture was stirred for 90 min. more. The aqueous layer was separated, extracted with ether to remove neutral impurities, and treated with charcoal. The filtrate was mixed with 100 ml. of ether and acidified with 6*N* hydrochloric acid to *p*H 1.6 with stirring at 5°. The aqueous phase was separated and extracted with 3 more 100-ml. portions of ether. The combined *p*H 1.6 ether extracts were dried over anhydrous sodium sulfate, and treated with charcoal. The ether filtrate was colorless, but formed a reddish-violet residue if allowed to evaporate. The ether filtrate was mixed with 50 ml. of water, and 2*N* sodium hydroxide was added with stirring until the *p*H of the aqueous phase was 7.5–8.0. The aqueous phase was separated and treated in the manner described for the hydrogenation filtrate in the preceding section to give 2.88 g. (68% yield) of crude Na-X, dec. 306°. Chromatographically pure Na-X was obtained by a single recrystallization from methanol-ether (1:1).

C. Decomposition of 3-indolylglycolic acid (X).[68] A solution of 1.06 g. (0.005 mole) of Na-X in 50 ml. of methanol was shaken for 5 min. with 20 ml. of Dowex 50-X16 resin (hydrogen cycle, 2.6 m. eq./ml.) which had been washed well with water, boiling ethanol, and boiling methanol. The resin was removed by filtration, and the colorless filtrate was concentrated to dryness at a reduced pressure. The reddish-purple residue was shaken with 100 ml. of anhydrous ether to give an almost colorless solution; part of the residue remained undissolved. The mixture was treated with charcoal and filtered; 100 ml. of petroleum ether (b.p. 30–60°) was added to the filtrate to give an initially colorless flocculent precipitate which darkened rapidly. The mixture was

(66) In one run, the aqueous phase was acidified while hot; rapid decomposition ensued and no indoleglyoxylic acid was recovered.

(67) See (65): samples dissolved in methanol were chromatographed for 15 hours with isopropyl alcohol-aqueous ammonia-water (8:1:1) as the solvent. Colors developed by spraying with Ehrlich's reagent[9] and R_f values were Na-X, rose, 0.39; indoleacetic acid, blue-purple, 0.47; by-product, yellow, 0.43; VIII, no color with spray, dark blue under ultraviolet light, 0.48.

(68) A nitrogen atmosphere was used in this procedure until solid X had been isolated.

allowed to stand for 10 min.; 0.38 g. of rose-colored powder was recovered, dec. 203° (in bath at 200°, 3° per minute). Carbon dioxide was evolved when a sample was dissolved in 1*N* sodium bicarbonate; the bicarbonate solution was examined by paper chromatography.[67] The powder contained <10% indoleglycolic acid and at least four unidentified decomposition products.

3-Cyanoindole (XIII). *A. From* VIII. A mixture of 18.92 g. (0.10 mole) of crude VIII, 13.90 g. (0.20 mole) of hydroxylamine hydrochloride, 80 ml. (1.0 mole) of pyridine (distilled over barium oxide) and 80 ml. of absolute ethanol was refluxed for 4 hr. The solvents were removed at a reduced pressure; the residue was concentrated to dryness with three successive portions of absolute ethanol and then shaken with 100 ml. of water for several minutes until crystallization was complete. Following refrigeration, 11.64 g. (82% yield) of yellow-brown powder was obtained, m.p. 179–181°. Crude XIII was recrystallized from 50% aqueous ethanol with charcoal treatment and was recovered (91%) as light yellow clustered blades, m.p. 181–182°, unchanged by further recrystallization from benzene-methanol (12:1) (lit.[31] m.p. 178–180.5°).

Anal. Calcd. for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.7. Found: C, 75.80; H, 4.28; N, 20.0.

B. From 3-formylindole. 3-Formylindole[67] (14.52 g., 0.10 mole) was subjected to the procedure described in the preceding section, with refluxing for 2 instead of 4 hr. Crude 3-indolylaldoxime (XIV) was obtained as peach-colored crystals; 15.87 g. (99% yield), m.p. 193–195° (dec.) (in bath at 190°, 3° per minute). A sample was recrystallized twice from ethanol-water (1:3) with charcoal treatment, and then from ethyl acetate, m.p. 201–202° (dec.) (lit.[69] m.p. 197–198°). Crude XIV was dehydrated with thionyl chloride[40] to give dark brown flakes of XIII (83% yield), m.p. 179–181°, unchanged by recrystallization from 50% aqueous ethanol. A sample (2.60 g.) of XIII suspended in 50 ml. of 50% aqueous ethanol at room temperature was dissolved by adding 30 ml. of 0.5*N* sodium hydroxide in 50% aqueous ethanol. The solution was decolorized by treatment with charcoal and the filtrate was adjusted to *p*H 6.5 with 6*N* hydrochloric acid. Following refrigeration, 2.20 g. (85% recovery) of colorless dendritic blades was obtained m.p. 182°, not depressed by admixture with XIII prepared from VIII.

3-Indolylcarboxylic acid (XV). A suspension of 7.11 g. (0.05 mole) of crude XIII in 75 ml. of 10*N* sodium hydroxide was refluxed under a stream of nitrogen for 7 hr. Crystals of indole (0.30 g., m.p. 50–51°) collected in the condenser; evolution of ammonia diminished in the last hour. The orange hydrolyzate was cooled to 5°, diluted with 300 g. of crushed ice, and acidified to *p*H 7.5 with 12*N* hydrochloric acid with stirring and continued cooling. The solution was extracted with 3 portions of ethyl acetate to remove neutral impurities; the aqueous phase then was filtered to eliminate gelatinous silica. The filtrate was stirred at 5° and acidified to *p*H 2.0 with 2*N* hydrochloric acid. The resulting XV was collected after refrigeration; 7.31 g. (91% yield), dec. 247° (in bath at 240°, 3° per minute), dec. 240° (in bath at 220°, 3° per minute) (lit.[40] dec. 220–224°); colorless needles after recrystallization from acetone-benzene (1:4) with charcoal treatment, dec. 247°.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.01; H, 4.38; N, 8.77.

3-Indolylacetamide (XVI). To a stirred solution of 4.38 g. (0.025 mole) of indoleacetic acid in 100 ml. of anhydrous ether at −10°, 5.73 g. (0.0275 mole) of phosphorus pentachloride was added in small portions during 20 min.; stirring was continued for 10 min. more. The solution was concentrated to 40 ml. at a reduced pressure, treated with 400 ml. of cold petroleum ether (b.p. 30–60°) and filtered quickly to remove a small amount of dark red amorphous precipitate. Pale pink plates were collected after 4 hours at 5°; 1.55 g., m.p. 67–68° (dec.) (lit.[46] m.p. 68°). The filtrate was concentrated to 100 ml. at a reduced pressure to give 2.46 g. of cream-colored plates, m.p. 65–66° (dec.). Each crop was dried briefly *in vacuo* over phosphorus pentoxide and potassium hydroxide to remove phosphorus oxychloride; the total yield of indoleacetyl chloride was 83%.

A brisk current of dry ammonia was passed through a solution of the 2 crops of acid chloride in 100 ml. of anhydrous tetrahydrofuran (distilled over lithium aluminum hydride) at 5° for 30 min.[70] The mixture was filtered after 30 min. more to remove ammonium chloride. The filtrate was concentrated to dryness at a reduced pressure. The residue was crystallized from ethyl acetate-cyclohexane (1:1) with charcoal treatment; 3.10 g. (86% yield from the acid chloride, 71% from indoleacetic acid) m.p. 153–154°. Colorless blunt needles of XVI were obtained by recrystallization from ethyl acetate, m.p. 154° (lit.[48] m.p. 153°).

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(69) N. Putochin, *Ber.*, 59, 1987 (1926).

(70) Up to this point, equipment was thoroughly dried, and exposure to atmospheric moisture was kept to a minimum.

[CONTRIBUTION FROM THE INSTITUTE OF APPLIED MICROBIOLOGY, UNIVERSITY OF TOKYO]

Studies on the Synthesis of Matrine. II. The Synthesis of Octadehydromatrine and Allomatridine[1]

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Saponification of 11-ethoxycarbonyl-10-oxo-1,2,3,5,6,7-hexahydroquinolizo[1,8-*a*,*b*]quinolizine (Ia) yielded an acid Ib, m.p. 270–272°, which on heating with quinoline and copper sulfate formed octadehydromatrine (II). Catalytic hydrogenation of II over platinum oxide yielded didehydromatrine (III) which was converted to *rac*-allomatridine (IV) by high-pressure hydrogenation with copper chromite catalyst.

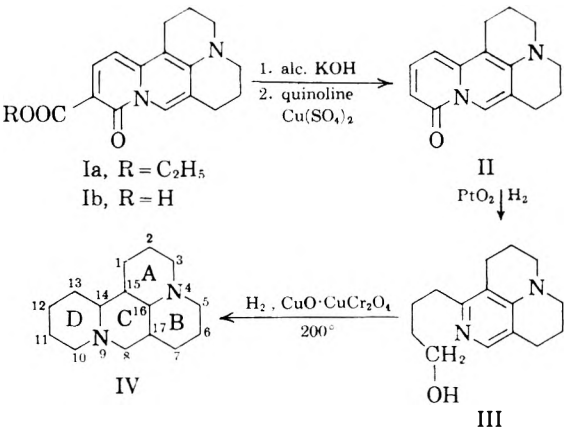
From the conformational analyses of the allomatrine series and its isomeric matrine series, the structure of allomatrine (Va), allomatridine (Vb), matrine (VIa), and matridine (VIb) were assigned.

Saponification of 11-ethoxycarbonyl-10-oxo-1,2,3,5,6,7-hexahydroquinolizo [1,8-*a*,*b*]quinolizine[3] afforded a carboxylic acid (Ib), m.p. 270–272°, and its decarboxylation by heating in quinoline with copper sulfate gave 10-oxo-1,2,3,5,6,7-hexahydroquinolizo[1,8-*a*,*b*]quinolizine (II), m.p. 174–176°; λ_{max}^{EtOH} mμ (log ε): 230 (4.36), 270 (4.05), 395 (4.22); ν quinolizone 1647 and 1518 cm.$^{-1}$ (KBr pellet). This was identified with octadehydromatrine,[4] obtained by the dehydrogenation of matrine with palladium, by mixed melting point and by comparison of their ultraviolet and infrared spectra.

Hydrogenation of II in acetic acid with platinum oxide catalyst afforded didehydromatrine,[4,5] whose ultraviolet spectrum exhibited absorption maxima at 226 mμ (log ε 4.32) and 274 mμ (log ε 4.18), and its hydrochloride showed maxima at 230 mμ (log ε 4.14) and 296 mμ (log ε 4.24). These absorption curves were similar to those[6] of dehydro-α-matrinidine (8-methyl-9-azajulolidine) and its hydrochloride, so that this hydrogenated product probably has a structure similar to those compounds, *i.e.* 8-alkyl-9-azajulolidine. The infrared spectrum of didehydromatrine had an absorption band at 3145 cm.$^{-1}$ besides those for the pyridine ring at 1592, 1558, and 1506 cm.$^{-1}$ (in Nujol). Since its benzoyl compound (as a hydrochloride) shows infrared absorption bands for ester C=O (1722 cm.$^{-1}$) and for C–O– (1281 and 1120 cm.$^{-1}$) (KBr pellet), the band at 3145 cm.$^{-1}$ is the absorption of OH. Therefore, it seems most appropriate to assume that didehydromatrine is 1-ω-hydroxybutyl-4,5,6,-8,9,10-hexahydropyrido [3,4,5-*i*,*j*]quinolizine (8-ω-hydroxybutyl-9-azajulolidine) (III) and this structure was conclusively determined by the formation of *rac*-allomatridine (IV) from III by the hydrogenation of the pyridine ring.

Therefore, this reaction effected reductive splitting of the =N–CO– bond in the quinolizone accompanied by aromatization to the pyridine ring, resulting in rearrangement to a 9-azajulolidine system. It is known that the 9-azajulolidine system is stable and is easily formed since it is obtained in good yield by the palladium dehydrogenation of 9-azahexahydrojulolidine;[3] furthermore the main reaction product from the palladium dehydrogenation of matrine is 8-propyl-9-azajulolidine,[5] and the soda-lime distillation of matrine affords a comparatively large amount of 9-azajulolidine, 8-methyl-9-azajulolidine, and 8-ethyl-9-azajulolidine.[4,7]

High-temperature and high-pressure hydrogenation of III with copper chromite catalyst resulted in the hydrogenation of the pyridine ring, with subsequent dehydration between the secondary amine in the piperidine ring and the primary alcohol group, affording perhydroquinolizo[1,8-*a*,*b*]quinolizine (IV) in a good yield. IV melts at 53–55° and agrees well with *rac*-allomatridine.[8] Through the hydrogenation of II with copper chromite catalyst below 170° gave III but IV was produced directly



(1) A brief report on this work appeared as a Communication to the Editor, *Pharm. Bull.* (*Tokyo*), **5**, 285 (1957).

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(8) C. Schöpf, H. Arm, G. Benz, and H. Krim, *Naturwissenschaften*, **38**, 186 (1951); T. F. Platonov and A. D. Kuzovkov, *Zhur. Obshchei Khim.*, **26**, 283 (1956).

from II when the reaction temperature was above 200°.

In the ring system of matridine, there are eight geometrical isomers, two of which are matridine and allomatridine. There is some evidence useful in the conformational analysis of allomatrine and matrine. Matridine and allomatridine are respectively formed from matrine and allomatrine by reduction with lithium aluminum hydride[9] through the conversion of lactam carbonyl in the starting materials to methylene groups. It is clear that the allo series is more stable because matrine is isomerized to allomatrine on catalytic hydrogenation with platinum oxide[9] and forms allomatridine by high-temperature hydrogenation with copper chromite catalyst.[10]

In the present series of experiments, on the palladium dehydrogenation of matrine and matridine at 280°, we obtained allomatrine[11] and allomatridine. Isomerization of matridine with aluminum trichloride[12] at 220° afforded allomatridine. These reactions are analogous to those reported before in the conversion of sparteine[12] to α-isosparteine ($AlCl_3$) and in the conversion of sparteine[13] and anagyrine[14] respectively to α-isosparteine and thermopsine(Pd). Przbylska and Barnes[15] have definitely determined the conformation of α-isosparteine to have the all *trans* chair form by x-ray crystal analysis. Therefore, we can conceive that the allo series takes the most stable conformation *i.e.* all four ring-junctures with the chair form[16] are *trans*.

Measurement of palladium–dehydrogenation velocity[17] at 280° indicated that the evolution of hydrogenation in allomatrine was 27% of that of matrine 5 min. later, and that of allomatridine was 68% of that of matridine 5 min. later, showing that the dehydrogenation velocity of matridine series was always faster than that of allo series. This proves that the matridine series contains a larger number of *cis*-hydrogens and this agrees with the foregoing observation.

On the other hand, both matrine and allomatrine suffer cleavage of the lactam ring by the action of alcoholic potassium hydroxide to form the alkali salts of matrinic acid[4,18] and allomatrinic acid.[9] When the respective alkali solution is refluxed for a few hours, treated with ammonium chloride to form the original acid, and then heated, they respectively return to matrine and allomatrine without isomerization into the other series during this reaction. Soda-lime distillation of potassium matrinate affords matrine and its isomer is not obtained.

From the foregoing facts and the results of following experiments, it is concluded that the formula (V) should be assigned to the allomatridine series and formula (VI) for matridine series.

Matrine (VIa) remains inert to heating with cyanogen bromide in benzene, and the starting material is recovered,[5] while allomatrine (Va) forms bromoallomatrine-cyanamide (IX), m.p. 167–168.5°, in good yield under the same conditions.

Matridine (VIb),[19] when refluxed for 1 hr. in methanol with methyl iodide, forms N^9-methiodide[20] (XI), but allomatridine (Vb) forms N^4,N^9-dimethiodide (X), m.p. 296°, by the same reaction. Similar phenomena are observed in the reaction of potassium matrinate (XIII) and potassium allomatrinate (XII) with methyl iodide. While XIII forms N^9-methylmatrinate N^9-methiodide[21] (XV), XII forms N^9-methylallomatrinate N^4,N^9-dimethiodide (XIV).[9] These experimental facts indicate that the nitrogen atoms at 4 and 9 in allomatridine series are open to the attack of reagents while in matridine series, the nitrogen at 9 is open to the attack but that at 4 is shielded.

These properties can be explained by assuming all *trans* juncture for the ring system (V) in allomatridine series, and the formulas (VI and VI′) for matridine series. Of the six formulas (VI, VI′, VII, VII′, VIII, VIII′), the front side of nitrogen at 4 in VII, VII′, VIII, and VIII′ is shielded by the B- and C-rings, but the side of lone pair electrons of nitrogen is open to rear-side attack, while the lone-pair electron side of nitrogen in formulas VI and VI′ is shielded by the C-ring, so that the attack of chemical reagent on nitrogen at 4 is interfered with.

(9) E. Ochiai, S. Okuda, and H. Minato, *Yakugaku Zasshi*, **72**, 781 (1952); *Chem. Abstr.*, **48**, 2724 (1954).

(10) E. Ochiai, J. Haginiwa, and S. Okuda, *Yakugaku Zasshi*, **71**, 1279 (1951); *Chem. Abstr.*, **46**, 5604 (1952).

(11) The recovery of matrine reported by H. Kondo and K. Tsuda (footnote 5) was found to have been incorrect by later experiments.

(12) F. Galinovsky, P. Knoth, and W. Fischer, *Monatsh. Chem.*, **86**, 1014 (1955).

(13) N. J. Leonard, P. D. Thomas, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 1552 (1955).

(14) Unpublished data of Tsuda, *et al.*

(15) M. Przbylska and W. H. Barnes, *Acta Cryst.*, **6**, 377 (1953).

(16) From this deduction, in this paper, we use chair form for all structures.

(17) Data regarding the difference in dehydrogenation velocity in *cis*- and *trans*-fused ring systems will be given in the following paper. *Cf.* M. Ehrenstein and W. Bunge, *Ber.*, **67**, 1715 (1935); B. Witkop, *J. Am. Chem. Soc.*, **70**, 2617 (1948); N. J. Leonard and B. L. Ryder, *J. Org. Chem.*, **18**, 598 (1953); E. Wenkert and L. H. Lin, *Experientic*, **11**, 302 (1955); E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **79**, 1519 (1957).

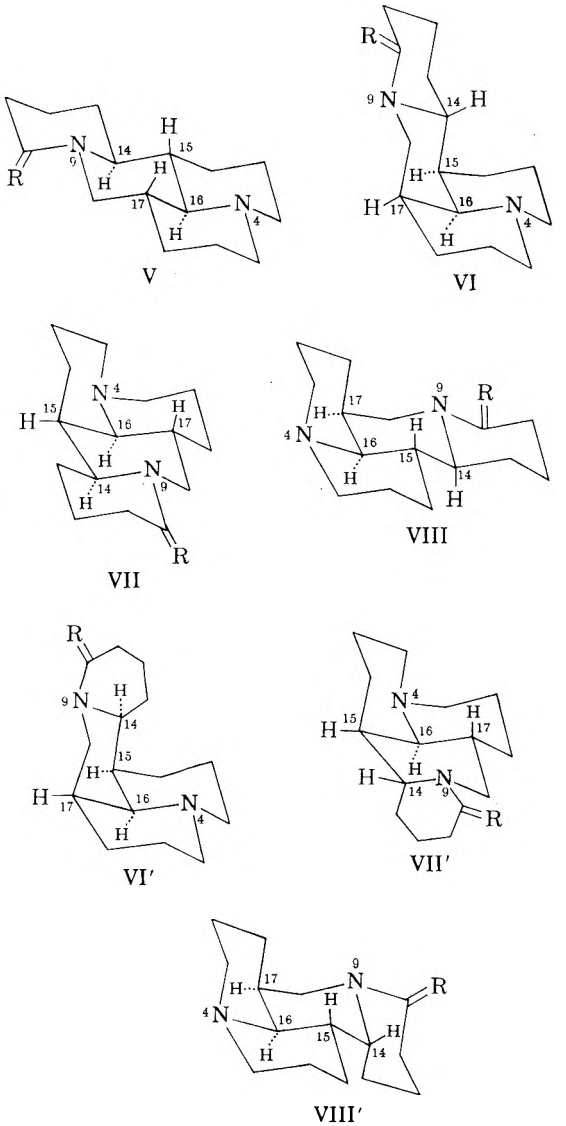
(18) H. Kondo and E. Ochiai, *Arch. Pharm.*, **266**, 4 (1928).

(19) Matrine is recovered when it is refluxed with methyl iodide for 5 hr. but matrine methiodide is obtained when a mixture of matrine and methyl iodide is heated in a glass tube at 100°.

(20) E. Ochiai and H. Minato, *Yakugaku Zasshi*, **73**, 914 (1953); *Chem. Abstr.*, **48**, 11438 (1954).

(21) Although reference to this salt was made earlier (see footnote 19), there was no proof whether the ammonium-type nitrogen was at 4 or 9. In the present case, it must be considered identical with that of matridine (see footnote 20).

Catalytic conversion of the matrine series to the allo series can well involve isomerization at both C-14 and C-16, so we could consider[22] the existence of an isomer of VI, VI′ with rings C/D *cis*-fused and the side chain axial (C-14). This would afford even greater hindrance to reactions involving *N*-4 than does structure VI.



a, R = O (matrine, allomatrine)
b, R = H_2 (matridine, allomatridine)

However, we can assume from the analogous result[23] in the reaction of methyl iodide toward a pair of isomers of hexahydrojulolidine (picrates, m.p. 187° and 226°) that the shielding effect would be afforded even by the C-ring of VI and that the greater hindrance due to C/D-*cis* isomer, VI′, would not be essential for the explanation of the hindrance. Moreover, the steric hindrance between the hydrogen atoms at C-2 and C-13 in VI′ would be inadequate to explain the stability of matrine (or matridine) during the drastic reactions of matrine series, such as soda-line distillation. Thus one can eliminate VI′ for matrine series leaving only VI for it.

Support[24] for formulas V and VI from dipole moment data will be reported in a separate paper.

EXPERIMENTAL[25]

11-Carboxy-10-oxo-1,2,3,5,6,7-hexahydroquinolizo[1,8-a,b]quinolizine (Ib). To a solution of 280 mg. of the ester (Ia) dissolved in 20 ml. of 95% ethanol, an aqueous solution of potassium hydroxide (130 mg. in 2 ml. of water) was added and the mixture was refluxed for 3 hr. Ethanol was distilled from the solution, 20 ml. of water was added to the residue, and the solution was neutralized with hydrochloric acid. A yellow substance was precipitated at *p*H 6 to give 200 mg. of crystals, m.p. 250° (with decomp.); yield, 77%. Several recrystallizations from pyridine raised the decomposition point to 272°.

Anal. Calcd. for $C_{16}H_{16}O_3N_2$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.72; H, 5.85; N, 10.07.

λ_{max}^{EtOH} mμ (log ε): 230 (4.36), 270 (4.05), 395 (4.22). ν (COOH) 1712 cm^{-1}, ν (quinolizone) 1656, 1658, and 1661 $cm.^{-1}$ (KBr pellet).

10-Oxo-1,2,3,5,6,7-hexahydroquinolizo[1,8-a,b]quinolizine (II). A solution of 410 mg. of Ib dissolved in 5 ml. of quinoline, in which 40 mg. of crystalline copper sulfate was suspended, was heated for 2 hr. at 210–240° (bath temp.), quinoline was distilled off under reduced pressure, and the residue was dissolved in benzene. The benzene solution was washed with 10% sodium carbonate solution, dried over potassium carbonate, and passed through an alumina layer. Benzene was evaporated from the effluent and 50 mg. of yellow crystals, m.p. 167–170°, were obtained. Recrystallization from acetone raised the melting point to 174–176°, undepressed on admixture with the octadehydromatrine obtained by the palladium dehydrogenation of matrine.

Anal. Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.02; H, 6.80; N, 11.68.

1-ω-Hydroxybutyl-4,5,6,8,9,10-hexahydropyrido[3,4,5-i,j]-quinolizine (didehydromatrine) (III). This was prepared from II by catalytic hydrogenation with platinum dioxide according to procedures described in the literature,[5] or by the following method.

A solution of 1 g. of II dissolved in 10 ml. of dioxane was mixed with 0.75 g. of copper chromite. The mixture was heated for 4 hr. at 160–170°, with initial hydrogen pressure of 100 atm. Recrystallization of the product from acetone gave colorless crystals of m.p. 105–106°.

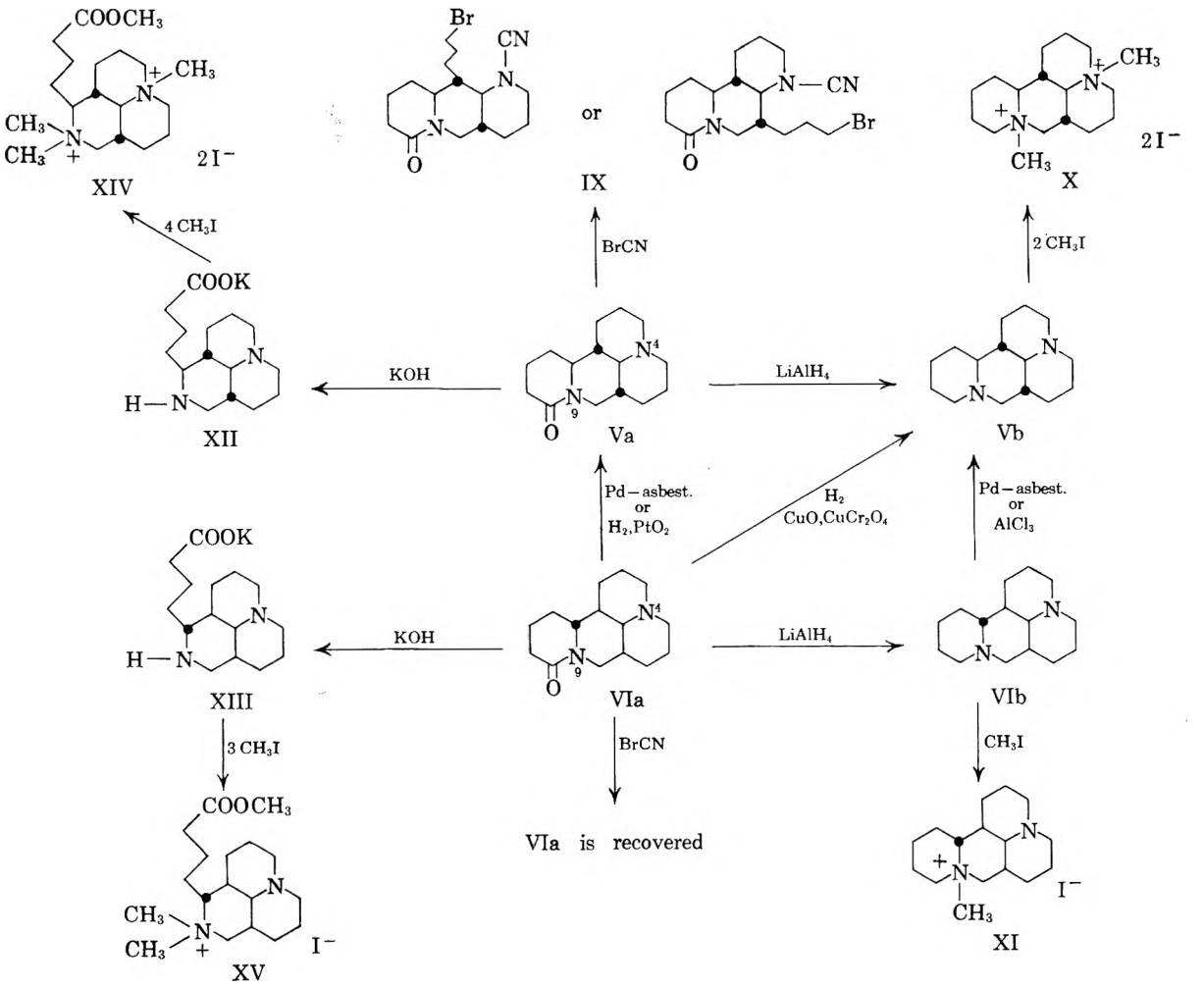
Anal. Calcd. for $C_{15}H_{22}ON_2$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.07; H, 8.87; N, 11.72.

(22) We are greatly indebted to the referees of this paper. They kindly pointed out that we overlooked this isomer at first.

(23) Unpublished work has revealed the following facts: hydrogenation of julolidine affords a pair of hexahydrojulolidines, one of which (picrate, m.p. 187°) reacts with methyl iodide while another (picrate m.p. 226°), which is convertible to the former with aluminum chloride, does not.

(24) After the appearance of our brief report (footnote 1), Bohlmann, *et al.* assigned the same structures for matrine and allomatrine by infrared spectra between 2700–2800 $cm.^{-1}$ and by some other chemical evidences which differ from ours. [F. Bohlmann, W. Weise, and D. Rahtz, *Angew. Chem.*, 69, 642 (1957); *cf.* F. Bohlmann, W. Weise, H. Sauder, *Ber.*, 90, 653 (1957)].

(25) All melting points and boiling points are uncorrected. Microanalyses were done by Mr. T. Onoe of the Takamine Research Laboratory, Sankyo Co., Ltd. Infrared spectra were measured on a Perkin-Elmer Model 21 double-beam recording spectrophotometer.



Perhydroquinolizo[1,8-a,b]quinolizine (IV) (*rac-allomatridine* IV). To a solution of 1.40 g. of III dissolved in 16 ml. of dioxane was added 0.60 g. of copper chromite and the mixture was heated for 3 hr. at 200–210° with an initial hydrogen pressure of 120 atm. The base obtained as a product was recrystallized from petroleum ether, m.p. 53–55°.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.95. Found: C, 76.92; H, 11.24; N, 12.12.

IV was also obtained from II under the same conditions. There was observed no depression of the melting point on admixture of IV with *d,l*-allomatridine,[8] m.p. 53–54°, by Schöpf.

Dehydrogenation of matridine with palladium-asbestos. A mixture of 5 g. of matridine[26] (VIb), m.p. 60°, and 2 g. of 40% palladium-asbestos was heated at 310–340° for 3 hr., during which 1200 ml. of hydrogen was generated. The base obtained was distilled to collect the fraction of b.p. 98–130°/1 mm., to which acetone and concd. hydriodic acid was added. The hydriodide (4.5 g.) so formed was recrystallized from acetone-methanol to give 3 g. of plates, m.p. over 220°. Further recrystallizations from the same solvent separated it into two kinds of crystals; the sparingly soluble needles, m.p. 305–310°, and somewhat soluble plates, m.p. 285–290°. Liberation of the base from the high-melting salt afforded allomatridine[27] (Vb), m.p. 76–78°, and the lower-melting salt regenerated the starting matridine.

The mother liquor left after separation of the hydriodides was concentrated and crystals that separated out were recrystallized from acetone to give 200 mg. of colorless plates, m.p. 194–195°.

(26) Optically active. α_D −11.6°.

Anal. Calcd. for $C_{15}H_{22}N_2 \cdot HI$: C, 50.20; H, 6.42; N, 7.82 Found: C, 50.44; H, 6.42; N, 8.58.

Ultraviolet absorption: λ_{max}^{EtOH} 296 mμ (log ε 4.22).

The structure of this substance has not been determined but it is assumed to be of 9-azajulolidine system because of its infrared absorptions at 1639, 1597, and 1548 cm.$^{-1}$ (KBr pellet) indicating the presence of a pyridine ring, the formation of a monohydriodide, and the character of its ultraviolet absorption curve.

Isomerization of matridine with aluminum chloride. A mixture of 2.6 g. of matridine[26] (VIb) and 2.6 g. of aluminum chloride was kept at 220° for 9 hr. in a nitrogen stream. This was dissolved in 5% hydrochloric acid, basified, and extracted with ether. The base obtained on evaporation of ether was distilled under reduced pressure. The distillate deposited 0.5 g. of crystals, m.p. 72–74° when petroleum ether was added. Recrystallization raised the melting point to 76–78°, identical with allomatridine[27] (Vb).

Dehydrogenation of matrine,[28] *allomatrine,*[29] *matridine,*[25] *and allomatridine.*[27] The apparatus and method followed those reported by Hyman.[30] Five hundred milligrams of the base and 200 mg. of 40% palladium-asbestos were used. The reaction vessel was immersed in a metal bath of 280° and the mixture was heated rapidly to 307° ± 3° in carbon

(27) Optically active. α_D +28.2°.

(28) Natural substance shows α_D +39.1°.

(29) Prepared by the isomerization of matrine. α_D +77.9°.

(30) L. F. Fieser, *Experiments in Organic Chemistry,* 2nd Ed., D. C. Heath and Co., New York, 1941, pp. 458–464.

	Hydrogen Gas Generated, Ml.								
Time (min.)	1	2	3	4	5	6	7	10	13
Sample									
Matrine	8.5	29.3	50.0	65.3	78.0	87.3	—	—	—
Allomatrine	1.1	5.1	10.2	15.2	21.1	26.2	31.0	43.9	54.1
Matridine	0.5	2.1	4.4	7.1	9.1	10.2	11.4	14.0	15.0
Allomatridine	0.4	2.0	4.1	5.2	6.2	7.0	7.2	8.2	—

dioxide stream and the hydrogen gas that generated was determined by azotometer.

Reaction of matrine and allomatrine with cyanogen bromide. A solution of 5 g. of allomatrine[29] dissolved in 30 ml. of dry benzene was warmed on a water bath to 60–70° and a solution of 2.3 g. of cyanogen bromide dissolved in 20 ml. of dry benzene was added dropwise. The mixture was heated for 30 min., the solvent was distilled off, and the residue was dissolved in chloroform. The chloroform solution was washed with 10% hydrochloric acid, dried over potassium carbonate, and the solvent distilled off. Addition of acetone to the residue separated some crystals which were washed with acetone and afforded 4.0 g. of bromoallomatrine cyanamide (IX), m.p. 153–157°. Further crystallization from acetone gave plates, m.p. 167–168°.

Anal. Calcd. for $C_{16}H_{24}ON_3Br$: C, 54.23; H, 6.80; N, 11.86. Found: C, 54.03; H, 6.85; N, 12.00.

The reaction of matrine with cyanogen bromide has already been described.[5]

Reaction of matridine[26] *and allomatridine*[27] *with methyl iodide.* A solution of 500 mg. of the base dissolved in 2 ml. of methanol and 1 g. of methyl iodide was refluxed for 1 hr., cooled, and crystals that separated out were recrystallized.

Allomatridine N^4,N^9-dimethiodide (X): plates (from methanol-water), m.p. 293–296° (decomp.).

Anal. Calcd. for $C_{15}H_{26}N_2 \cdot 2CH_3I$: C, 38.80; H, 6.58; N, 4.80. Found: C, 39.00; H, 6.41; N, 4.90.

Matridine N^9-methiodide (XI): white prisms (from acetone), m.p. 238–239°.

Anal. Calcd. for $C_{15}H_{26}N_2 \cdot CH_3I$: C, 50.10; H, 7.71; N, 7.44. Found: C, 50.75; H, 7.75; N, 7.29.

Acknowledgment. We thank Dr. C. Schöpf (Darmstadt) for kindly supplying a sample of *rac*-allomatridine. We are also very grateful to Dr. T. F. Platonov (Moscow), who had generously given us a sample of isoleontine.

Hongo, Tokyo, Japan

[Contribution from the Pharmaceutical Laboratory, Medical School Keio-Gijuku University]

Santonin and Related Compounds. XVII.[1] Reactions of the Bromo Derivatives of 4,9-Dimethyl-Δ^4-3-octalone-6-acetic Acid with Bases

SEIICHI INAYAMA

Received January 20, 1958

The monobromides (IIa and IIb) of the *trans*- and *cis*-ketones (Ia and Ib) mentioned in the title were treated with a variety of bases. In most cases, the $\Delta^{4,5}$-dienones (IV and V) and the lactones (IIIa and IIIb) were obtained as the expected products. With aqueous alkali, each of the monobromides was converted in low yield to the corresponding α-ketol (VIIa or VIIb) under allylic rearrangement. As other anomalous products, a bromo lactone (VIa) and the $\Delta^{1,4}$-dienone acid (VIIIa) were obtained from the *trans*-monobromide (IIa) in a few instances. Reactions of the dibromides (IXa and IXb) with bases led predominantly to the bromo lactones (VIa and VIb), respectively. A probable mechanism for the unusual reactions of the monobromides with bases is discussed.

Miki has reported[2] that treatment of the 5-bromo compound (II) of the keto acid (I) with alkali led to a liquid lactone (III) in unspecified yield. Gunstone and Tulloch[3] have disclosed the isolation of a solid lactone (III) in low purity from the same monobromide (II) on reaction with sodium ethoxide. Ishikawa[4] has reported that the enol acetate of the malonate analog of the acetic acid compound (I), which was said to be a precursor for I, was treated with peracid followed by hydrolysis-decarboxylation of the resulting lactone ester to give two solid isomers of III. The melting points reported for these solid lactones were rather different. The starting keto acid (Ia), at that time regarded as *cis*, was recently revised to be *trans*, possessing the acetic acid side chain axial.[5] From steric considerations, it is obvious that the result of Ishikawa[4] is most unlikely. The purpose of this investigation was to reexamine the reaction of the *trans*-monobromide (Ia) with base and to study, for comparison purposes, the behavior of the *cis*-monoenone (Ib)[5] upon bromination and subsequent treatment with bases.

It has been reported[2,3] that monobromination of the *trans*-monoenone (Ia) with *N*-bromosuccinimide afforded a good yield of the 5-bromo compound (IIa). The simpler procedure using one equiv-

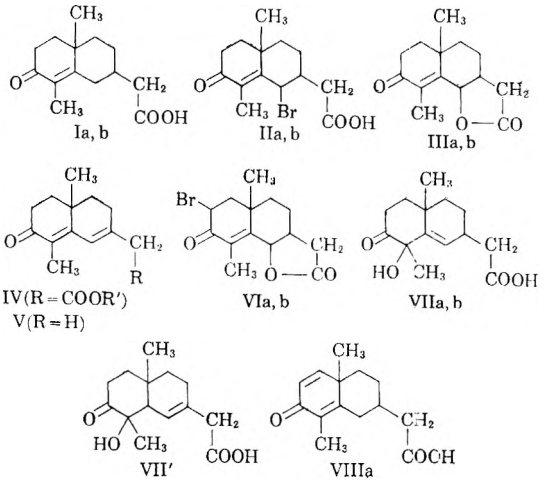
(1) Part XVI, M. Yanagita, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 841 (1958).

(2) T. Miki, *J. Pharm. Soc. Japan*, **75**, 399 (1955).

(3) F. D. Gunstone and A. P. Tulloch, *J. Chem. Soc.*, 1130 (1956).

(4) H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 494 (1956).

(5) M. Yanagita, S. Inayama, N. Hirakura, and F. Seki *J. Org. Chem.*, **23**, 690 (1958).



alent of bromine was found to give the same result. Also, bromination of the *cis*-keto acid (Ib) was well effected with *N*-bromosuccinimide to form the corresponding monobromide (IIb) in comparable yield. However, bromination of Ib with bromine proceeded much more slowly, as compared with that of the *trans* isomer (Ia). When the reaction of Ib with one equivalent of bromine was accelerated by exposure to sunlight, the dibromide (IXb) was isolated in appreciable amount, with recovery of the unchanged starting ketone. This relative inertness of Ib to bromine may be attributed to an increase in steric hindrance due to the combined effects of the two *cis*-substituents at the 6- and 9-positions, which may prevent an axial approach of bromine to the carbon at the 5-position.

Reactions of each isomer of the monobromides (IIa and IIb) with a variety of bases were carried out under relatively mild conditions, and the products, except crystalline compounds, were isolated as 2,4-dinitrophenylhydrazones by reaction with Brady's reagent.[6] When the *trans*-monobromide (IIa) was heated with anhydrous sodium acetate in glacial acetic acid, the known *trans*-keto lactone (IIIa) was chiefly obtained, along with a small amount of the $\Delta^{4,5}$-dienone (V), from the neutral fraction. With Brady's reagent, the acidic fraction formed a 2,4-dinitrophenylhydrazone of the ethyl ester (IV, R′ = C_2H_5) of the $\Delta^{4,5}$-dienone acid, indicating the presence of IV (R′ = H) in the reaction mixture. On the contrary, the *cis*-monobromide (IIb) on acetolysis furnished predominantly the dienone (V), together with a minute amount of the crystalline *cis*-keto lactone (IIIb).[7] The structure for the *cis*-keto lactone was inferred from its behavior with alkali and the ultraviolet spectrum, λ_{max}^{EtOH} 244 mμ (log ε 4.13), being rather close to those reported for the similar lactones.[8] Assignments of the structures (IV, R′ = H and R′ = C_2H_5) to the dienone acid and its ester rest mainly on the ultraviolet spectra of the compounds and their 2,4-dinitrophenylhydrazones, resembling respectively those of bicyclic $\Delta^{4,5}$-3-ketones and their hydrazone derivatives.[5,9] On warming with ethanol, the hydrazone of the *cis*-keto lactone (IIIb) was transformed into the same derivative of the ethyl ester (IV, R′ = C_2H_5) of the dienone acid, affording support for the above structures. That the neutral dienone which is probably a secondary product of the dienone acid (IV, R′ = H) possesses the structure V is evidenced by the ultraviolet spectrum and by its formation from IV (R′ = H) on heating.

It is of interest that treatment of the *trans*-monobromide (IIa) with aqueous sodium bicarbonate led chiefly to the known 2-bromo lactone (VIa),[2] accompanied with a small amount of the dienone acid (IV, R′ = H). On the other hand, the *cis*-monobromide (IIb) with bicarbonate gave in a good yield the crystalline dienone acid (IV, R′ = H), along with lesser amount of the dienone (V). When the *trans*-monobromide was dissolved in 10% aqueous sodium hydroxide, the dienone acid (IV, R′ = H), the bromo lactone (VIa), and the keto lactone (IIIa) were obtained. In addition, a new acid was isolated in minute amount from the less-soluble crop. On similar treatment with alkali, the *cis*-monobromide afforded a corresponding isomer of this new acid. Both are isomeric with the hydroxy acid resulting from hydrolysis of the keto lactone (III), but exhibit no ultraviolet absorption bands corresponding to that of the α,β-unsaturated ketones. Their infrared spectra possess bands at 3374 or 3367 cm.$^{-1}$ (OH), 1733 cm.$^{-1}$ (COOH), 1715 cm.$^{-1}$ (C=O in six-membered rings), and 1681 and 813 cm.$^{-1}$ (R_1R_2C=CHR_3).[10] With Brady's reagent, these acids formed no precipitates at room temperature, but when warmed, both were converted to the same 2,4-dinitrophenylhydrazone of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5). These results indicated that the new acids could have either the α-ketol structure VII or VII′, but the latter structure (VII′) was excluded by the formation of different ketols from IIa and IIb.

Reaction of the *trans*-monobromide (IIa) with 2,4-dinitrophenylhydrazine in hot acetic acid furnished the hydrazones of the dienone acid (IV, R′ = H) and of the dienone (V). In contrast, the *cis*-monobromide (IIb) on similar treatment was converted to the hydrazones of the *cis*-keto lactone (IIIb) and the parent acid (Ib). Refluxing of the

(6) A saturated ethanolic solution of 2,4-dinitrophenylhydrazine and concentrated sulfuric acid.

(7) The melting point reported by Miki[2] for the hydrazone of the *trans*-keto lactone (IIIa) is 10° lower than that of our sample, but identical with that of the same derivative of the *cis*-isomer (IIIb).

(8) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **75**, 2567 (1953); Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956).

(9) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1439 (1952).

(10) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 33.

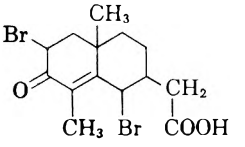
trans-monobromide (IIa) with methanol resulted in the formation of the neutral ester mixture, which on hydrolysis produced, besides the predominant $\Delta^{4,5}$-dienone acid, a minute amount of the cross-conjugated dienone acid (VIIIa) reported previously.[11] Also the *cis*-monobromide (IIb) on methanolysis was mostly converted to the neutral mixture, from which only the $\Delta^{4,5}$-dienone acid was isolated after hydrolysis. The above cited reactions of the monobromides (II) with bases are summarized in Table I.

TABLE I

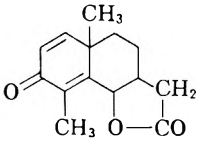
IIa	NaOAc	IIIa + IV + V
IIb	NaOAc	IIIb + IV + V
IIa	KOH–MeOH	IIIa + IV
IIa	$NaHCO_3$	IV + V + VIa
IIb	$NaHCO_3$	IV + V
IIa	aq. KOH	IIIa + IV + VIa + VIIa
IIb	aq. KOH	IIIb + VIIb
IIa	2,4-Dinitrophenyl-hydrazine	IV + V
IIb	2,4-Dinitrophenyl-hydrazine	Ib + IIIb
IIa	MeOH	IV + V + VIIIa
IIb	MeOH	IV + V
IIa	γ-collidine	V + VIIa
IIb	γ-collidine	IIIb + V

It has been reported that the 2,5-dibromo compound (IXa), prepared from the *trans*-keto acid (Ia) with bromine, was treated with potassium carbonate or γ-collidine to give the bromo lactone (VIa)[2] or the $\Delta^{1,4}$-dienone lactone (Xa),[3] respectively. It was now found that the same bromo lactone was obtained in a good yield from the dibromide (IXa) on acetolysis or by treatment with aqueous bicarbonate. However, the reported elimination of the dibromide to Xa with hot γ-collidine could not be duplicated in our laboratory. The only product isolated from the reaction was a new bromo lactone, which is isomeric but not identical with VIa. The structure (XI) for this bromo lactone was established by its ultraviolet spectrum, λ_{max}^{EtOH} 255 mμ (log ε 4.12), indicative of the Δ^1-2-bromo-3-keto moiety in an octaline ring.[12] The *cis*-dibromide (IXb) on acetolysis afforded in 30% yield the *cis*-bromo lactone (VIb) as the only product isolated. Attempted dehydrobromination of these bromo lactones (VI) into the corresponding $\Delta^{1,4}$-dienones resulted in failure. The equatorial orientation of bromine at the 2-position in the dibromides (IXa and IXb) is shown by the shift (*ca.* 20 cm.$^{-1}$) of the infrared carbonyl band over that of the corresponding monobromides (IIa and IIb). Hence, it may be assumed that the bromine in the bromo lactones (VIa and VIb) takes up the same equatorial conformation.

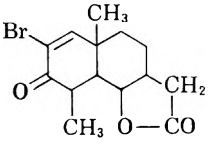
Miki[11] has reported that in the *trans*-dienone lactone (Xa), the hydroxyl group of the lactone ring, at that time regarded as axial, was readily eliminated with zinc and acetic acid. The above bromo lactones (VIa and VIb) were found to be smoothly reduced to the respective parent monoenones (Ia and Ib) with the same reagents. Molecular models clearly showed that the hydroxyl group of the lactone ring in the *trans*-series can occupy only an equatorial position. Obviously, the present and earlier results[11] of hydrogenolyses of VI and X do not conform to the suggestion by Miki[13] that in Δ^4-3-octalone systems, only the axial hydroxyl function at the 5-position is sterically favored for elimination with zinc and acetic acid.



IXa, b



Xa



XI

It is reasonable to assume that the aforementioned reactions of the monobromides (IIa and IIb) with bases proceeded mostly by the unimolecular mechanism. The resulting carbonium ion (XII) would be expected to suffer allylic rearrangement to XIII, in which attack of hydroxide ion upon the cationic center would form the α-ketol (VII). In a previous paper[14] of this series it has been shown that 5-bromo-9-methyl-Δ^4-3-octalone on acetolysis was rearranged to give a small amount of the cross-conjugated dienone. The formation of the similar dienone (VIIIa) from IIa on methanolysis provided an additional example of such rearrangement. As suggested previously,[14,15] it probably involves an intermediate formation of cyclopropane ring in the ion (XIII). The direct esterification of the monobromides on methanolysis, which seems somewhat unusual, may be accounted for by the assumption that the active center in the carbonium

(11) T. Miki, *J. Pharm. Soc. Japan*, **75**, 410 (1955).

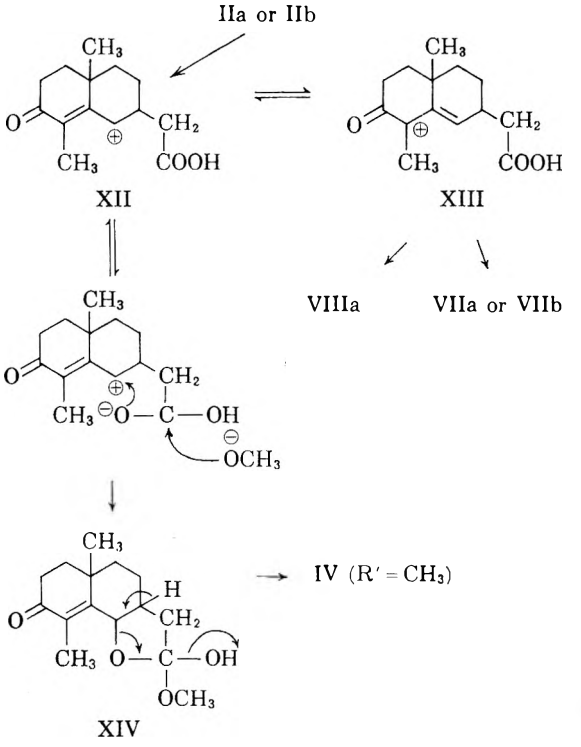
(12) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953); M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).

(13) T. Miki, *J. Pharm. Soc. Japan*, **75**, 412 (1955).

(14) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955).

(15) M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954).

ion (XII) would be intramolecularly attacked by carboxyl-oxygen to form XIV, which then could be



dehydrated to the ester. It is conceivable, however, that the monobromides would be eliminated to the $\Delta^{4,5}$-dienone acid (IV, R′ = H), which then would be esterified directly. This possibility was excluded by the result that on refluxing with methanol under the conditions employed for methanolysis of II, IV (R′= H) gave only the dienone (V) together with the recovered acid. In the aforementioned reactions of the monobromides with bases, the *trans*-isomer (IIa) showed a greater tendency to form the lactone ring, while the *cis*-isomer (IIb) was more readily dehydrobrominated to the $\Delta^{4,5}$-dienone compound (IV or V). These observations are consistent with the configurations of IIa and IIb, in which the axial substituent at the 6-position more readily participated in the above reactions.

EXPERIMENTAL[16]

All temperatures are uncorrected.

Bromination of trans-4,9-dimethyl-Δ^4-3-octalone-6-acetic acid (Ia). (*a*) *With N-bromosuccinimide.* According to the procedure reported previously,[2,3] 0.37 g. of the *trans*-monoenone[5] (Ia) in 70 cc. of carbon tetrachloride was refluxed with 0.28 g. of *N*-bromosuccinimide in the presence of traces of benzoyl peroxide. After about 3 min., bromination was completed, considerably reducing the reported reflux time (30 min.[2] or 2 hr.[3]). The bromide (IIa), amounting to 0.27 g. (55%), was recrystallized from ethyl acetate to give colorless prisms, m.p. 134–136°: λ_{max}^{EtOH} 255.5 mμ (log ε 4.07): $\nu_{max}^{CHCl_3}$ 1695 (COOH), 1661 (C=O), and 1597 cm.$^{-1}$ (C=C). Reported, m.p. 135°[2] and 126–129°:[3] λ_{max}^{EtOH} 246 mμ (log ε 4.12).[2]

The bromide remained unaffected on standing with hydrobromic acid in acetic acid overnight.

(*b*) *With one equivalent of bromine.* The *trans*-monoenone (Ia, 0.945 g.) was treated with 0.65 g. of bromine in 4 cc. of chloroform at room temperature in the usual manner. The bromine uptake took place somewhat slowly. There was obtained 0.8 g. (63%) of the crude product (IIa), which was recrystallized from ethyl acetate by addition of petroleum ether to give colorless prisms, m.p. 125–127° and mixed m.p. 128–134°.

Anal. Calcd. for $C_{14}H_{19}BrO_3$: C, 53.32; H, 6.08. Found: C, 53.13; H, 6.11.

(*c*) *With two equivalents of bromine.* By the procedure described above, 0.945 g. of the *trans*-monoenone (Ia) was brominated with 1.3 g. of bromine to give 1.16 g. (73%) of the dibromide (IXa), m.p. 129–132°. Recrystallization from ethyl acetate–methanol by addition of petroleum ether gave colorless prisms, m.p. 130–132°: λ_{max}^{EtOH} 260 mμ (log ε 4.04): $\gamma_{max}^{CHCl_3}$ 1684 cm.$^{-1}$ (C=O). Reported, m.p. 122°[2] and 123–125°;[3] λ_{max}^{EtOH} 242 mμ (log ε 4.08)[2] and 253 mμ (log ε 4.04).[3]

Anal. Calcd. for $C_{14}H_{18}Br_2O_3$: C, 42.65; H, 4.61. Found: C, 42.15; H, 4.58.

Bromination of cis-4,9-dimethyl-Δ^4-3-octalone-6-acetic acid (Ib). (*a*) *With N-bromosuccinimide.* By the procedure described above, the *cis*-monoenone (Ib) was treated with *N*-bromosuccinimide. After refluxing of the mixture for 10–15 min., the bromination was completed. The monobromide, m.p. 135–140°, obtained in 60% yield, was recrystallized from ethyl acetate to give colorless prisms, m.p. 141–142°: λ_{max}^{EtOH} 256 mμ (log ε 4.15): $\nu_{max}^{CH\ Cl}$ 1701 (COOH), 1663 (C=O), and 1597 cm.$^{-1}$ (C=C).

Anal. Calcd. for $C_{14}H_{19}BrO_3$: C, 53.32; H, 6.08. Found: C, 53.66; H, 6.12.

The bromide remained unaffected on standing with hydrobromic acid in acetic acid overnight.

(*b*) *With one equivalent of bromine.* Under the same conditions as described for the *trans*-isomer (Ia), 0.708 g. of the *cis*-monoenone[5] (Ib) was treated with 0.49 g. of bromine in 3 cc. of chloroform. When about two fifths of the bromine had been added, the bromine uptake became considerably slower. The remaining bromine was added with exposure to sunlight for 1.5 hr. Evaporation of the light brown reaction mixture left a red-brown viscous oil which soon partly solidified. By trituration with a little ether, 0.4 g. (39%) of the dibromide (IXb), m.p. 134–135°, was obtained. Recrystallization from ethyl acetate gave colorless prisms, m.p. 139–140°: λ_{max}^{EtOH} 261 mμ (log ε 4.10): $\gamma_{max}^{CHCl_3}$ 1683 cm.$^{-1}$ (C=O). It showed obvious depression of the melting point (10–15°) on admixture with the above monobromide (IIb) of the *cis*-monoenone.

Anal. Calcd. for $C_{14}H_{18}Br_2O_3$: C, 42.65; H, 4.61. Found: C, 42.52; H, 4.70.

The mother liquor of the dibromide gave 0.15 g. (21%) of the starting ketone (Ia), m.p. and mixed m.p. 135–138°.

Acetolysis of the trans-5-bromo compound (IIa). The above *trans*-monobromide (IIa, 0.70 g.) was heated with 3 g. of anhydrous sodium acetate in 10 cc. of glacial acetic acid on a boiling water bath for 2 hr. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed successively with sodium bicarbonate, sodium hydroxide solution, and water. The bicarbonate solution gave a small amount (0.04 g.) of a light brown oil, which with Brady's reagent formed in low yield a 2,4-dinitrophenylhydrazone mixture. Repeated recrystallizations from ethyl acetate–methanol gave deep red scales, m.p. 168–170°, undepressed on admixture with the hydrazone of the $\Delta^{4,6}$-dienone ethyl ester (IV, R′ = C_2H_5) described below.

The above ether solution remaining from the alkali extraction was dried and evaporated to leave a red-orange viscous oil (0.30 g.), λ_{max}^{EtOH} 246 mμ (log ε 4.03) and 300 mμ

(16) Microanalyses were carried out by Miss Ch. Shibuya and the ultraviolet measurements by Miss M. Suzuki, both of this school.

(log ϵ 3.30). This oil formed almost quantitatively a 2,4-dinitrophenylhydrazone mixture, which on repeated recrystallization from ethyl acetate gave the derivative of the *trans*-keto lactone (IIIa) as red fine needles, m.p. 236–238° (dec.): $\lambda_{max}^{CHCl_3}$ 262 mμ (log ϵ 4.22), 293 mμ (log ϵ 4.03) (inf.), and 385 mμ (log ϵ 4.50). Reported, m.p. 228°.[2]

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.94; H, 5.37; N, 13.30.

The mother liquor of recrystallization of the hydrazone of IIIa afforded dark red crystals, melting in the range 251–265° (dec.). Purification by passing through a neutral alumina column in chloroform solution gave the derivative of the $\Delta^{4,5}$-dienone (V) as lustrous deep red plates, m.p. 269–271°. Recrystallization from benzene raised the melting point to 271–273°: $\lambda_{max}^{CHCl_3}$ 266 mμ (log ϵ 4.22), 316 mμ (log ϵ 4.17), and 411 mμ (log ϵ 4.54).

Anal. Calcd. for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.23; H, 5.56; N, 15.01.

Acetolysis of the cis-5-bromo compound (IIb). The *cis*-monobromide (IIb, 0.4 g.) was treated with sodium acetate by the procedure described above for the *trans*-isomer (IIa). The neutral product (0.17 g.), a pale yellow oil, partly solidified on treatment with a little ether. The *cis*-keto lactone (IIIb, 0.02 g.), m.p. 159–162°, so obtained, was recrystallized from ethyl acetate by addition of petroleum ether to give colorless prisms, m.p. 167–169°: λ_{max}^{EtOH} 244 mμ (log ϵ 4.14): $\nu_{max}^{CHCl_3}$ 1669 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.49; H, 7.74.

It formed a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to give silky yellow needles, m.p. 225–227°: $\lambda_{max}^{CHCl_3}$ 260 mμ (log ϵ 4.09), 290 mμ (log ϵ 3.85) (inf.), and 380 mμ (log ϵ 4.35).

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.62; H, 5.21; N, 13.74.

The mother liquor of crystallization of IIIb gave a yellow oil (0.13 g.), which was twice fractionated to an almost colorless oil, b.p. 122–125° at 1 mm.: λ_{max}^{EtOH} 298 mμ (log ϵ 4.36). It consisted mainly of the $\Delta^{4,5}$-dienone (V), forming its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°.

Reaction of the trans-5-bromo compound (IIa) *with methanolic potassium hydroxide.* The *trans*-monobromide (IIa, 0.1 g.) was dissolved in 1 cc. of 10% methanolic potassium hydroxide and allowed to stand in a stream of nitrogen at room temperature for 2 days. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in water, acidified, and extracted with ether. After shaking with bicarbonate and then with potassium hydroxide solution, the ether solution was dried and evaporated to give an oil (20 mg.), which formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 237–239°, of the *trans*-keto lactone (IIIa). Its ultraviolet spectrum was superimposable on that of the above sample.

With Brady's reagent, the alkali- (5 mg.) and the bicarbonate-soluble fractions (20 mg.) formed, respectively, the 2,4-dinitrophenylhydrazones of IIIa and of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5).

Reaction of the trans-5-bromo compound (IIa) *with sodium bicarbonate solution.* A solution of 50 mg. of the *trans*-monobromide (IIa) in chloroform–ethyl acetate was shaken with a saturated sodium bicarbonate solution. The shaking was maintained until no more turbidity appeared in the aqueous layer on standing. The organic layer was separated, washed with water, dried, and evaporated to leave a pale yellow oil (35 mg.), which gave crystals, m.p. 109–110°, from ethyl acetate solution by addition of petroleum ether. Further recrystallizations from ethyl acetate formed colorless prisms, m.p. 110–112° (dec.), undepressed on admixture with the *trans*-bromo lactone (VIa) described below. The acidic fraction formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 176–178°, of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5).

Another run was carried out in the absence of the organic solvent. The *trans*-monobromide (IIa, 0.2 g.) was added to 4 cc. of saturated bicarbonate solution and the mixture was stirred at room temperature for 30 min. The separated oil was taken up in ether, and evaporation of the dried ether solution gave a pale yellow oil (0.118 g.), which could not be induced to crystallize. Distillation under reduced pressure gave a little oil (V) identified through the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°.

Reaction of the cis-5-bromo compound (IIb) *with aqueous sodium bicarbonate.* By the procedures described above for IIa, the *cis*-monobromide (IIb) was treated with sodium bicarbonate. After shaking 50 mg. of IIb in the organic solvent with aqueous bicarbonate, the bicarbonate solution was acidified to precipitate 15 mg. of the $\Delta^{4,5}$-dienone acid (IV, R′ = H) as yellowish prisms, m.p. 129–132°, which was not raised on further recrystallization from ethyl acetate–hexane. It had λ_{max}^{EtOH} 294 mμ (log ϵ 4.48).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.39; H, 7.34.

With Brady's reagent, it formed a 2,4-dinitrophenylhydrazone, m.p. 250–251°, after recrystallization from ethyl acetate. It showed no depression of melting point of the same derivative of the free acid (IV, R′ = H) described below.

It is to be noted that with Brady's reagent, the acid (IV, R′ = H) in crystalline state formed only the hydrazone of the free acid, while, when it was contained in the acid fraction of the reaction products of II, the hydrazone of the ester (IV, R′ = C_2H_5) was always obtained.

This acid on pyrolysis was converted to the $\Delta^{4,5}$-dienone (V) identified through the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°. Also, refluxing of this acid with methanol for 4 hr. gave in 50% yield $\Delta^{4,5}$-dienone (V), along with recovery of the unchanged acid (40%).

A solution of 0.10 g. of the *cis*-monobromide (IIb) in aqueous bicarbonate was allowed to stand at room temperature overnight. The nearly clear bicarbonate solution was acidified to give a pale yellow oil, which solidified on standing in a refrigerator. There was obtained 0.06 g. (80%) of the dienone acid (IV, R′ = H), melting in the range 100–112° (dec.). Recrystallization from ethyl acetate–hexane gave pale yellow prisms, m.p. and mixed m.p. 128–131°: λ_{max}^{EtOH} 294 mμ (log ϵ 4.48).

From the mother liquor of this acid, the $\Delta^{4,5}$-dienone (V) was isolated as the 2,4-dinitrophenylhydrazone.

Reaction of the trans-5-bromo compound (IIa) *with aqueous potassium hydroxide.* The *trans*-monobromide (IIa, 0.7 g.) was dissolved in 7 cc. of 10% potassium hydroxide solution and the undissolved oil was taken up in ether. The ether solution gave traces of the bromo lactone (VIa), m.p. 105–108° and mixed m.p. 111–112°. The alkaline solution, after standing for 4 hr., was acidified under cooling, and the separated oil was taken up in ether. On standing in a refrigerator, the ether solution deposited 0.05 g. of the *trans*-ketol (VIIa) as white crystals, m.p. 190–195°. Recrystallization from ethyl acetate–petroleum ether gave fine white prisms, m.p. 201–203°: ν_{max}^{KBr} 3364, 1733, 1715, and 1681 cm.$^{-1}$ It showed no ultraviolet absorption bands corresponding to that of the α,β-unsaturated ketones.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.70; H, 7.61.

This formed no hydrazone on standing with Brady's reagent at room temperature for 2 weeks. When warmed with this reagent, however, the ketol (25 mg.) was converted to the 2,4-dinitrophenylhydrazone (*ca.* 20 mg.), melting in the range 140–155°, of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5). Recrystallization from ethyl acetate–ethanol gave deep red scales, m.p. and mixed m.p. 173–175°.

The ketol remained unchanged on standing with 5% sulfuric acid at room temperature, but, when the mixture was warmed for 2 hr., there was obtained the $\Delta^{4,6}$-dienone

(V) identified through the 2,4-dinitrophenylhydrazone, m.p. 260–265° and mixed m.p. 265–268°.

The ether filtrates from the ketol were shaken with aqueous bicarbonate. Acidification of the bicarbonate solution gave an oil (0.34 g.), forming a 2,4-dinitrophenylhydrazone mixture which was fractionally recrystallized from ethyl acetate. The less-soluble crop was further recrystallized from the same solvent to give the hydrazone, m.p. and mixed m.p. 236–238°, of the *trans*-keto lactone (IIIa). The more-soluble crop was further recrystallized from ethyl acetate–ethanol to give the hydrazone, m.p. 162–164° (mixed m.p. 170–172°), of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5). It had λ_{max}^{EtOH} 266 mμ (log ε 4.20), 315 mμ (log ε 4.17), and 405 mμ (log ε 4.49). The discrepancy of the melting points of the hydrazones of IV (R′ = C_2H_5) may be due to dimorphism.

Anal. Calcd. for $C_{22}H_{28}N_4O_6$: C, 59.72; H, 5.92. Found: C, 59.31; H, 5.89.

Reaction of the cis-5-bromo compound (IIb) *with aqueous potassium hydroxide.* By the procedure described above for IIa, 0.4 g. of the *cis*-monobromide (IIb) was treated with 4 cc. of 10% potassium hydroxide solution. The alkaline reaction solution, in which, unlike the above case, no turbidity appeared on standing at room temperature, was acidified and extracted with ether. The ether solution, which gave no precipitates on standing in a refrigerator, was repeatedly shaken with aqueous sodium bicarbonate. Acidification of the combined bicarbonate solutions gave a viscous oil (0.34 g.), which on treatment with a little ether gave 0.045 g. of the *cis*-ketol (VIIb) as fine white crystals, m.p. 227–229°. Recrystallization from ethyl acetate–petroleum ether did not alter the melting point: ν_{max}^{KBr} 3367, 1733, 1715, and 1681 cm.$^{-1}$ It showed no ultraviolet absorption bands corresponding to that of the α,β-unsaturated ketones.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 67.03; H, 8.23.

As described with VIIa, the *cis*-ketol (VIIb) was warmed with Brady's reagent to form the hydrazone of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5).

The oily residue from the mother liquor of the *cis*-ketol formed in 40% yield the 2,4-dinitrophenylhydrazone of the *cis*-keto lactone (IIIb) as silky yellow needles, m.p. and mixed m.p. 237–239° (after chromatography on alumina and recrystallization from ethyl acetate–ethanol).

Reaction of the trans-5-bromo compound (IIa) *with 2,4-dinitrophenylhydrazine.* The *trans*-monobromide (IIa, 63 mg.) was heated with 40 mg. of 2,4-dinitrophenylhydrazine and 17 mg. of anhydrous sodium acetate in 1 cc. of glacial acetic acid in an oil bath (120–140°) for 10 min. On cooling, the solution deposited 15 mg. of the hydrazone of the $\Delta^{4,5}$-dienone acid (IV, R′ = H), m.p. 232–240°. Recrystallization from ethyl acetate and then from acetic acid furnished red scales, m.p. 250–255° (dec.): $\lambda_{max}^{CHCl_3}$ 267 mμ (log ε 4.05), 315 mμ (log ε 4.07), and 411 mμ (log ε 4.38).

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35. Found: C, 57.75; H, 5.86.

The mother liquor of this hydrazone gave the same derivative, m.p. and mixed m.p. 268–270°, of the $\Delta^{4,5}$-dienone (V) (after chromatography on alumina and recrystallization from ethyl acetate).

Reaction of the cis-5-bromo compound (IIb) *with 2,4-dinitrophenylhydrazine.* By the procedure described above for IIa, 25 mg. of the *cis*-monobromide (IIb) was treated with 15 mg. of the hydrazine. On cooling, the reaction solution deposited crystals (10 mg.), melting in the range 200–223°. Recrystallization from ethyl acetate gave deep red scales, m.p. 239–243°, undepressed on admixture with the same derivative of the parent monoenone (Ib).[5] Its ultraviolet spectrum is superimposable on that of the sample reported previously.[5] The mother liquor of this derivative gave the hydrazone, m.p. and mixed m.p. 225–227°, of the *cis*-keto lactone (IIIb) (after recrystallization from ethyl acetate–ethanol).

On warming with a small amount of ethanol on the water bath, the hydrazone of the lactone (IIIb) was converted to the same derivative of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5).

Reaction of the trans-5-bromo compound (IIa) *with methanol.* A solution of 0.45 g. of the *trans*-monobromide (IIa) in 10 cc. of absolute methanol was heated to reflux for 4 hr. Evaporation of the solvent under reduced pressure left an oil, which was mixed with water and extracted with ether. The ether solution was shaken successively with aqueous sodium bicarbonate, 2% sodium hydroxide, and water. Acidification of the bicarbonate solution afforded a pale yellow oil (20 mg.), which with Brady's reagent formed the hydrazone, m.p. and mixed m.p. 174–175°, of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5) (after recrystallization from ethyl acetate).

The neutral product, a light brown oil (0.32 g.), was fractionated to 0.23 g. of a pale yellow oil, b.p. 173–175° at 3 mm. With Brady's reagent, it formed almost quantitatively a hydrazone, m.p. 189–195°, of methyl ester (IV, R′ = CH_3) of the $\Delta^{4,5}$-dienone acid. Recrystallization from ethyl acetate–ethanol gave dark red fine plates, m.p. 206–207°: $\lambda_{max}^{CHCl_3}$ 266 mμ (log ε 4.19), 315 mμ (log ε 4.17), and 402.5 mμ (log ε 4.54).

Anal. Calcd. for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65. Found: C, 59.19; H, 5.45.

The methyl ester, prepared from the acid (IV, R′ = H) with diazomethane, formed the same hydrazone, m.p. and mixed m.p. 206–207°.

The above fractionated oil (0.2 g.) was heated to reflux in 1 cc. of 10% methanolic potassium hydroxide for 1 hr. Evaporation of the red-brown solution under reduced pressure left an oil, which was mixed with water and extracted with ether. The ether solution gave a little oil, forming the hydrazone, m.p. and mixed m.p. 265–268°, of the $\Delta^{4,5}$-dienone (V) (after recrystallization from ethyl acetate). The alkali solution, separated from the neutral product, was acidified under cooling and extracted with ether. The dried ether solution was evaporated to small bulk, and petroleum ether was added. On standing in a refrigerator, the solution deposited two forms of light brown crystals (0.07 g.), which were separated mechanically. One crop (0.035 g.) was recrystallized from ethyl acetate–hexane to give the $\Delta^{4,5}$-dienone acid (IV, R′ = H), light brown prisms, m.p. and mixed m.p. 128–131°. Another crop consisted of 0.01 g. of white prisms, m.p. 183–186°, which was recrystallized from ethyl acetate to raise the melting point to 188–192°: λ_{max}^{EtOH} 243 mμ (log ε 4.05). It showed no depression of the melting point on admixture with the $\Delta^{1,4}$-dienone acid (VIIIa) kindly furnished by Dr. Miki.[11]

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.40.

It formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 245–250°, which was recrystallized from ethyl acetate to give red plates, m.p. 243–245°: $\lambda_{max}^{CHCl_3}$ 259 mμ (log ε 4.25), 312 mμ (log ε 3.80), and 402 mμ (log ε 4.52).

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.95; H, 5.35; N, 13.52. Found: C, 58.24; H, 5.65; N, 13.10.

With diazomethane in ether solution, the acid gave a *methyl ester*, which formed a *2,4-dinitrophenylhydrazone*, m.p. 198–200° (after recrystallization from ethyl acetate–ethanol): $\lambda_{max}^{CHCl_3}$ 258 mμ (log ε 4.29), 312 mμ (log ε 3.85), and 406 mμ (log ε 4.58).

Anal. Calcd. for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08. Found: C, 58.92; H, 5.55; N, 13.56.

Reaction of the cis-5-bromo compound (IIb) *with methanol.* By the procedure described above for IIa, 0.27 g. of the *cis*-monobromide (IIb) was treated with 8 cc. of absolute methanol. The neutral oily product (0.18 g.) formed almost quantitatively the 2,4-dinitrophenylhydrazone, melting in the range 175–201°, of the $\Delta^{4,5}$-dienone methyl ester (IV, R′ = CH_3). Recrystallization from ethyl acetate gave dark red plates, m.p. and mixed m.p. 206–208°: $\lambda_{max}^{CHCl_3}$ 266 mμ (log ε 4.27), 314 mμ (log ε 4.29), and 405 mμ (log ε 4.61).

Hydrolysis of the above neutral oil gave, along with a small amount of the $\Delta^{4,5}$-dienone (V), the $\Delta^{4,5}$-dienone acid (IV, R′ = H), but the corresponding $\Delta^{1,4}$-dienone acid (VIII) could not be detected from the acid fraction.

Reaction of the trans-5-bromo compound (IIa) *with γ-collidine.* The *trans*-monobromide (IIa, 0.25 g.) was heated with 1.5 cc. of purified γ-collidine (b.p. 169-170°) at 170–180° for 15 min. The reaction mixture was diluted with ether to give a quantitative yield of the collidone hydrobromide. The ether solution was washed successively with dilute hydrochloric acid, water, and aqueous sodium bicarbonate. The neutral fraction, an oil (0.132 g.), which partly solidified, was triturated with ether to give 12 mg. of the *trans*-ketol (VIIa) as light brown crystals, m.p. 183–191°. Recrystallization from ethyl acetate raised the melting point to 200–203° (mixed m.p. 201–203°). The mother liquor of VIIa formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 266–270°, of the $\Delta^{4,5}$-dienone (V) (after repeated recrystallization from ethyl acetate).

Acidification of the bicarbonate solution gave a pale yellow oil (10 mg.), which formed with Brady's reagent the hydrazone, m.p. and mixed m.p. 170–172°, of the $\Delta^{4,5}$-dienone ethyl ester (IV, R′ = C_2H_5).

Reaction of the cis-5-bromo compound (IIb) *with γ-collidine.* By the procedure described above for IIa, 0.15 g. of the *cis*-monobromide (IIb) was heated with γ-collidine, forming a quantitative yield of the collidine salt. The neutral oily fraction (0.07 g.) gave 0.015 g. of the *cis*-keto lactone (IIIb) as light brown crystals, m.p. 155–157°, from ether solution by addition of hexane. Recrystallization from ethyl acetate–hexane raised the melting point to 167–169° (mixed m.p.).

The mother liquor of IIIb gave a brown oil (0.05 g.), which formed almost quantitatively the 2,4-dinitrophenylhydrazone, melting in the range 250–265°, of the $\Delta^{4,5}$-dienone (V). Purification by passing through an alumina column in chloroform solution and recrystallization from ethyl acetate gave a pure sample, m.p. and mixed m.p. 271–273°.

Acetolysis of the trans-2,5-dibromo compound (IXa). By the procedure described above for the *trans*-monobromide (IIa), 0.93 g. of the *trans*-dibromide (IXa) was heated with 3 g. of anhydrous sodium acetate in 12 cc. of glacial acetic acid. The ether solution, containing the neutral products, was dried and concentrated to deposit 0.47 g. (64%) of the *trans*-bromo lactone (VIa) as light brown crystals, m.p. 99–100°. Recrystallization from methanol with charcoal afforded white prisms, m.p. 110–112° (dec.): λ_{max}^{EtOH} 250 mμ (log ε 4.04): $\nu_{max}^{CHCl_3}$ 1684 cm.$^{-1}$ (C=O). Reported,[2] m.p. 107–112° and λ_{max}^{EtOH} 242 mμ (log ε 4.03).

Anal. Calcd. for $C_{14}H_{17}BrO_3$: C, 53.67; H, 5.47. Found: C, 53.19; H, 5.42.

The bromo lactone (0.1 g.) was refluxed with 1.0 g. of activated zinc dust in 10 cc. of ethanol containing 0.1 cc. of acetic acid for 15 min. After removal of zinc by filtration, the filtrate was evaporated under reduced pressure to leave a viscous oil, which was mixed with water and extracted with ether. The ether solution was shaken with aqueous sodium carbonate, and the carbonate solution was acidified to separate a brown oil which soon solidified. Recrystallization from methanol gave 0.05 g. (57%) of the starting monoenone (Ia), m.p. and mixed m.p. 132–135°.

Treatment of the bromo lactone with hot collidine in the usual manner formed in 83% yield the collidine salt, but no tractable products were isolated from the reaction mixture.

Acetolysis of the cis-2,5-dibromo compound (IXb). The *cis*-dibromide (IXb, 0.5 g.) was subjected to acetolysis under the conditions described above for IXa. From the neutral fraction, 0.18 g. (45%) of the *cis*-bromo lactone (VIb) was isolated as pale yellow crystals, m.p. 190–193° (dec.), which was recrystallized from ethyl acetate and then methanol to give yellowish prisms, m.p. 180–181° (dec.): λ_{max}^{EtOH} 248 mμ (log ε 4.13): $\nu_{max}^{CHCl_3}$ 1686 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{14}H_{17}BrO_3$: C, 53.67; H, 5.47. Found: C, 54.01; H, 5.81.

The residual oil of the mother liquor of VIb formed the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 271–273°, of the $\Delta^{4,5}$-dienone (V) (after chromatography on alumina with chloroform elution and recrystallization from ethyl acetate).

Hydrogenation of the *cis*-bromo lactone with zinc dust, as described above for VIa, furnished the starting *cis*-ketone (Ib), m.p. and mixed m.p. 142–144°.[5] Like VIa, VIb could not be dehydrobrominated to the dienone (X) with hot collidine.

Reaction of the trans-2,5-dibromo compound (IXa) *with sodium bicarbonate.* A solution of 0.05 g. of the *trans*-dibromide (IXa) in ether was shaken with aqueous bicarbonate, as described above for the *trans*-monobromide (IIa). The ether solution, separated from the aqueous layer, gave a light brown oil (0.05 g.), which was again dissolved in a little ether and stored in a refrigerator. There was obtained 0.02 g. of the *trans*-bromo lactone (VIa) as light brown crystals, m.p. 100–105°. Recrystallization from ethyl acetate gave colorless prisms, m.p. and mixed m.p. 110–112°.

Reaction of the trans-2,5-dibromo compound (IXa) *with γ-collidine.* According to the procedure reported by Gunstone and Tulloch,[3] 0.8 g. of the *trans*-dibromide (IXa) was heated with 23 cc. of purified γ-collidine. The crude product, a dark brown oil, was dissolved in ether, and the ether solution was shaken with aqueous sodium bicarbonate and then with 1% sodium hydroxide. The alkaline solution gave only traces of a brown oil. Evaporation of the dried ether solution left a dark brown oil (0.23 g.) which was chromatographed on silica gel (1.5 × 22 cm.) and eluted with chloroform. The early eluted fraction afforded a small amount of the bromo lactone (XI), m.p. 132–135°. Recrystallization from methanol gave colorless plates, m.p. 136–138°: λ_{max}^{EtOH} 255 mμ (log ε 4.12).

Anal. Calcd. for $C_{14}H_{17}BrO_3$: C, 53.67; H, 5.47. Found: C, 53.23; H, 5.37.

The mother liquor of XI gave no tractable products.

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SHINJUKU-KU, TOKYO, JAPAN

[CONTRIBUTION FROM THE DIVISION OF STEROID METABOLISM AND BIOCHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Synthesis of 1,3,5(10)-Estratriene-3,16β,17α-triol[1]

JACK FISHMAN AND WARREN R. BIGGERSTAFF[2]

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The preparation of 1,3,5(10)-estratriene-3,16β,17α-triol is described. The 16α and 16β bromo epimers of estrone were also prepared and some of their reactions were studied.

Of the four possible estriols isomeric at carbons 16 and 17 only three are known. They include the original estriol, or 1,3,5(10)-estratriene-3,16α,17β-triol (I), and the two cis isomers, 1,3,5(10)-estratriene-3,16β,17β-triol (II) and 1,3,5(10)-estratriene-3,16α,17α-triol (III). All three have been synthesized[3] and the former two have also been identified as metabolites of estradiol in the human[4]. Our interest in the metabolism of estrogens and in the chemistry of these stereoisomers prompted us to undertake the preparation of the remaining isomer 1,3,5(10)-estratriene-3,16β,17α-triol (IV).

The initial attempts were directed towards reduction of the readily available 3,16β-dihydroxy-1,3,5(10)-estratriene-17-one (XVa), or its acetate,[5] with less stereospecific reagents than lithium aluminum hydride. All the reductants tried, however, gave only 1,3,5(10)-estratriene-3,16β,17β-triol (II). The preparation of IV by the action of acetic acid on the 16α,17α oxide XIVa was then studied. Despite the previous failure to isolate any products from this reaction,[3a] we were able to obtain a small amount of the new estriol. Since, however, the α-oxide is not easily accessible, synthesis of the desired estriol isomer in more substantial quantities required another approach. The work of Fajkos[6] in the androstane series appeared to offer an attractive route to IV.

Bromination of estrone enol diacetate V gave 16α-bromoestrone acetate (VIa), a compound previously prepared[7] but in which the orientation of the bromine had not been defined. From analogy with the androstane series[6] the α-orientation was assumed, and this was borne out by subsequent reactions. Reduction at 0° of 16α-bromoestrone acetate (VIa) with lithium aluminum hydride gave the *trans* bromohydrin VIII, which was directly transformed to 16β,17β-epoxy-1,3,5(10)-estratriene-3-ol (XII) by refluxing in alkaline solution. The structure of the new oxide XII was established by reduction with lithium aluminum hydride to yield 16β-estradiol (XVb), identical (infrared spectrum and mixture melting point comparison) with a sample prepared from 1,3,5(10)-estratriene-16-one (XVI) by sodium borohydride reduction.[8] Refluxing the oxide XII with acetic acid followed by hydrolysis of the products gave a mixture of the two isomeric *trans* estriols I and IV, from which the new 1,3,5(10)-estratriene-3,16β,17α-triol (IV) was obtained in about 50% yield by chromatography and fractional crystallization.

It was of interest to prepare 16β-bromoestrone acetate (VIIa) and to compare the reactions of the two bromoketones epimeric at C-16. Although acid hydrolysis of VIa at room temperature gave 16α-bromoestrone (VIb), hot acid hydrolysis resulted in epimerization to give predominantly 16β-bromoestrone (VIIb). Acetylation of VIIb gave 16β-bromoestrone acetate (VIIa). VIIa could also be obtained directly from VIa in lower yield by partial epimerization on alumina, followed by careful chromatography and fractional crystallization. The two epimeric bromoestrones, VIb and VIIb, had the same melting point with little depression on admixture. They were not separated by alumina or chromatography on paper in several systems, but were separated by fractional crystallization. The specific rotation was found to be an acceptable criterion of purity. The acetates VIa and VIIa showed similar behavior although the mixture melting point depression was considerable. Lithium aluminum hydride reduction followed directly by alkaline reflux was then carried out on both epimers VIb and VIIb. The 16α-bromoketone VIa afforded in addition to the 16β, 17β-oxide XII, about 10% of estrone (XIII) derived from the *cis* 16α, 17α-bromohydrin

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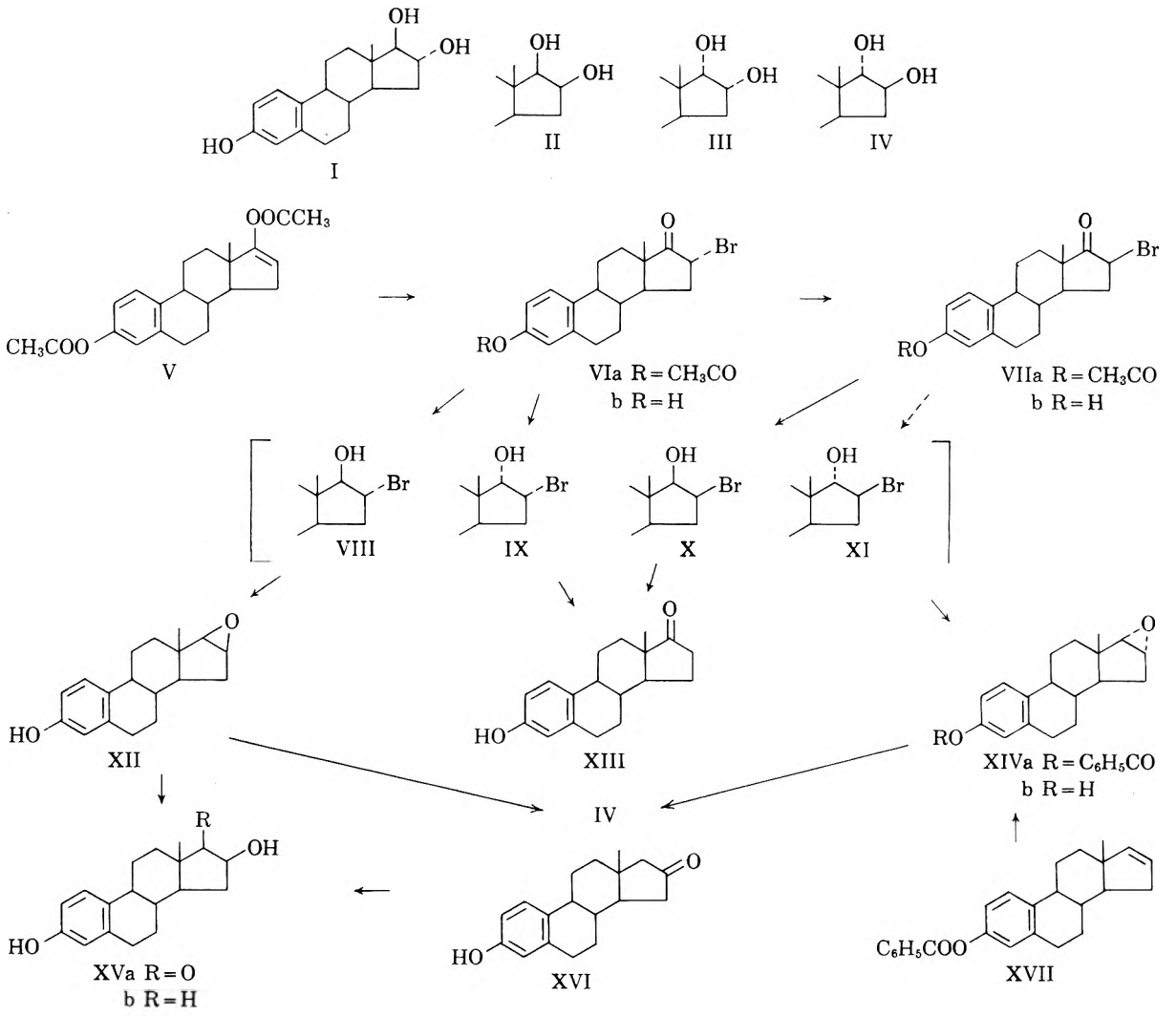

IX formed during the reduction.[9] The 16β-bromoestrone (VIIb) gave rise only to estrone derived from the *cis*-16β,17β-bromohydrin X; none of the 16α,17α-oxide XIVb expected from the *trans* bromohydrin XI was found. These results not only confirm the assignment of the bromine orientation in the two isomers but also support the previous finding[5] that a 16β-substituent results in stereospecific β reduction of the 17-ketone while a 16α-substituent makes the reduction only stereoselective, with about 10-15% of α-reduction.

The contribution of the new estriol to the metabolism of estradiol in man is at present being investigated.

EXPERIMENTAL[10]

16α-Bromoestrone acetate (VIa). One gram of estrone enol diacetate (V) in carbon tetrachloride containing some potassium carbonate was treated with one equivalent of bromine in carbon tetrachloride following the procedure of Johnson and Johns.[7] The usual work-up gave 700 mg. of product of m.p. 163–167°. Four recrystallizations from methanol gave 16α-bromoestrone acetate, m.p. 169–171°; $[\alpha]_D^{24}$ +119° (chloroform). Literature m.p. 168–170°.

16α-Bromoestrone (VIb). A solution of 300 mg. of the acetate VIa in 4% ethanolic sulfuric acid was allowed to stand for 20 hr. at room temperature. Dilution with water and extraction with chloroform gave 243 mg. of 16α-bromoestrone, crystallized from benzene as long needles, m.p. 225–228°; $[\alpha]_D^{24}$ +120° (chloroform).

Anal. Calcd. for $C_{18}H_{21}O_2Br$: C, 61.89; H, 6.02. Found: C, 62.33; H, 6.28.

Acetylation with acetic anhydride and pyridine regenerated VIa.

16β-Bromoestrone acetate (VIIa). Five hundred milligrams of the crude α-bromoacetate VIa in the minimum amount of 1:1 benzene-petroleum ether mixture was adsorbed on a column of 100 g. of alumina. After standing overnight the column was eluted in 100 cc. of fractions first with 3:2 benzene–petroleum ether and then with the same solvents in 4:1 ratio. The various fractions were combined on the basis of their melting points. The first 5 fractions gave on crystallization from methanol 0.23 g. of plates of pure 16α-bromoestrone acetate (VIa). Fractions 6–10 were mixtures.

(9) The estrone could also be derived from the β-*cis* bromohydrin (X) which could result by epimerization of the α-bromine prior to reduction. This, however, is unlikely in view of the low temperature, inert solvent, and the rapidity of the reduction.

(10) Melting points were obtained on a Kofler hot stage apparatus and are corrected. Analyses are by Spang Microanalytical Laboratories.

Fractions 10 to 14 crystallized from methanol to give 47 mg. of β-bromoestrone acetate (VIIa) as needles, m.p. 166–169°. The analytical sample melted at 170–173°; $[\alpha]_D^{25}$ +156° (chloroform).

Anal. Calcd. for $C_{20}H_{23}O_3Br$: C, 61.38; H, 5.92. Found: C, 61.45; H, 5.88.

Subsequent fractions eluted from the column with more polar solvents proved to be a mixture of the hydrolyzed α and β isomers. A mixture melting point of VIIa with the 16α isomer (VIa) showed a depression of 40°. The infrared spectra of the two compounds in carbon disulfide were different in the 1400–650 cm.$^{-1}$ region, but there was no difference in the position of the ketone band at 1758 cm.$^{-1}$ Paper chromatography in several systems failed to separate the two isomers.

16β-Bromoestrone (VIIb). Room temperature hydrolysis of 16β-bromoestrone acetate VIIa with 4% ethanolic sulfuric acid for 20 hr. gave the free phenol VIIb, which crystallized from benzene as short needles, m.p. 224–227° with sublimation. Mixed melting point with the α-isomer VIb was 213–220°. The infrared spectra of the two compounds in chloroform showed significant differences in the 1150–800 cm.$^{-1}$ region. Paper chromatography in various systems again failed to separate the two compounds. The analytical sample melted at 225–228°; $[\alpha]_D^{24}$ +154° (chloroform).

Anal. Calcd. for $C_{18}H_{21}O_2Br$: C, 61.89; H, 6.02. Found: C, 62.06; H, 6.03.

The same compound could be obtained by refluxing the α-bromoestrone acetate VIa with 4% ethanolic sulfuric acid overnight. The resultant mixture was predominantly 16β-bromoestrone (VIIb), which could be obtained pure by fractional crystallization. Acetylation with acetic anhydride in pyridine gave 16β-bromoestrone acetate (VIIa).

16β,17β-Epoxy-1,3,5(10)-estratriene-3-ol (XII). One gram of α-bromoestrone acetate VIa was stirred for 2 hr. at 0° with an excess of lithium aluminum hydride in anhydrous ether. The excess reagent was destroyed with water; acidification with dilute hydrochloric acid and evaporation of the organic phase gave 0.78 g. of a gum, the infrared spectrum of which lacked any carbonyl absorption. Without further purification the material was refluxed for 4 hr. with 5% ethanolic potassium hydroxide. Dilution with water and extraction with chloroform gave 0.58 g. of solid which was chromatographed on 50 g. of alumina. A total of 0.24 g. of the 16β,17β-oxide (XII) was eluted first with 9:1 benzene–petroleum ether. Subsequent fractions contained 92 mg. of estrone. The oxide crystallized from benzene–petroleum ether as short needles, m.p. 198–202°. The analytical sample melted 200–204°; $[\alpha]_D^{25}$ +119° (chloroform).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.25. Found: C, 80.15; H, 8.22.

Reduction of the oxide (XII) with lithium aluminum hydride gave 1,3,5(10)-estratriene-3,16β-diol (XVb), m.p. 224–226° identical with a sample prepared by sodium borohydride reduction of 1,3,5(10)-estratriene-16-one (XVI).

When 150 mg. of the 16β-bromoestrone acetate (VIIa) was reduced under identical conditions with lithium aluminum hydride followed by heating with alkali 94 mg. of estrone was obtained. No 16α,17α-oxide XIVb was isolated.

1,3,5(10)-Estratriene-3,16β,17α-triol (IV). (a) A solution of 300 mg. of the β oxide XII in 30 cc. of glacial acetic acid was refluxed for 4 hr. Removal of the acetic acid under vacuum left an oily residue, which was refluxed in 6% ethanolic potassium hydroxide for 1.5 hr. Dilution and acidification with dilute hydrochloric acid and thorough extraction with chloroform gave 300 mg. of a white solid which was chromatographed on 25 g. of alumina. The first fractions eluted with 900 cc. of chloroform containing 3% methanol were combined to give 124 mg. of material which crystallized from benzene-methanol as prisms, m.p. 245–248°. Further recrystallization raised the melting point to 248–250°; $[\alpha]_D^{25}$ +61° (ethanol).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.74; H, 8.30.

The subsequent fractions eluted weighed 64 mg. and proved to be the other *trans* isomer, 1,3,5(10)-estratriene-16α,17β-triol (I).

The infrared spectrum of the new estriol in potassium bromide showed differences from the other three estriol isomers. Paper chromatography in a benzene-methanol: water-ethyl acetate system separated the new estriol from its isomers. The compound was somewhat less polar than 1,3,5(10)-estratriene-3,16α,17β-triol (I), but considerably more polar than the two *cis* triols in the solvent system used.

(b) A solution of 100 mg. of 1,3,5(10),16-estratetraene-3-ol benzoate (XVII), m.p. 161–166° in ether was treated with perbenzoic acid. On working up the reaction, 111 mg. of crude 16α,17α-epoxy-1,3,5(10)-estratriene-3-ol benzoate (XVIa) was obtained. Without further purification this material was refluxed for 2 hr. in 3 cc. of glacial acetic acid under nitrogen. The acetic acid was removed and the residue refluxed in 8% ethanolic potassium hydroxide for 1.5 hours. The isolated product was a yellow semisolid weighing 73 mg. The material was decolorized with charcoal and crystallized from acetone–petroleum ether to give 23 mg. of crystals, m.p. 200–235°. It was then dissolved in benzene containing 10% ethyl acetate and chromatographed through a 1 × 10 cm. silica column. The combined material eluted with 50% ethyl acetate-benzene weighed 12 mg., m.p. 228–240°. One recrystallization raised the melting point to 244–246°. Mixture melting point determination and infrared spectra comparison established the identity with the 1,3,5(10)-estratriene-3,16β,17α-triol (IV) prepared from the β oxide XII.

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[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE[1]]

A New Route to 3- and 2,6-Substituted Fluorenes[2]

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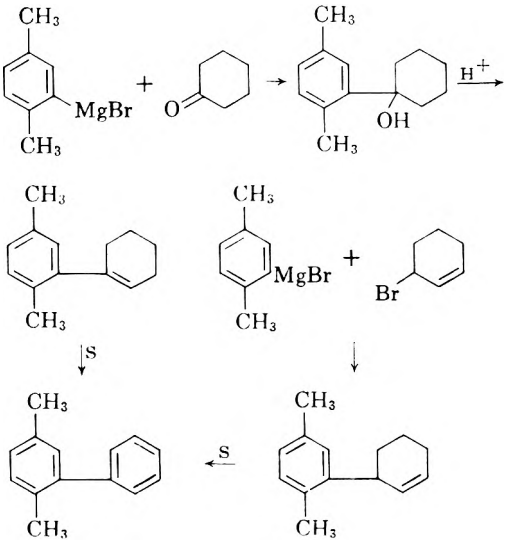
The isomeric 1- and 3-(2,5-xylyl)cyclohexene were prepared from 2,5-xylylmagnesium bromide and cyclohexanone, or 3-bromocyclohexene, respectively. Comparative ultraviolet absorption data on these and the related saturated molecule suggest a steric inhibition of resonance in the first compound owing to the 2-methyl group. Dehydrogenation of the cyclohexene derivatives led to 2,5-dimethylbiphenyl which was oxidized to 2,5-biphenyldicarboxylic acid. Ring closure gave 9-oxo-3-fluorenecarboxylic acid which was the starting material for the preparation of a number of 3- and 2,6-substituted fluorene derivatives. The ultraviolet absorption spectra of these compounds are discussed in relation to the resonance interaction of a substituent at the 3- and as compared to the 2-position of fluorene.

Direct substitution by electrophilic reagents in the polynuclear hydrocarbon fluorene usually involves the 2-position.*cf.*[3] Further reaction affects the 7-, and also to some extent the 5-position, when the group in the 2-position is electron-attracting. On the other hand, the second substituent enters the 7-, 3-, and 1-positions, in order of decreasing quantitative importance, if the 2-positions contain an electron-donating substituent. Therefore, only the 2-monosubstituted and the 2,7-and the 2,3-disubstituted derivatives of fluorene are readily available using the hydrocarbon itself as starting material. Compounds with substituents at the other carbon atoms are in general prepared by degrading a larger ring system or by building up the fluorene skeleton. Fluorenes or fluorenones with a substituent in the 3-position have been synthesized from properly substituted 2-aminobenzophenones *via* a Pschorr reaction,[4] from biphenyl derivatives by ring closure,[5] by elimination of a substituent at the 2-position in 2,3-disubstituted fluorenes,[5b,6] or by building up the fluorene ring system from indane derivatives.[7] The problem of the synthesis of 3-substituted fluorenes thus hinges on the development of satisfactory methods for the preparation of the crucial intermediates. This paper presents a simple procedure leading to 2,5-biphenyldicarboxylic acid, which can be converted readily into 9-oxo-3-fluorenecarboxylic acid. This compound and the corresponding fluorene derivative have been found useful for the further preparation of 3-fluorenamine and of a number of 2,6-disubstituted fluorenes.

The reaction of 2,5-xylylmagnesium bromide with cyclohexanone furnished the readily dehydrated 1-(2,5-xylyl)cyclohexanol. Hydrolysis of the Grignard reaction mixture had to be performed by saturated ammonium chloride rather than by an acid solution if dehydration of some of the tertiary alcohol were to be avoided. However, the ease with which loss of water occurred under the influence of hydrogen ion facilitated the preparation of the desired 1-(2,5-xylyl)cyclohexene in a single step without isolating the intermediate cyclohexanol.



The isomeric 3-(2,5-xylyl)cyclohexene was prepared by an adaptation of the method used by

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(2) Presented in part before the Division of Organic Chemistry, at the 131st meeting of the American Chemical Society, Miami, Florida, April, 1957; abstracts of papers, p. 69-0.

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(7) *cf.* H. Bryant and E. Sawicki, *J. Org. Chem.*, **21**, 1322 (1956) for pertinent references.

Biggerstaff *et al.*,[8] namely reaction of 2,5-xylylmagnesium bromide with 3-bromocyclohexene. For the purpose of comparative studies of the spectra in this series of compounds the corresponding saturated (2,5-xylyl)cyclohexane was also synthesized by the alkylation of cyclohexene with *p*-xylene. Curiously, both the wave lengths of maxima of absorption in the ultraviolet and the molar extinction coefficients at the maxima are very similar for all three compounds (Fig. 1). This is not the case

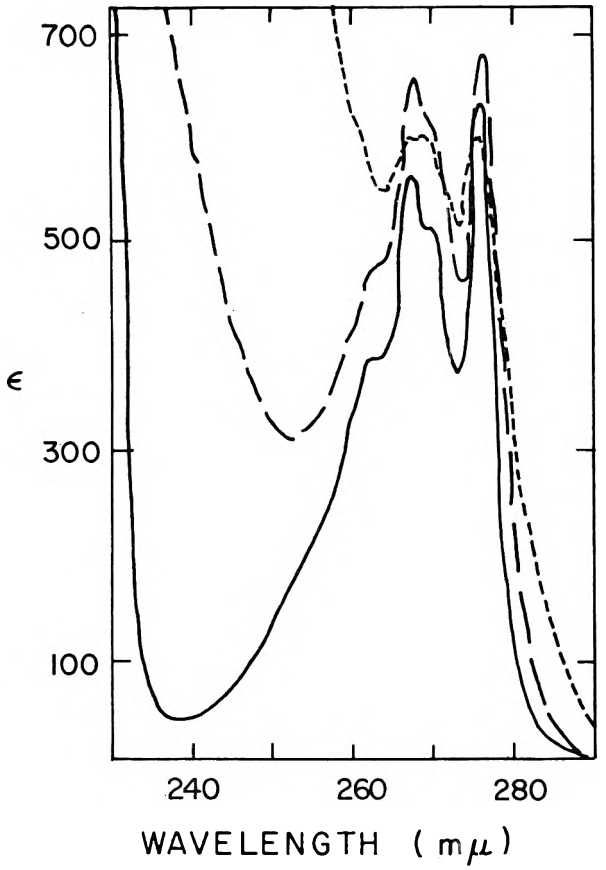


Fig. 1. Ultraviolet absorption spectra of; ——— 2-cyclohexyl-1,4-dimethylbenzene, - - - - 1-(2,5-xylyl)cyclohexene, and — — — 3-(2,5-xylyl)cycohexene

with the corresponding phenylcyclohexane and cyclohexenes[9a] which suggests that the methyl group in the 2-position interferes with the planarity of the exocyclic (to the aromatic ring) double bond in 1-(2,5-xylyl)cyclohexene. Molecular models show that the methyl group at the 2-position prevents a planar configuration of the double bond in relation to the aromatic ring. Carlin and Landerl[9b] and Carlin and Constantine[9c] have also concluded that a methyl group in the 2-position can interfere with the planarity of the molecules; this is reflected in their physical properties. A comparison of the refractive indices in this series of compounds (*cf.* Experimental section and reference 9a) supports this concept.

Dehydrogenation of either the 1- or 3-cyclohexene derivative to give 2,5-dimethylbiphenyl proceeded readily with sulfur at 220–240° as an exothermic reaction. In two cases the reaction was followed by collecting the evolved hydrogen sulfide, which was obtained in a quantitative yield. However, the recovery of 2,5-dimethylbiphenyl was only 50–60%, and the balance of the material was a non-distillable, somewhat viscous residue. Further study of this reaction might be of some interest. Johnson[10] noted recently that dehydrogenations performed with a mixture of sulfur and palladium-on-charcoal facilitated the reaction and gave somewhat higher yields than with sulfur alone. Another method, dehydrogenation with chloranil, was considerably more cumbersome and did not lead to improved yields.

The permanganate oxidation of 2,5-dimethylbiphenyl was a slow process owing to the relative insolubility of the hydrocarbon in the aqueous oxidation system. A fair proportion of the compound was recovered unchanged even after a long reaction period (10 hours). Attempts to obviate the difficulty by addition of a solvent, pyridine, were only moderately successful. The oxidation was more rapid and all of the added hydrocarbon was oxidized. However, a considerable excess of permanganate was required, since pyridine itself was attacked under the conditions of the reaction. In addition, the resulting 2,5-biphenyldicarboxylic acid was not as pure as that obtained by oxidation without the added solvent.

Ring closure of 2,5-biphenyldicarboxylic acid to yield 9-oxo-3-fluorenecarboxylic acid was performed with polyphosphoric acid. The Wolff-Kishner reduction of the fluorenone derivative proceeded at an unusually low temperature. Gas evolution started at 120°, and was substantial at 140°. This might be the result of a strong electron-attracting group, the carboxyl ion, in a *para* position to the ketone function.

3-Fluorenecarboxylic acid was readily converted to 3-fluorenamine *via* the diacetyl derivative in a modified Curtius reaction, which had been successfully used with another fluorenecarboxylic acid under analogous conditions,[11] and where the normal Curtius procedure failed owing to the difficulty in securing hydrolysis of the intermediary urethan. The more direct Schmidt reaction likewise was unsuitable, probably owing to concomitant sulfonation. The sequence of reactions described thus furnishes another approach leading to 3-fluoren-

(8) W. R. Biggerstaff, A. P. Menditto, and I. Yokoyama, *J. Org. Chem.*, 19, 934 (1954).

(9) (a) E. L. Eliel, J. W. McCoy, and C. C. Price, *J. Org. Chem.*, 22, 1533 (1957); (b) R. B. Carlin and H. P. Landerl, *J. Am. Chem. Soc.*, 75, 3969 (1953); (c) R. B. Carlin and D. A. Constantine, *J. Am. Chem. Soc.*, 69, 50 (1947). We are indebted to the reviewers of this paper for drawing our attention to references 9b and 9c.

(10) E. A. Johnson, *J. Chem. Soc.*, 4155 (1957).

(11) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, 18, 864 (1953).

amine, a compound of some interest in cancer research.[12] In addition, certain 2,3-disubstituted fluorenes can be derived from this amine, since the amino group facilitates further substitution in the same ring.

3-Fluorenecarboxylic acid, on the other hand, could be made the starting point for some 2,6-disubstituted fluorenes, since the carboxyl function hinders substitution in the same ring, and thereby directs the entering group into the unsubstituted ring. In concordance with the expected reactivity of the fluorene molecule, nitration occurred mainly at the 7-position, yielding 3,7-(or 2,6-)disubstituted derivatives. Proof that the substitution had occurred at the 7-position was adduced from the fact that 2-nitrofluorene was obtained from the deamination of 7-nitro-3-fluorenamine, itself derived from 7-nitro-3-fluorenecarboxylic acid. These methods have permitted the synthesis of a number of 2,6-disubstituted fluorenes (I) bearing a variety of functional groups. Heretofore, only 2-nitro-6-bromofluorene[6e] and the corresponding fluorenone,[5b] and 2,6-diaminofluorenone[6f] had been available.

The ultraviolet spectra of 3-substituted fluorenes exhibit a characteristic arrangement of triple peaks, which also persists in 2,6-disubstituted derivatives (Figs. 2 and 3). This can be tentatively

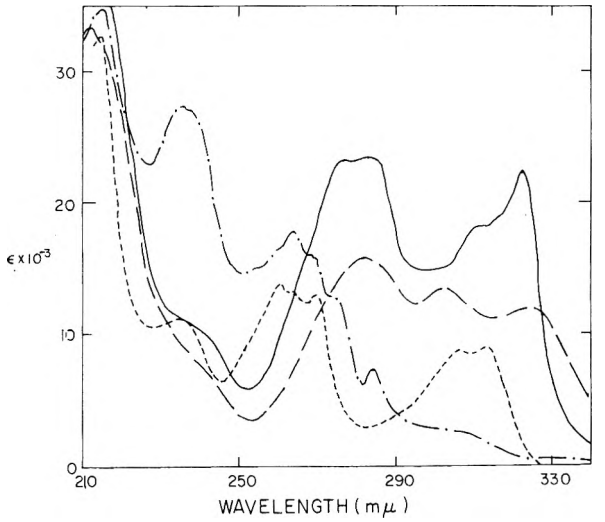


Fig. 2. Ultraviolet absorption spectra of: ——— *N*-(6-hydroxy-2-fluorenyl)acetamide, – – – – 3-fluorenol, — — — 7-amino-3-fluorenol, and — • — 3-fluorenecarboxylic acid

ascribed to the fact that the 3-position of fluorene is somewhat independent of the main resonance interactions in this hydrocarbon which involve the extended biphenyl system, *i.e.* the 2- and 7-positions. Therefore, a substituent (carboxyl, amino, hydroxyl, amido) which can participate in electron exchanges located in the 3-position might give rise to a supplementary disturbance of the

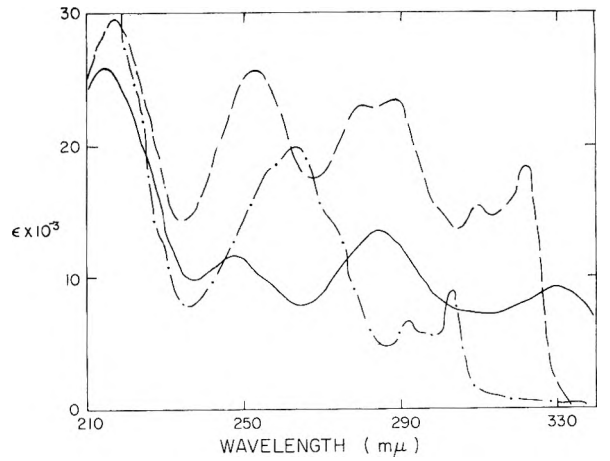
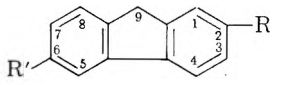


Fig. 3. Ultraviolet absorption spectra of; ——— 2,6-fluorenediamine, — — — *N,N'*-2,6-fluorenylenebisacetamide, and — • — *N*-3-fluorenyldiacetamide

electron field which would be reflected in the ultraviolet spectra as an additional maximum.



I

R	R'	R	R'
NO_2	COOH	NH_2	$NHCOCH_3$
NO_2	COCl	NH_2	NH_2
NO_2	CON_3	$NHCOCH_3$	$NHCOCH_3$
NO_2	$N(COCH_3)_2$	NO_2	OH
NO_2	NH_2	NH_2	OH
NO_2	$NHCOCH_3$	$NHCOCH_3$	OH

Where the substituent does not provide a sizable electron interchange, as is the case with the diacetamide (Fig. 3), the spectrum does not show a triple peak, and indeed, is quite similar to that of fluorene.[13] Parallel correlations exist in the case of *N*-2-fluorenyldiacetamide, which also has a spectrum not unlike that of fluorene. A general lack of resonance interactions of the functional group in diacetamides is also evidenced by their relatively low melting points and high solubilities in organic solvents.

EXPERIMENTAL

The melting points were determined in a capillary tube and are uncorrected. The ultraviolet spectra were recorded by Mr. P. H. Grantham on a Cary recording spectrophotometer as 0.05-millimolar solutions in ethanol, and the infrared spectra on a Perkin-Elmer spectrophotometer, Model 21, as solids in potassium bromide disks. We are indebted to Dr. W. C. Alford, and Mr. R. Koegel, and their staffs, for the microanalyses.

1-(2,5-Xylyl)cyclohexanol. A Grignard reagent was prepared in 1.5 hr. in a nitrogen atmosphere from 25 g. of magnesium and 185 g. (1 mole) of 2-bromo-1,4-dimethylbenzene

(12) E. K. Weisburger and J. H. Weisburger, *Advances in Cancer Research*, 5, 331 (1958).

(13) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, New York, 1951, spectrum Number 311.

(Eastman Kodak Organic Chemical No. 4670) in 500 ml. of distilled anhydrous ether. A few crystals of iodine were required to initiate the reaction, which was vigorous. A solution of 98.1 g. of redistilled cyclohexanone in 300 ml. of ether was added, with stirring, to the Grignard reagent at the boiling point over a period of 40 min., and refluxing was continued for 4 hr. longer. After hydrolysis with saturated ammonium chloride solution, the solvent was distilled off. The residue was fractionated at 0.5 mm. pressure using a 30-cm. long Widmer column. The fraction boiling at 85 to 120°, n_D^{25} 1.5370, was a light yellow viscous liquid weighing 110 g. Redistillation of a sample through a 15-cm. Vigreux column gave a constant boiling fraction, b.p. 119–120° (0.5 mm.), n_D^{25} 1.5410, d^{28} 1.0030. Ultraviolet spectrum: λ_{max} 263.5 (ϵ = 381) inflection point, 269 (ϵ = 511), and 277 mμ (ϵ = 492); λ_{min} 243.5 (ϵ = 167), and 274 mμ (ϵ = 381).

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.16; H, 9.91.

1-(2,5-Xylyl)cyclohexene. A. Concentrated hydrochloric acid (0.5 ml.) was added to a boiling solution of 50 g. of the cyclohexanol derivative in 100 ml. of acetic acid. A slightly exothermic reaction was accompanied by some darkening. The mixture was refluxed 15 min. longer, then subjected to vacuum distillation through a 30-cm. Vigreux column. The fraction (40 g.) boiling between 70 and 95° (0.5 mm.) was 1-(2,5-xylyl)cyclohexene, n_D^{28} 1.5355. Refractionation of a sample gave a colorless mobile liquid, b.p. 84° (0.5 mm.), n_D^{28} 1.5362, d^{28} 0.9241. Ultraviolet spectrum: max. 269 (ϵ = 600), and 276 mμ (ϵ = 600); min. 264 (ϵ = 550), and 273.5 mμ (ϵ = 514).

Anal. Calcd. for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.15; H, 9.95.

B. This compound was obtained directly from the Grignard reaction without isolation of the intermediate cyclohexanol as follows: The Grignard reaction mixture was hydrolyzed with dilute hydrochloric acid. After removal of the ether by distillation, the residue was fractionated at 0.5 mm. pressure through a 30-cm. Widmer column. However, the distillation was stopped when the vapor at the top of the column reached 45°. The pot contents from a 1-mole scale reaction were diluted with 150 ml. of acetic acid, the solution heated to the boiling point, and 1 ml. of concentrated hydrochloric acid was added. After the initial vigorous reaction subsided, the mixture was refluxed for 0.5 hr., cooled, and then subjected to fractional vacuum distillation in the same equipment. The fraction (109 g.), with a boiling point of 80–90° (0.5 mm.), n_D^{28} 1.5340, was allowed to stand overnight over solid potassium hydroxide pellets. Refractionation through the 30-cm. Widmer column gave 94 g. (0.5 mole) of a colorless liquid, b.p. 80–86° (0.5 mm.), n_D^{28} 1.5358, identical to the material obtained above.

3-(2,5-Xylyl)cyclohexene. Over a period of 3 hr., a Grignard reagent (17 g. of magnesium, 119 g. of 2-bromo-1,4-dimethylbenzene, 500 ml. of ether) was dropped into a stirred refluxing solution of 102 g. of 3-bromocyclohexene in 140 ml. of ether and refluxing was continued for another 4 hr. After hydrolysis by the slow addition of 550 ml. of 1.6*N* hydrochloric acid, the ether layer was separated and washed. The solution was fractionated at 0.5 mm. pressure. A forerun weighing 42 g., b.p. to 65°, was composed of *p*-xylene and unchanged 3-bromocyclohexene. The main fraction, b.p. 65–120° (0.5 mm.), wt. 60.1 g., was redistilled to give 49.5 g. or 51% (based on the 85% yield of Grignard reagent) of a colorless oily product, b.p. 90–110° (0.5 mm.), n_D^{22} 1.5435, d^{27} 0.930. Ultraviolet spectrum: max. 263 (ϵ = 480), 267.5 (ϵ = 654), and 276.5 mμ (ϵ = 680); min. 253 (ϵ = 313), 264 (ϵ = 476), and 274 mμ (ϵ = 465).

Anal. Calcd. for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.55; H, 9.16.

2-Cyclohexyl-1,4-dimethylbenzene. To a stirred and ice-cooled mixture of 25 ml. of concentrated sulfuric acid and 370 ml. of *p*-xylene, 102 ml. of cyclohexene was added dropwise over a period of 75 min. Stirring was continued for another 75 min. The sulfuric acid was decanted and the organic layer washed rapidly with 25 ml. of cold sulfuric acid, water, 3% sodium hydroxide solution, and water. Upon distillation *p*-xylene (194 g.), b.p. 134–135.5° was recovered. Further distillation at 1 mm. pressure gave 84 g. of a colorless liquid, b.p. 80–120° and a solid residue in the still. Redistillation of the liquid gave 25 g. of a forerun, b.p. 77–98° (1 mm.), n_D^{22} 1.5253, and 55 g. of pure 2-cyclohexyl-1,4-dimethylbenzene, b.p. 98–100° (1 mm.), n_D^{22} 1.5262, d^{27} 0.926. Ultraviolet spectrum: max. 262 (ϵ = 385,) 268 (ϵ = 564), 270 (ϵ = 511), and 276 mμ (ϵ = 632); min. 237 (ϵ = 34), 263.5 (ϵ = 380), 270 (ϵ = 506), and 274 mμ (ϵ = 367). Bodroux[14] reported the following physical constants for this compound: b.p. 261–263° (759 mm.), n_D^{18} 1.529, d^{18} 0.936.

This compound could not be aromatized with sulfur under the condition where the cyclohexene derivatives were smoothly converted to biphenyls.

Anal. Calcd. for $C_{14}H_{28}$: C, 89.29; H, 10.71. Found: C, 89.70; H, 10.98.

The still residue was dissolved in 220 ml. of hot acetic acid. On cooling 20 g. of material, m.p. 145–150°, crystallized. Two recrystallizations from 150 ml. of acetic acid gave 13.5 g. of 1,4-dicyclohexyl-2,5-dimethylbenzene, m.p. 157° (lit.[14] m.p. 156–157°).

Anal. Calcd. for $C_{20}H_{30}$: C, 88.82; H, 11.18. Found: C, 88.62; H, 10.92.

2,5-Dimethylbiphenyl. A. By dehydrogenation of 3-(2,5-xylyl)cyclohexene with sulfur. A mixture of 14.5 g. (78 mM.) of 3-(2,5-xylyl)cyclohexene and 5.9 g. of sulfur was heated in a slow stream of nitrogen. The gas was scrubbed in traps containing an acidified solution of copper sulfate. Evolution of hydrogen sulfide commenced when the reaction mixture reached a temperature of 180° and was rapid at 210°. The temperature rose spontaneously to 245° and was then maintained near the boiling point of 270° for 20 min. longer. A quantitative yield of copper sulfide (14.7 g.) was obtained in the traps. Upon vacuum distillation of the pot contents, 8.3 g. (45 mM.) of 2,5-dimethylbiphenyl distilled at 106–115° (2 mm.) as a colorless liquid, n_D^{22} 1.5785. Upon refractionation a sample had a b.p. 107–109° (2 mm.), n_D^{22} 1.5800, and d^{27} 0.9814. The ultraviolet spectrum had a maximum at 238 mμ (ϵ = 9,180), an inflection point at 275 mμ (ϵ = 1,080), and a minimum at 231 mμ (ϵ = 8,400).

Anal. Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.03; H, 7.89.

B. By dehydrogenation of 1-(2,5-xylyl)cyclohexene with sulfur. A mixture of 94 g. (0.5 mole) of 1-(2,5-xylyl)cyclohexene and 35 g. of sulfur was slowly heated and maintained at the boiling point for 0.5 hr. The cooled mixture was distilled *in vacuo* through a Claisen head giving 72 g. of a colorless liquid, b.p. 80–110° (0.5 mm.), n_D^{28} 1.5795. Redistillation through a 30-cm. Vigreux column yielded 50 g. (0.27 mole) of 2,5-dimethylbiphenyl, b.p. 88° (0.5 mm.), n_D^{28} 1.5758.

C. By dehydrogenation of 1-(2,5-xylyl)cyclohexene with chloranil. A solution of 63 g. of chloranil and 19.2 g. (103 mM.) of 1-(2,5-xylyl)cyclohexene in 200 ml. of xylene was refluxed for 5.5 hr. The precipitate obtained on cooling to 4° was filtered off and washed twice with xylene. The combined filtrate and washings were diluted with 250 ml. of ether and extracted repeatedly with 5% potassium hydroxide solution and water. The dried ether solution was distilled and the residue was fractionated to give 10.2 g. of a slightly yellowish liquid, b.p. 88–90° (0.5 mm.), n_D^{28} 1.5718. This material, diluted with 50 ml. of petroleum ether, was percolated through a 2 × 15 cm. column of alumina. The column was washed with petroleum ether and 250 ml. of eluate was collected. Upon distillation 8.2 g. (45%)

(14) D. Bodroux, *Ann. chim.* (*Paris*), [10], **11**, 511 (1929).

of colorless 2,5-dimethylbiphenyl, b.p. 78–80° (0.4 mm.), n_D^{18} 1.5725 was obtained.

2,5-Biphenyldicarboxylic acid. A. Without solvent. The procedure was patterned after that described for *o*-chlorobenzoic acid.[15] A well stirred suspension of 45.1 g. of 2,5-dimethylbiphenyl in a solution of 158 g. of potassium permanganate in 4 l. of water was kept under gentle reflux for 10 hr. at which time the permanganate was exhausted. The mixture was allowed to cool to 70°, then was extracted 3 times with 100 ml. of benzene which removed 16 g. of unoxidized material (35%). Steam distillation was impractical owing to the slow rate of distillation of 2,5-dimethylbiphenyl. The aqueous phase was filtered by suction, and the precipitate of manganese dioxide was washed 3 times with a total of 1 l. of hot water. Acidification of the filtrate and cooling to 4° gave 29 g. of white 2,5-biphenyldicarboxylic acid (74% yield based on the amount of material oxidized), m.p. 278°. Recrystallization of 134 mg. by solution in 3.5 ml. of ethanol and addition of 15 ml. of hot water gave 96 mg. of white crystals, m.p. 280°. Ultraviolet spectrum: max. 230 (ϵ = 24,000), and 295 mμ (ϵ = 2,400); min. 217 (ϵ = 19,500), and 280 mμ (ϵ = 2,100).

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.78; H, 4.30.

B. With solvent. To a stirred and boiling solution of 56 g. of 2,5-dimethylbiphenyl in 610 ml. of pyridine a hot solution of 325 g. of potassium permanganate in 3.2 l. of water was added over a period of 105 min. The permanganate solution was kept hot in order to prevent crystallization of the material. After 75 min. of gentle refluxing 1 l. of hot water was added and the mixture was filtered by suction. The precipitate was reextracted twice with a total of 2 l. of boiling 0.3% potassium hydroxide solution. The combined colorless filtrates were reduced in volume to about 2 l. Acidification and cooling afforded 57 g. (75%) of powdery white material, m.p. 267–269°.

3-Fluorenecarboxylic acid. A mechanically stirred suspension of 20.4 g. of 2,5-biphenyldicarboxylic acid in 630 g. of polyphosphoric acid was heated to 200° over a period of 0.5 hr. Upon cooling to 100° ice was added to a volume of 2 l. The filtered yellow precipitate was dissolved in a warm solution of 7 g. of sodium hydroxide in 1.8 l. of water and treated with 1 g. of Norit for 1 hr. Acidification of the filtered solution gave 17.3 g. (97%) of 9-oxo-3-fluorenecarboxylic acid, m.p. 299° (lit.[5b] 304°).

A solution of 14 g. of this compound, 5 g. of sodium hydroxide, and 19 ml. of 85% hydrazine hydrate in 120 ml. of diethylene glycol was refluxed for 1.5 hr. A considerable evolution of gas occurred between 120 and 140° (the liquid temperature at the boiling point was 150°). The reaction mixture was diluted with 1 l. of water and neutralized with 75 ml. of 6*N* hydrochloric acid. The precipitate and 1.2 g. of Norit in 800 ml. of 1.4% sodium bicarbonate solution was refluxed 0.5 hr. The filtered solution was neutralized with 100 ml. of 3*N* hydrochloric acid to give a white powder (11.5 g., 88%), m.p. 224°. Recrystallization of 450 mg. from 4.5 ml. of acetic acid yielded 340 mg. of 3-fluorenecarboxylic acid m.p. 227–228° (lit.[5b] 230°).

3-Fluorenamine. The acid chloride, m.p. 121–122°, was prepared from 2 g. of 3-fluorenecarboxylic acid by refluxing with thionyl chloride. A solution of 0.75 g. of sodium azide in 5 ml. of water was added to an ice-cold solution of the acid chloride in 75 ml. of acetone and stirred for 3 hr. Dilution with water gave 2.16 g. of 3-fluorenecarbonyl azide, m.p. 94° (dec.). The azide was refluxed in 25 ml. of acetic anhydride, yielding 2.3 g. of *N-3-fluorenyldiacetamide*, m.p. 143–144°, after crystallization from benzene–petroleum ether. Ultraviolet spectrum: max. 262 (ϵ = 19,800), 292 (ϵ = 6,400), and 303 mμ (ϵ = 8,800); min. 236 (ϵ = 7,800), 287 (ϵ = 4,800), and 297 mμ (ϵ = 5,400).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70. Found: C, 76.79; H, 5.69.

Hydrolysis of the diacetamide in 1:1 ethanol-6*N* hydrochloric acid afforded 3-fluorenamine, m.p. 149–151° (lit.[5d] 152–153°). The over-all yield of amine from the acid was 90%. Acetylation of the amine in benzene yielded *N*-3-fluorenylacetamide, m.p. 189–190° (lit.[5d] 189–190°). Conversion of the amine to 3-fluorenol by standard procedures gave a product, m.p. 138° (lit.[5g,7] m.p. 137–138°).

2-Nitro-3-fluorenamine. *N*-3-Fluorenylacetamide (1 g.) in 20 ml. of acetic acid was nitrated by the addition of 2.2 ml. of concentrated nitric acid (d = 1.42) and heating to 65°. On cooling 1 g. of bright lemon yellow needles, m.p. 210°, crystallized. Recrystallization from ethanol gave *N-(2-nitro-3-fluorenyl)acetamide*, m.p. 210–210.5°. Ultraviolet spectrum: max. 218 (ϵ = 21,200), 238 (ϵ = 15,300), 266 (ϵ = 11,800), and 338 mμ (ϵ = 12,000); min. 232 (ϵ = 14,800), 255 (ϵ = 10,600), and 284 mμ (ϵ = 5,300).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51. Found: C, 67.41; H, 4.65.

Hydrolysis in ethanol–hydrochloric acid yielded *2-nitro-3-fluorenamine*, light orange needles, m.p. 195°. Ultraviolet spectrum: max. 227 (ϵ = 16,600), 243 (ϵ = 14,500) (inflection point), 330 (ϵ = 14,600), and 425 mμ (ϵ = 7,400); min. 223 (ϵ = 16,500), 285 (ϵ = 4,100), and 378 mμ (ϵ = 4,200).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46. Found: C, 68.91; H, 4.43.

Low pressure catalytic reduction of 2-nitro-3-fluorenamine in ethanol over platinum oxide gave 2,3-fluorenediamine, m.p. 192°, identical in melting point and infrared spectrum with an authentic sample prepared by the reduction of 3-nitro-2-fluorenamine.[5a]

7-Nitro-3-fluorenecarboxylic acid. A solution of 75 ml. of yellow fuming nitric acid (d = 1.50) and 18 g. of 3-fluorenecarboxylic acid in 360 ml. of acetic acid was warmed to 85° whereupon the reaction occurred. Upon cooling 15.5 g. of yellow fluffy needles, m.p. 285°, crystallized. Recrystallization from acetic acid (60 ml./g.) and from ethanol gave pale yellow needles, m.p. 305°. Ultraviolet spectrum: max. 245 (ϵ = 11,400), and 324 mμ (ϵ = 14,500); min. 268 mμ (ϵ = 3,100).

Anal. Calcd. for $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.57; H, 3.99; N, 5.38.

7-Nitro-3-fluorenamine. Fourteen grams of 7-nitro-3-fluorenecarboxylic acid was converted to the acid chloride, m.p. 163–167°, with thionyl chloride. Reaction of the acid chloride in 950 ml. of acetone with 5 g. of sodium azide in 25 ml. of water yielded 15 g. of the azide, m.p. 143–145°. The azide was refluxed for 3 hr. in 250 ml. of acetic anhydride to give 15 g. of *N-(7-nitro-3-fluorenyl)diacetamide*, m.p. 198–198.5° after crystallization from benzene-ethanol. Ultraviolet spectrum: max. 324 mμ (ϵ = 21,200); min. 263 mμ (ϵ = 3,400).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.66; H, 4.86; N, 9.06.

Hydrolysis of 14 g. of the diacetamide by refluxing for 4 hours in 1:1 ethanol and 6*N* hydrochloric acid gave 11 g. of reddish-orange 7-nitro-3-fluorenamine,[16] m.p. 192–195°. Repeated recrystallizations from benzene, or percolation of a benzene solution through a column of alumina followed by crystallization, raised the melting point to 210°. Ultraviolet spectrum: max. 327 (ϵ = 10,200), and 290 mμ (ϵ = 6,200) (inflection point); min. 260 mμ (ϵ = 4,600). After reaching the peak at 327 mμ the spectrum exhibits a long shallow curve (minor inflection point about 358 mμ) and shows appreciable absorption even beyond 400 mμ.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.39. Found: C, 69.07; H, 4.77; N, 11.98.

(15) H. T. Clarke and E. R. Taylor, *Org. Syntheses*, Coll. Vol. II, 135 (1943).

(16) Removal of the amino group (diazotization followed by hypophosphorous acid) yielded 2-nitrofluorene, m.p. 150°, with an infrared spectrum identical to that of authentic 2-nitrofluorene.

The acetyl derivative, N-(7-nitro-3-fluorenyl)acetamide, prepared by the action of acetic anhydride in benzene, melted at 260–260.5° after recrystallization from 60% aqueous acetic acid. Ultraviolet spectrum: max. 230 (ϵ = 22,000), 260–265 (ϵ = 11,200) (inflection point), and 340 mμ (ϵ = 13,600); min. 219 (ϵ = 18,000), and 281 mμ (ϵ = 4,600).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51. Found: C, 66.74; H, 4.69.

N-(7-Amino-3-fluorenyl)acetamide. Low pressure (40–50 p.s.i.) hydrogenation in ethanol over platinum oxide of 0.2 g. of the nitro derivative gave 0.12 g. of white crystals, m.p. 212.5–213.5°, after crystallization from 50% ethanol and from benzene. Ultraviolet spectrum: max. 219 (ϵ = 27,800), 251 (ϵ = 24,200), 290 (ϵ = 19,900), and 323 mμ (ϵ = 10,900) (inflection point); min. 236 (ϵ = 16,300), and 269 mμ (ϵ = 12,500).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92. Found: C, 75.42; H, 6.02.

2,6-Fluorenediamine. Catalytic reduction (ethanol, platinum oxide) of 0.35 g. of 7-nitro-3-fluorenamine afforded 0.17 g. of an almost white product, m.p. 153–154.5°, after 2 crystallizations from 50% ethanol and one from benzene. Ultraviolet spectrum: max. 214 (ϵ = 25,800), 247 (ϵ = 11,800), 284 (ϵ = 13,500), and 300 mμ (ϵ = 9,400); min. 237 (ϵ = 9,800), 264 (ϵ = 7,800), and 316 mμ (ϵ = 7,200).

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.17. Found: C, 79.36; H, 6.40.

The *diacetyl derivative, N,N'-2,6-fluorenylenebisacetamide*, prepared with acetic anhydride in benzene, melted at 277–278°, after crystallization from ethanol. Ultraviolet spectrum: max. 217 (ϵ = 29,600), 253 (ϵ = 25,600), 280 (ϵ = 23,000), 289 (ϵ = 23,400), 309.5 (ϵ = 15,500), and 322 mμ (ϵ = 18,400); min. 234 (ϵ = 14,400), 267 (ϵ = 17,600), 283 (ϵ = 22,800), 304.5 (ϵ = 13,600), and 313 mμ (ϵ = 14,600).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: N, 10.00. Found: N, 9.62.

7-Nitro-3-fluorenol. The outcome of the reaction described below is materially affected by the experimental conditions. The best procedure was found to be as follows: 7-Nitro-3-fluorenamine (1 g.) was dissolved by warming in a mixture of 25 ml. of acetic acid and 10 ml. of water. A thick mush formed upon cooling in an ice bath and adding 25 ml. of concentrated sulfuric acid. A solution of 0.4 g. of sodium nitrite in 10 ml. of water was stirred in, causing most of the precipitate to dissolve. After another 1.25 hr., the diazonium solution was dropped over a period of 15 min. into a refluxing solution of 100 ml. of water, 10 ml. of sulfuric acid, and 20 ml. of acetic acid. The mixture was poured on ice after an additional 15 min. The crude yellow material, 0.95 g., m.p. 247°, was twice recrystallized from 65% ethanol (Norit) to give 0.59 g. of fine yellow needles, m.p. 257°. Ultraviolet spectrum: max. 271 (ϵ = 8,500), and 349 mμ (ϵ = 18,600); min. 251 (ϵ = 6,500), and 281 mμ (ϵ = 5,600).

Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.17. Found: C, 68.45; H, 4.12; N, 6.39.

7-Amino-3-fluorenol. Catalytic reduction (platinum oxide) of 0.48 g. of 7-nitro-3-fluorenol in ethanol gave 0.41 g. of amine, m.p. 248° (dec.). Recrystallization of 65 mg. of product from 30 ml. of 50% aqueous ethanol yielded 60 mg. of small white needles, m.p. 255° (dec.). Ultraviolet spectrum: max. 212 (ϵ = 32,700), 243 (ϵ = 7,100) (inflection point), 281 (ϵ = 15,700), 302 (ϵ = 13,200), and 324 mμ (ϵ = 11,800); min. 253 (ϵ = 3,600), 295 (ϵ = 12,200), and 316 mμ (ϵ = 11,000).

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 78.69; H, 5.60.

N-(6-Hydroxy-2-fluorenyl)acetamide. A hot solution of 0.4 g. of 7-amino-3-fluorenol in 50 ml. of 0.1*N* hydrochloric acid was filtered and cooled. After the addition of 3 g. of sodium acetate and 4 ml. of acetic anhydride the mixture was stirred in an ice bath for 5 hr. The white precipitate, 0.46 g., m.p. 238°, was recrystallized twice from 30% aqueous ethanol giving 0.34 g. of fine needles, m.p. 241°. Further crystallization from aqueous ethanol and xylene raised the melting point to 246°. Ultraviolet spectrum: max. 240 (ϵ = 10,500) (inflection point), 277 (ϵ = 23,100), 284 (ϵ = 23,400), 310 (ϵ = 18,000) (inflection point); and 322 mμ (ϵ = 22,200); min. 252 (ϵ = 5,600), 279 (ϵ = 22,900), and 295 mμ (ϵ = 14,800).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.48. Found: C, 75.31; H, 5.55.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE FOREST PRODUCTS LABORATORY, UNIVERSITY OF CALIFORNIA]

Extractive Components from Incense Cedar Heartwood (*Libocedrus decurrens* Torrey). VI. On the Occurrence of 3-Libocedroxythymoquinone

EUGENE ZAVARIN

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A new quinoid pigment has been isolated from the heartwood of incense cedar and its structure deduced on the basis of the presented spectroscopic, degradative, and synthetic experimental evidence. It has been demonstrated that the isolated quinone occurs *in situ* as well as forming through air oxidation of the other incense cedar extractives.

During our investigation of the extractive components of incense cedar heartwood, *Libocedrus decurrens* Torrey,[1] the petroleum ether extract of the sawdust was found to have a reddish color. This could not be caused by the formation of the quinquidrone type compounds between the various phenols present and thymoquinone[2] since it persisted upon removal of the latter either by distillation or by conversion to its semicarbazone followed by extraction with alkali. This indicated the presence of an unknown coloring matter which prompted us to investigate this component.

On extracting incense cedar heartwood sawdust with petroleum ether, a 1.5% yield (dry wood basis) of a mixture of various components was obtained. Chromatography on alumina yielded a red fraction

(1) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **20**, 788 (1955).

(2) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **20**, 82 (1955).

which, upon treatment with methanol and cooling, crystallized to yield 1.6% (0.024% dry wood basis) of a dark red coloring matter. The resulting material analyzed for $C_{32}H_{40}O_6$ and contained two methoxy groups. The molecular weight determined by Rast method agreed with the above formula. The C-methyl determination pointed to the presence of at least 6 methyls bonded to carbon.

The ultraviolet and infrared spectra of the compound (Figs. 1 and 2) were similar to those of

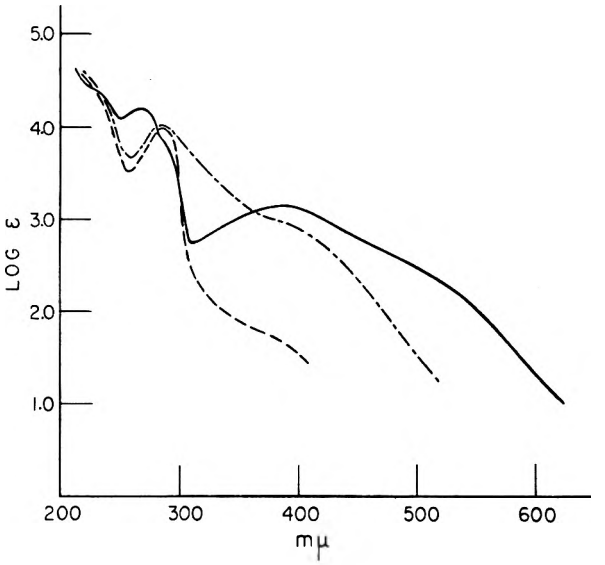


Fig. 1. Ultraviolet absorption spectra, ——— 3-libocedroxythymoquinone, - - - - hydro-3-libocedroxythymoquinone, — - — epoxy-3-libocedroxythymoquinone

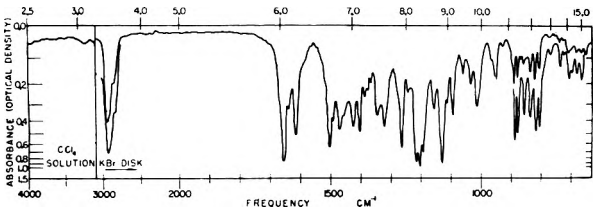
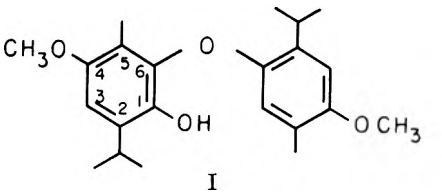


Fig. 2. Infrared spectrum of 3-libocedroxythymoquinone

libocedroquinone.[1] The former showed three inflection points at 225, 285, and 450–510 mμ arising from the benzenoid K-band, benzenoid B-band,[3] and the quinoid C-band and two maxima at 267 and 389 mμ arising from the quinoid A and B bands.[4] The increase in intensity of the benzenoid K and B bands seem to indicate the increased proportion of the benzenoid chromophores in the molecule as compared with libocedroquinone. In the infrared, in addition to a weaker band at 1645 cm.$^{-1}$, the compound exhibited a strong carbonyl band at 1660 cm.$^{-1}$, and a strong double bond band at 1620 cm.$^{-1}$ No band corresponding to hydroxyl stretching could be detected.

The compound is readily reduced to the colorless, amorphous hydroquinone by stannous chloride, sodium hydrosulfite, or catalytically with hydrogen over platinum, or palladium-on-charcoal. The resulting hydroquinone is again easily oxidized with ferric chloride to the original compound. The volume of hydrogen absorbed during hydrogenation corroborates the figure obtained for the molecular weight. The ultraviolet absorption spectrum of the hydroquinone shows a single benzenoid maximum at 286 mμ (Fig. 1). In infrared, a strong hydroxyl band is present but no carbonyl band.

This seems to substantiate the quinoid structure of the red compound and to indicate that the remaining two oxygens must be of an ether nature.



I

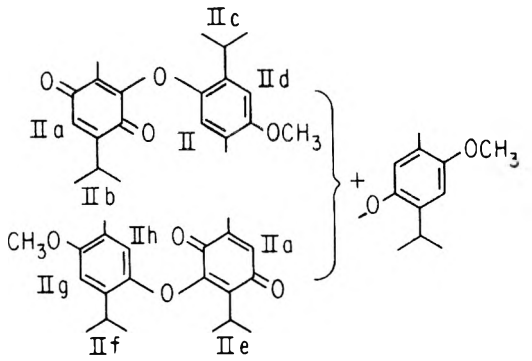
Further insight into the structure of the isolated quinone was obtained by the study of the reaction of libocedrol (I) with alkaline ferricyanide. The reaction gave a greenish-yellow solution which, upon evaporation, yielded a yellow amorphous solid. After shaking its ethyl ether solution with 10% hydrochloric acid, the organic phase assumed an intense red coloration and gave, in addition to a 19% yield of the starting material, 11% of *p*-methoxythymol, 4% of libocedroquinone, and 46% yield of a red quinone which was found to be identical with the quinone from the heartwood of incense cedar by mixed melting point and infrared techniques.

This synthesis, together with information obtained previously, seems to demonstrate that the red compound is composed of three units each derived from *p*-methoxythymol. One unit is present in the form of quinone, the other two units are benzenoid. The attachment seems to take place through ether linkages, since the carbon to carbon bonds would necessitate the presence of the free hydroxyls which is excluded on the basis of infrared evidence. This attachment must also involve the aromatic nuclei or, less likely, the tertiary positions on the isopropyl groups[5]; the isopropyl methyls are too far away and the attachment to the aromatic methyls is excluded on the basis of the C-methyl determination. The quinoid nucleus must carry at least one oxygen in addition to the carbonyl oxygens, since according to Braude's rules[4] for the positions of the absorption maxima in ultraviolet, the bathochromic shift of the quinoid B band is far too great to be caused by the alkyl substituents alone. All this leaves nine theoretically possible formulations for the red quinone.

(3) A. E. Gillam, E. C. Stern, and E. R. H. Jones, *Electronic Absorption Spectroscopy*, Edward Arnold Publishers, Ltd., London 1954, p. 116.

(4) E. A. Braude, *J. Chem. Soc.*, 490 (1945).

(5) C. D. Cook, N. G. Nash, and H. R. Flanagan, *J. Am. Chem. Soc.*, **77**, 1783 (1955).



The application of the nuclear magnetic resonance methods[6] narrowed the number of possible structures still further. Several preliminary runs on model compounds including *p*-methoxythymol, libocedrol, benzoquinone, thymoquinone, 3-bromothymoquinone, and libocedroquinone indicated that absorption arising from the quinoid hydrogens falls in approximately the region of the absorption of benzenoid hydrogens. Contrary to the benzenoid state, the quinoid state promotes strong band splitting resulting from the spin-spin coupling of the quinoid hydrogens with the hydrogens in the α-position of the chain. Thus, in the case of thymoquinone, there resulted a split of quinoid maxima into 1:1 doublet (hydrogen in the 6 position), and into 1:3:3:1 quadruplet (hydrogen in the 3 position). Other quinones fell into the same line. This permits the differentiation between benzenoid and quinoid hydrogens and, in favorable cases, between the quinoid hydrogens.

The nuclear magnetic resonance spectrum of the unknown quinone together with the spectra of some of the model compounds are reproduced in Fig. 3. The spectrum bears a great similarity to the spectrum of libocedroquinone and shows two isopropyl doublets, one seems to result from the methyls of the two isopropyl groups on the benzenoid nuclei and the other from the methyls of the isopropyl group on the quinoid nucleus. This is followed by two peaks resulting from three aromatic methyls, a multiplet corresponding to the tertiary hydrogens of the isopropyl groups split by the corresponding hydrogens from methyl groups, and two peaks resulting from the hydrogens on two methoxy methyls. In the aromatic region, we find three maxima resulting from the hydrogens on the benzenoid nuclei and one quinoid doublet. The identification of the quinoid maximum eliminates formulation IIa which involves a completely substituted quinoid nucleus. The appearance of this maximum as a doublet instead as a 1:3:3:1 quadruplet seems to favor the quinone's being substituted in the 3 rather than in the 6 position; the latter needs further substantiation however, inasmuch as the resolution is not entirely satisfactory. The presence of the three benzenoid hydrogen peaks with 1:1:1 intensities seems to exclude the structures IIb, IIc, IIe, and IIf which possess four benzenoid hydrogens.

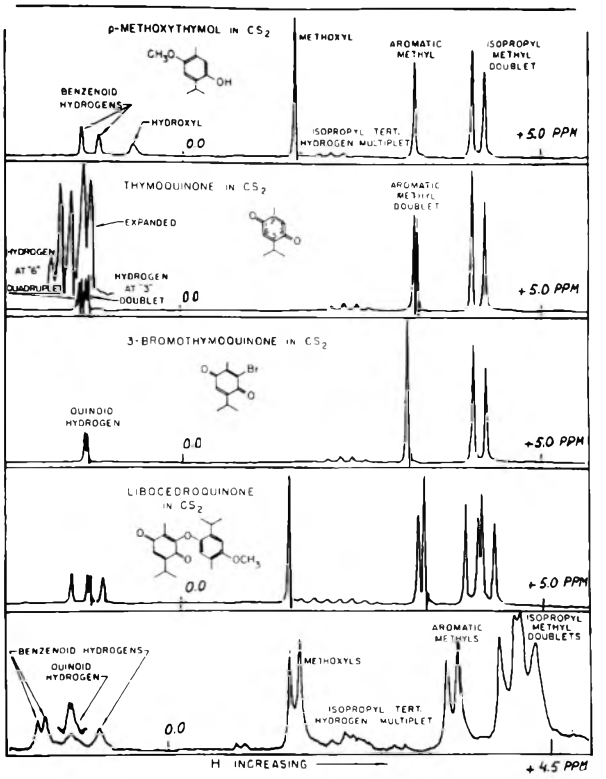
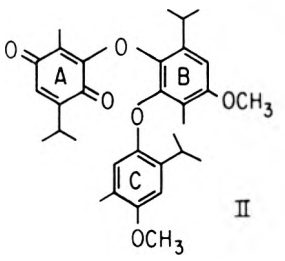


Fig. 3. Nuclear magnetic resonance spectra of various model compounds and 3-libocedroxythymoquinone. In the latter case the quinoid peak was resolved into doublet (upper curve) by using the heated sample in the experiment.

When the quinone was reduced to hydroquinone and heated under reflux with hydrogen bromide in acetic acid, a 22% yield of 3-hydroxythymoquinone was obtained upon oxidizing the resulting mixture with ferric chloride at room temperature. This excludes structures IIa, IIb, IIe, IIf, and IIg which should not yield this compound.

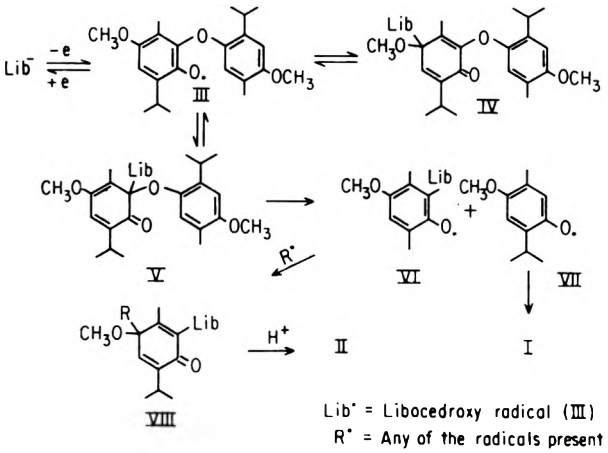
Of the remaining three structures, structure IIh appears to be rather improbable in view of the nuclear magnetic resonance indications of a free quinoid hydrogen in 6 position and also because in the hydrogen bromide cleavage, it would be expected to yield either 6-hydroxythymoquinone or a mixture of 6- and 3-hydroxythymoquinone, whereas pure 3-hydroxythymoquinone was obtained. As far as structure IId is concerned, the point of attachment of the third *p*-methoxythymol derived unit seems to indicate that the rather improbable meta coupling had taken place; with structure II, the corresponding attachment involves the same ortho linkage found in libocedrol. Thus, it would seem that the structure of the isolated pigment should correspond to formulation II.

(6) W. A. Anderson, *Phys. Rev.*, **102**, 151 (1956); J. T. Arnold, *Phys. Rev.*, **102**, 136 (1956); L. H. Meyer, A. Saika, and H. S. Gutowsky, *J. Am. Chem. Soc.*, **75**, 4567 (1953).



II

The nature of the synthetic sequence leading from libocedrol to 3-libocedroxythymoquinone can be rationalized in connection with the work on oxidation of the hindered phenols with alkaline ferricyanide done by Mueller, Cook, Waters, and others. The evidence obtained indicates that an equilibrium sets in between the ferricyanide and phenoxide ions on one side and ferrocyanide ion and phenoxy radical (III) on the other[7] with the latter again existing in equilibrium with its cyclohexadienone dimers[8] (IV, V) (depicted for libocedrol).



The yellowish, crude, amorphous oxidation product of libocedrol exhibited in infrared a strong carbonyl band at 1665 cm.$^{-1}$ while the intensity of the hydroxyl band decreased nearly fivefold; in ultraviolet in additon to the expected strong benzenoid B-band at 289 mμ, it exhibited two characteristic inflection points at 231 and 328 mμ. This is quite in agreement with the data given by Mueller for the oxidation dimers of some related compounds.[8] In the visible portion of the spectrum the material exhibited three peaks at 377, 397, and 650 mμ with the extinction coefficients increasing with dilution, temperature, or polarity of the solvent. This suggests the reversible dissociation of the material into colored components.

The electron paramagnetic resonance studies indicated the presence of unpaired electrons in the solid; the intensity of the signal markedly increased upon dissolving the material in chloroform. This seems to suggest the free radical nature of the dissociating compounds and substantiates further the depicted scheme.

Among the several possible cyclohexadienones existing in equilibrium with the libocedroxy radicals, structure V may dissociate into *p*-methoxythymoxy (VII) and 6-libocedroxy-*p*-methoxythymoxy radicals (VI) also. Once formed, the *p*-methoxythymoxy radicals will irreversibly dimerize to give libocedrol.[9] The 6-libocedroxy-*p*-methoxythymoxy radicals, on the other hand, should associate with the other radicals largely to give the corresponding 2,5-cyclohexadienones (VIII),[10] which, being ketals, should easily hydrolyze upon acidification to 3-libocedroxythymoquinone.[11] The preferential formation of libocedroquinone in ferric sulfate oxidation of libocedrol[1] can be explained by the acidic conditions forcing the formed, 2,5-cyclohexadienone to hydrolyze before *p*-methoxythymoxy substituent had time to exchange.

Oxidation of the isolated quinone with alkaline hydrogen peroxide resulted in formation of the corresponding quinone mono-epoxide which was stable to treatment with strong acids. It represents a convenient derivative for characterization of the compound.

Treatment of the quinone with semicarbazide hydrochloride did not result in formation of the semicarbazone. Libocedroquinone gave a very good yield of the adduct under these conditions. Originally this was held to support structure IIa. Examination of the molecular models revealed, however, that in the case of structure II, ring C with its side chains can also interfere sterically with the carbonyl of ring A.

Attempts to prepare the *p*-nitrobenzoate ester of hydro-3-libocedroxythymoquinone resulted in isolation of yellow materials that could not be induced to crystallize. Extension of the heating time converted the material into mixtures consisting largely of the original quinone.

In connection with isolation of 3-libocedroxythymoquinone from incense cedar heartwood, the question might be posed as to whether the compound is present in the wood, *in situ*, or whether it was formed during the process of isolation. To resolve this point, fresh green incense cedar heartwood was cut cross grain into three slabs. These slabs were immediately extracted with petroleum ether in nitrogen atmosphere and protected from direct light. The extract was stored under nitrogen at $-5°$. Chromatography of the extract gave a

(7) C. G. Haynes, A. N. Turner, and W. A. Waters, *J. Chem. Soc.*, 2829 (1956).

(8) E. Mueller, K. Ley, and G. Schlechte, *Ber.*, 90, 2660 (1957); K. Ley, E. Mueller, and G. Schlechte, *Ber.*, 90, 1530 (1957) and preceding papers.

(9) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, 22, 1122 (1957).

(10) The 2,5-cyclohexadienones should exist preferentially over 2,4-cyclohexadienones in the equilibrium mixture because of the known enhanced stability of the *p*-quinoid system and in this case, also, on sterical grounds.

(11) *p*-Methoxythymoxy radical could also participate in formation of various cyclohexadienones. The 2,5-cyclohexadienones would be expected to be particularly stable to redissociation. This would be one way of explaining the occurrence of *p*-methoxythymol in the reaction products.

fraction in which the above quinone could be identified. The amount of the quinone present was, however, considerably below that occurring in air-seasoned incense cedar heartwood used originally, indicating the possibility that the quinone might still form, in part, through air oxidation of the extractives during storage. Impregnation of the acetone-extracted Port Orford cedar sawdust with a mixture of libocedrol, *p*-methoxythymol, and thymoquinone, exposure of the sawdust for about three months to the action of air, extraction, and analysis of the extract resulted in identification of 3-libocedroxythymoquinone in the material obtained.

The importance in the determination of the structure of the 3-libocedroxythymoquinone is in its relationship to the other closely related materials isolated from incense cedar heartwood.[1,2,12] It extends the chain of compounds connected through the oxidative coupling mechanism. It is possible that, biosynthetically, the quinone is formed also by addition of libocedroxy radical to thymoquinone since quinones in general are known to undergo similar reactions.[13,14]

EXPERIMENTAL[15]

Isolation of 3-libocedroxythymoquinone. Sound air-dried heartwood from the butt log of incense cedar was ground in a Wiley mill to pass a 2-mm. screen. A total of 2900 g. of sawdust was extracted in Soxhlet extractors with petroleum ether to the point where no more coloring matter appeared. The petroleum ether extracts were combined and the solvent removed by evaporation on a steam bath to give 43 g. of a red viscous extract (1.65% yield, dry wood basis).

A 14.85-g. portion of the extract was dissolved in 50 ml. of *n*-hexane and chromatographed using 350 g. of alumina (Merck's acid-washed alumina, "suitable for chromatographic analysis"). The column was successively washed with 500 ml. of *n*-hexane, and 500 ml. of benzene. A portion of the benzene used produced a red-brown fraction that, upon removal of the solvent, weighed 7.7 g. This material was rechromatographed using 177 g. of the Woelm alumina. The column was successively washed with 250 ml. of *n*-hexane, 100 ml. of 10% benzene in hexane, 300 ml. of benzene, and four 100-ml: portions of 2, 5, 10, and 50% ether in benzene. The last 100 ml. of benzene and all of the subsequent fractions were reddish in color. They were combined and evaporated to dryness to give 2.6 g. of red viscous matter. The latter was dissolved in 20 ml. of methanol, and cooled to −5° for 10 days; the precipitate which formed was filtered, and washed with methanol to give 242 mg. of dark red crystalline material, m.p. 141–145° (1.63% yield from extract, 0.027% from wood). Further cooling produced no additional precipitate.

Purification of the material was achieved by repeated sublimation at 0.5–0.1 mm. pressure at 140–180° and crystallization from methanol, to give dark red crystals m.p. 154.5–155°.

Anal. Calcd. for $C_{32}H_{40}O_6$: C, 73.82; H, 7.74; OCH_3, 11.92; C—CH_3, 17.3; mol. wt., 521. Found: C, 73.84; H, 7.75; OCH_3, 12.05; C—CH_3, 14.0 (81%); mol. wt., 550 (camphor).

Libocedroquinone gave 82% and norlibocedroquinone 78% yield in the C—CH_3 analysis.[1]

The ultraviolet absorption spectrum of 3-libocedroxythymoquinone showed two maxima at 267 mμ (log ε 4.22) and 389 mμ (log ε 3.17) identified with Braude's A and B quinoid bands and three inflection points at 225 mμ (log ε 4.42), 285 mμ (log ε 3.88), and 450–510 mμ (log ε 2.8–2.3) identified with benzenoid K and B bands and quinoid C band[4] (Fig. 1).

In the infrared, using the potassium bromide pellet technique, the compound exhibited a strong carbonyl maximum at 1660 cm.$^{-1}$, a strong conjugated double bond maximum at 1620 cm.$^{-1}$, and a weaker band at 1645 cm.$^{-1}$ In carbon tetrachloride solution no hydroxyl band could be detected (Fig. 2).

The nuclear magnetic resonance spectra (Fig. 3) were obtained at 40 mc. frequency, using carbon disulfide as the solvent in case of *p*-methoxythymol, libocedrol, thymoquinone, 3-bromothymoquinone, and libocedroquinone and deuterated chloroform in case of 3-libocedroxythymoquinone. Due to unfavorable solubility characteristics, this compound produced a satisfactory spectrum only when the sample was heated during the experiment.

Hydrogenation of 3-libocedroxythymoquinone. The experiment was conducted in a micro apparatus at room temperature and atmospheric pressure using acetic acid as a solvent and platinum as a catalyst. The reaction was essentially over in 15 min., when the mixture became colorless and the absorption figure was equal to 523 mg. sample per mmole of hydrogen (calcd. 521 mg. sample per mmole of hydrogen). This fast uptake was followed by somewhat slower absorption which after 85 min. from the beginning of the reaction, lessened the above figure to 480 mg. of sample per mmole of hydrogen and was probably due to some side reactions.

Reduction of 3-libocedroxythymoquinone with stannous chloride. A 164-mg. sample of 3-libocedroxythymoquinone (m.p. 153–154°) was dissolved in 5 ml. of ethanol. To the resulting solution 0.5 g. of stannous chloride dihydrate was added and the mixture was heated on a steam bath until colorless. This required 15 to 20 min. To this material 25 ml. of petroleum ether was added followed by 10 ml. of 10% hydrochloric acid. The organic phase was separated and the aqueous phase washed with 10 ml. of petroleum ether. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, evaporated to dryness, and the residue kept in a desiccator evacuated to 0.1 mm. pressure for several days to remove the rest of the solvent. The material represented a fluffy, amorphous solid which weighed 150 mg. (91% yield). It did not possess a sharp melting point but slowly sintered to a thick liquid between 40 and 50°. It slowly oxidized in air assuming a red color.

Anal. Calcd. for $C_{32}H_{42}O_6$: C, 73.53; H, 8.10. Found: C, 73.05; H, 8.00.

In ultraviolet it exhibited a maximum at 286 mμ, identified with the benzenoid B band and an inflection point at 220 mμ identified with benzenoid K band. In infrared, using potassium bromide technique, it did not show the carbonyl stretching band; in carbon tetrachloride solution, it exhibited a strong band corresponding to the OH vibration at 3520 cm.$^{-1}$, and a somewhat weaker one at 3600 cm.$^{-1}$

Oxidation of the hydro-3-libocedroxythymoquinone with ferric chloride. A 37-mg. portion of 3-libocedroxythymoquinone (m.p. 154–155°) was dissolved in 2 ml. of acetic acid to which 100 mg. of stannous chloride dihydrate was added,

(12) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, 20, 443 (1955).

(13) F. J. L. Aparicio and W. A. Waters, *J. Chem. Soc.*, 4666 (1952).

(14) L. F. Fieser and A. E. Oxford, *J. Am. Chem. Soc.*, 64, 2060 (1942).

(15) All melting points are corrected; microanalysis by Microchemical Laboratory, University of California, Berkeley. Ultraviolet and infrared spectra were run on Beckman DK II and Perkin Elmer Model 21 recording spectrophotometers, respectively, and NMR and EPR spectra on Varian Associates spectrometers.

and the resulting mixture was heated on a steam bath until the red color disappeared. To this solution 1.0 g. of ferric chloride was added and the material heated over steam for 1 min. The resulting liquid was diluted with 30 ml. of water and extracted with 20 ml. of chloroform. The organic extract was dried over anhydrous sodium sulfate, filtered, evaporated to dryness, and the residue crystallized from 2 ml. of methanol to give 28 mg. (76%) of red crystals, m.p. 154–155° that did not depress the melting point of the original 3-libocedroxythymoquinone.

p-Nitrobenzoylation of 3-libocedroxythymoquinone. Hydro-3-libocedroxythymoquinone (101 mg.) was dissolved in 3 ml. of pyridine and 0.3 g. of *p*-nitrobenzoylchloride was added. This mixture was heated on a steam bath for 5 min. whereupon it acquired a yellow coloration, and was allowed to stand overnight at room temperature. To the resulting material 25 ml. of 10% sodium carbonate solution and 25 ml. of ethyl ether was added; the aqueous phase was separated and the ether washed with 10 ml. of 10% sodium carbonate followed by 50 ml. of 10% hydrochloric acid in two portions. The ether extract was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was dissolved in 10 ml. of iso-octane, filtered from 5 mg. of some insoluble impurities, and cooled. At this point the ester separated in the form of very fine droplets with unsharp melting point. Attempts to induce crystallization failed. Removal of iso-octane by evaporation on a steam bath and later under vacuum gave an amorphous yellow residue weighing 139 mg.

Repeating the reaction using 52 mg. of hydro-3-libocedroxythymoquinone but with the heating period increased to 90 min., crystallization of the reaction product from methanol-water resulted in the separation of 13 mg. of impure 3-libocedroxythymoquinone, m.p. 145–150° (25% yield).

Attempted preparation of 3-libocedroxythymoquinone semicarbazone. A 103-mg. portion of 3-libocedroxythymoquinone, m.p. 153.5–154.5°, was refluxed on a steam bath in 10 ml. of methyl alcohol with 0.5 g. of semicarbazide hydrochloride and 2 drops of concentrated hydrochloric acid for 5 min. The resulting mixture was then cooled and filtered, and the solid was washed with 10 ml. of hot methanol. To the filtrate was added 20 ml. of water and the separated precipitate filtered and recrystallized from 10 ml. of methanol to give 60 mg. (58%) of 3-libocedroxythymoquinone, m.p. 152.5–153.5° undepressed on admixture with authentic material.

Reaction of 3-libocedroxythymoquinone with alkaline hydrogen peroxide. A 50.6-mg. portion of 3-libocedroxythymoquinone, m.p. 154–155° was dissolved in 5 ml. of acetone to which 0.5 g. of potassium carbonate was added. To this mixture 1 ml. of 30% superoxol was added and then refluxed for 30 min. on a steam bath during which time the color of the solution changed from reddish to yellow. Most of the acetone was removed from the solution by evaporation and the residue diluted to 10 ml. with water. The resulting material was extracted once with 15 ml. of petroleum ether and once with 15 ml. of ethyl ether, and the combined organic extracts dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was dissolved in 7 ml. of methanol, filtered from a small amount of white impurity and the epoxide crystallized by addition of water and cooling to −5°. The reaction product represented a yellow powder, m.p. 124–126°, and weighed 33 mg. (67%).

Further purification was achieved by repeated crystallizations from iso-octane and methanol-water whereupon the melting point was raised to 127–128°.

Anal. Calcd. for $C_{32}H_{40}O_7$: C, 71.62; H, 7.51. Found: C, 71.82; H, 7.71.

In the ultraviolet the compound exhibited an absorption maximum at 285–286 mμ, log ε 4.04 and an inflection point at 370–400 mμ, log ε 3.03–289. In the infrared, in carbon tetrachloride solution, and in the 4000–3000 cm.$^{-1}$ region it did not show an OH stretching band. Pressed into a KBr pellet it exhibited a conjugated double bond band at 1615 cm.$^{-1}$, and two carbonyl maxima at 1675 and 1700 cm.$^{-1}$

Reaction of the 3-libocedroxythymoquinone with hydrobromic acid. A 91.5-mg. portion of 3-libocedroxythymoquinone, m.p. 153–154°, was dissolved in 7 ml. of glacial acetic acid. This solution was heated on a steam bath while stannous chloride dihydrate was added in very small portions to the point of discoloration. To this mixture, 4 ml. of 40–42% hydrobromic acid containing a few small crystals of stannous chloride was added, and the solution was refluxed for 2 hr. Upon cooling, ferric chloride was added to the solution to the point at which the mixture assumed a yellow color. The resulting liquid was diluted with 25 ml. of water and extracted with 25 ml. of ethyl ether in two portions. The organic extract was shaken with 50 ml. of 10% ammonia in three portions, whereupon the aqueous solution assumed an intense violet color. Upon acidification with hydrochloric acid, the aqueous phase was extracted with 10 ml. of ethyl ether in two portions, the extract dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The yellow residue was purified by sublimation at 3 mm. and 100° to give 15 mg. of yellow crystals, m.p. 167.5–168° (sealed capillary), undepressed on admixture with an authentic sample of 3-hydroxythymoquinone. This represents a 24% yield assuming complete cleavage of all ether linkages in the molecule. The infrared absorption spectrum of the yellow material, obtained by using the potassium bromide technique, was found to be identical with that of 3-hydroxythymoquinone. Aside from the strong chelated OH absorption at 3240 cm.$^{-1}$, the compound exhibited a conjugated double bond maximum at 1612 cm.$^{-1}$, and two bands at 1640 and 1665 cm.$^{-1}$ corresponding to the chelated and nonchelated quinoid carbonyl stretching. The split of the quinoid carbonyl absorption band into two bands due to the neighboring hydroxyl has also been noted in the case of various hydroxylated anthraquinones.[16]

Reaction of libocedrol with alkaline ferricyanide. A 3.0-g. portion of libocedrol, m.p. 86.5–88°, was dissolved in 30 ml. of ethyl ether and stirred for 1 hr. with a solution of 6 g. of potassium ferricyanide and 1.6 g. of sodium hydroxide in 60 ml. of water, whereupon the ether phase became green in color. The organic phase was washed with 200 ml. of water in four portions and shaken with 50 ml. of 10% hydrochloric acid, the liquid becoming dark red. The ether solution was separated, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was dissolved in 25 ml. of methanol and allowed to crystallize overnight at −5°. The combined aqueous extracts and washings were acidified with hydrochloric acid and extracted with ether. Upon drying, filtering, and evaporation of the solvent, the extract left only a negligible residue.

The precipitated material was filtered, washed with methanol, and dried to give 994 mg. of dark red crystals, m.p. 142–147° (45.5% yield). Recrystallization of the red crystals from methanol raised the melting point to 153–154°. The material was found to be identical with the naturally occurring 3-libocedroxythymoquinone by mixed melting point technique, and by comparison of the infrared spectra using the compounds themselves and their epoxy derivatives.

The mother liquors from the crystallization of 3-libocedroxythymoquinone were combined and evaporated to dryness. The residue was dissolved in 20 ml. of pyridine and 2.0 g. of *p*-nitrobenzoyl chloride was added. The resulting liquid was heated on a steam bath for 20 min., diluted with 40 ml. of 5% sodium carbonate solution, and extracted with 60 ml. of ethyl ether. The organic phase was washed with 60 ml. of water, followed by 80 ml. of 10% hydrochloric acid, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was crystallized from 20 ml. of methanol, the precipitate was filtered and recrystallized from methanol-acetone to give the first crop of 806

(16) M. St. C. Flett, *J. Chem. Soc.*, 1441 (1948).

mg., m.p. 171–171.5°. The filtrate was evaporated to dryness and crystallized from ethanol to give 297 mg. of a material melting at 116–120°. Recrystallization of the first crop from ethanol-acetone raised the melting point of the material to 173–174°, undepressed on admixture with the original libocedrol *p*-nitrobenzoate. The amount isolated accounts for 19% of the libocedrol used.

The second crop was recrystallized from *n*-hexane to give a material melting at 126–127.5°. The melting point was undepressed on admixture with an authentic *p*-methoxythymol *p*-nitrobenzoate. The amount of the material isolated accounts for 11% of the libocedrol used.

One half of the residue of the *p*-nitrobenzoate crystallization was distilled at 1 mm. pressure and 200°. The distillate was collected and crystallized from methanol to give a mixture of dark red crystals and some reddish material. The crystals were separated by virtue of their solubility in 10 ml. of iso-octane. Evaporation of the iso-octane left a residue that was recrystallized several times from methanol to give 58 mg. of a material melting at 93–94.5°. Admixture with the authentic libocedroquinone did not depress the melting point. The amount isolated accounts for 4% of the original libocedrol.

In another similar experiment using 0.704 g. of libocedrol in 50 ml. of *n*-hexane, 20 ml. of 2.5% sodium hydroxide solution, and 20 ml. of 2% potassium ferricyanide solution, the reaction was conducted in nitrogen atmosphere using deaerated water. After 30 min. of stirring, the organic phase became yellowish green and about as intensive in color as when the reaction was conducted in presence of air. Allowing air into the system did not produce any color change. The yield of the 3-libocedroxythymoquinone was 47%.

In another similar experiment, 550 mg. of libocedrol, m.p. 86.5–88°, was dissolved in 50 ml. of ethyl ether and stirred for 1 hr. with a solution of 2.5 g. of potassium ferricyanide in 50 ml. of 5% sodium hydroxide solution. The organic phase was washed thoroughly with water, dried over sodium carbonate, filtered, and evaporated to dryness on a steam bath. The last traces of solvent were removed in 0.1 vacuum at room temperature. The resulting material was slightly yellow, amorphous, fluffy solid. It weighed 539 mg. (98%) and melted, not very sharply, at 45–50°.

The substance was soluble in most of the organic solvents. It dissolved in petroleum ether, and similar hydrocarbon solvents with a yellow-green color, and in more polar solvents such as chloroform or acetone, with a green color. Heating intensified the green color and cooling decreased its intensity.

The infrared absorption spectrum obtained by potassium bromide technique was found to be similar to that of 3-libocedroxythymoquinone, with a carbonyl band at 1665 cm.$^{-1}$, a band at 1640 cm.$^{-1}$, and a conjugated double bond band at 1615 cm.$^{-1}$; the intensity of all three bands was, however, appreciably less than with the quinone. In carbon tetrachloride solution a hydroxyl stretching band was present at the same position as with libocedrol (3550 cm.$^{-1}$) but with intensity reduced nearly five times. In the ultraviolet region between 220 and about 330 mμ, in methylcyclohexane solution, the material seemed to obey Beer's law. It showed a benzenoid B-band with λ_{max} 289, log ϵ = 4.07 and λ_{max} 265 mμ, log ϵ = 3.82 and two inflection points at 231 and 328 mμ with log ϵ 4.57 and 3.15, respectively, assuming the molecular weight of the dimer of the libocedroxy radical for the calculation. Above about 330 mμ Beer's law was not obeyed. The nature of the spectrum was found to be dependent on the concentration and the solvent used. In methylcyclohexane solution, the material had the absorption maxima at 377, 397, and 650 mμ and in chloroform solution at 387, 402, and 650 mμ. The absorbance decreased less than proportional to the dilution and with about the same concentration of the solute was several times larger in chloroform. Thus, with methylcyclohexane $E^{1\%}_{1\,cm.}$ was 4.8 and 4.2 at a concentration of 0.51 g./l. and 3.6 and 3.1 at a concentration of 2.2 g./l. for the first two bands mentioned. With chloroform the respective values were 10.5 and 12.2 at a concentration of 0.50 g./l. and 7.8 and 8.7 at a concentration of 2.1 g./l. The third, 650 mμ band ($E^{1\%}_{1\,cm.}$ 0.66, cond. 2.1 g./l., chloroform as the solvent) behaved similarly in all respects. The absorbance tended to decrease with time particularly when chloroform was used as the solvent; with the more concentrated solution in the above experiment, the E-values decreased to 8.4 and 9.3 in 10 min.

In the electron paramagnetic resonance measurements a strong signal was obtained using 8.4 mg. of the solid material; dilution with a few drops of chloroform intensified the signal roughly 10 times (*g* about 2.0, line width around 8 gauss).

Determination of the presence of 3-libocedroxythymoquinone in fresh incense cedar heartwood. From fresh moist incense cedar heartwood, three cross grain slats with combined weight of 307 g. (dry weight) were prepared (25 × 6 × 1.8 cm.). All surfaces were freshly cut and cleaned by rubbing with a cloth moistened in acetone. The slats were extracted under nitrogen atmosphere with petroleum ether, b.p. 30–60° for 15 hr. From the extract most of the solvent was removed by evaporation on a steam bath and the remainder under vacuum at room temperature. The residue weighed 10.6 g. (2.9%) and was stored under nitrogen atmosphere at −5°.

A 9.2-g. portion of the above residue was treated with 50 ml. of cold *n*-hexane and filtered from the separated libocedrol/*p*-methoxythymol complex (2.4 g.), m.p. 91–92°. The filtrate was chromatographed using 50 g. of Woelm alumina. The red fraction which came with *n*-hexane was evaporated to dryness, dissolved in 20 ml. of *n*-hexane, and allowed to stand for 3 days at −5°, then was filtered from 1.65 g. of separated libocedrol/*p*-methoxythymol complex, m.p. 88–91°, and rechromatographed three times using 50-g. portions of Woelm alumina. In the latter case, a 200-ml. portion of 40% ethyl ether in *n*-hexane brought a red fraction that was evaporated to dryness. Spectroscopic examination of the residue revealed the presence of about 10 mg. of 3-libocedroxythymoquinone (0.004% of the dry wood weight). Crystallization from methanol yielded 1.0 mg. of the above compound, m.p. 152–153° undepressed on admixture with authentic sample.

Formation of 3-libocedroxythymoquinone by air oxidation. One hundred grams of acetone-extracted Port Orford cedar sawdust was mixed with a solution of 2.0 g. of libocedrol/*p*-methoxythymol addition complex and 0.1 g. of thymoquinone in 100 ml. of acetone and the solvent removed by evaporation. The prepared sawdust was spread on the paper and allowed to stand for 80 days with an air current gently blowing over it. Extraction of the sawdust with acetone for 8 hr., evaporation of the solvent, chromatography of the residue, and crystallization of the appropriate fraction from methanol gave 11 mg. of 3-libocedroxythymoquinone m.p. 145–148°. Further crystallization from the same solvent raised the melting point to 151–152° which remained undepressed upon admixture with an authentic sample of the quinone.

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Notes

A department for short papers of immediate interest.

A Study of the Preparation of Δ^9-Octalin

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In the course of an investigation of the stereochemistry of 9-substituted decalins,[1] the need arose for considerable quantities of pure Δ^9-octalin. Of the numerous preparations of this compound,[2] the one of choice is that described by Campbell and Harris[3] and which is a modification of the procedure of Linstead, Wang, Williams, and Errington.[4] This method involves the dehydration of 2-decalol, obtained by hydrogenation of 2-naphthol, with phosphoric acid and phosphorus pentoxide to yield a mixture of isomeric octalins which, in turn, are treated with phosphorus pentoxide to bring about conversion of the mixture to a practically pure Δ^9-octalin. Recently, Cope, Cotter, and Pike[5] have described a simplification which utilizes boric acid[6] for the initial dehydration step. Following this modification, in combination with the final phosphorus pentoxide treatment, the octalins obtained varied in refractive indices from run to run and the infrared spectrum of each preparation possessed a band at 3020 cm.$^{-1}$, an absorption characteristic of olefinic hydrogens. The nuclear magnetic resonance spectra of such preparations also displayed bands due to vinyl proton absorption.[7] From these latter spectra, it could be estimated that the Δ^9-octalin obtained by this method possessed 15–30% of other isomeric octalins, depending on whether the impurity was considered as a di- or a trisubstituted olefinic linkage.

It has been found, however, that purification of the mixed octalins *via* the blue nitrose chloride derivative, a derivative which can be prepared in 60% yield, does yield a pure Δ^9-octalin. The nuclear magnetic resonance spectrum of such a material showed the complete absence of any vinyl hydrogens. When this pure isomer was allowed to react with phosphorus pentoxide it was transformed into a mixture of octalins containing 10–20% of isomers with vinyl hydrogen atoms. Such a result clearly indicates, as might be expected, that phosphorus pentoxide treatment simply equilibrates the octalins and from such a procedure pure Δ^9-octalin cannot be obtained.

Recently, it has been reported that reduction of tetralin with lithium in either ethylamine[8] or ethylenediamine[9] yields practically pure Δ^9-octalin. When a procedure involving the dissolution of lithium in ethylenediamine prior to the addition of the tetralin was used, the reaction was erratic and the formation of the lithium derivative of the amine often resulted. It was found that by adding the lithium to a solution of tetralin in ethylenediamine, the reaction was reproducible and octalin was isolated in 70% yield. The nuclear magnetic resonance spectrum of the product, however, showed it to be a mixture of isomers containing 10–20% of material with di- or trisubstituted double bonds. It would thus appear that this method of preparation, as well as the phosphorus pentoxide method, yields an equilibrium mixture of octalins.

During the course of this work, the preparation of $\Delta^{1(9)}$-10-amino-octalin was attempted following the published procedure which allows the blue nitroso chloride to react with zinc and hydrochloric acid in ether.[10] In our hands, only a small yield of the amine was obtained, the principal product being Δ^9-octalin. This method of regeneration of pure octalin gives yields comparable to the normal sodium methoxide procedure.

EXPERIMENTAL

Preparation of octalins. (*A*) *From 2-decalol.* A mixture of 154 g. of isomeric decalols, prepared by hydrogenation of 2-naphthol, and 62 g. of boric acid was placed in a 500 ml. round-bottomed flask which was attached to a 5"-column packed with glass helices and the system arranged for distillation. The mixture was immersed in a bath at 170° and the bath temperature was allowed to gradually rise to 350° and the distillation of octalin and water had practically ceased. After cooling the distillation residue slightly, the system was evacuated to water aspirator vacuum and the distillation continued until no further product was obtained

(1) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *J. Am. Chem. Soc.*, **77**, 48 (1955).

(2) For a complete bibliography see Elsevier, *Encyclopedia of Organic Chemistry*, Elsevier Publishing Co., Houston, Tex., 1948, Vol. 12, p. 76.

(3) W. P. Campbell and G. C. Harris, *J. Am. Chem. Soc.*, **63**, 2721 (1941).

(4) R. P. Linstead, A. B. Wang, J. H. Williams, and K. D. Errington, *J. Chem. Soc.*, 1136 (1937).

(5) A. C. Cope, R. J. Cotter, and R. A. Pike, private communication.

(6) W. Brandenberg and A. Galat, *J. Am. Chem. Soc.*, **72**, 3275 (1950).

(7) These spectra were kindly determined by Dr. James N. Schoolery, Varian Associates, Palo Alto, Calif.

(8) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955).

(9) L. Reggel, R. A. Friedel, and I. Wender, *J. Org. Chem.*, **22**, 891 (1957).

(10) W. Hückel and M. Blohm, *Ann.*, **502**, 114 (1933).

The total distillate was dissolved in ether, the water separated, the ethereal layer dried, and the solvent evaporated. The crude octalin was distilled at atmospheric pressure, b.p. 189–193°, n_D^{25} 1.4890–1.4950, yield 110–130 g. (80–95%).

A mixture of three parts of octalin and one part of phosphorus pentoxide was heated at 140° for 3 hr. and processed in the usual manner.[3] The product was distilled at atmospheric pressure through an 18″ column packed with Podbielniak tantalum Heli-pak: fraction 1, b.p. 191–193°, n_D^{25} 1.4920–1.4940; fraction 2, b.p. 192–194°, n_D^{25} 1.4940–1.4970. Fraction 1 usually amounted to a 25% yield and fraction 2 to a 60% yield.

(*B*) *From tetralin.* In a three-necked, round-bottomed flask fitted with a glass stopper, a sealed all-glass stirrer and a reflux condenser closed with a calcium chloride tube were placed 500 ml. of ethylenediamine (distilled from sodium hydroxide pellets before use) and 66.1 g. (0.5 mole) of tetralin. Clean lithium wire (21 g., 3 moles) was cut into short pieces and a 5 g. portion was added to the reaction flask. Stirring was commenced and in about 20 min. the lithium began to dissolve and heat was evolved. When the bulk of the initial lithium had dissolved, the remainder of the lithium was added in portions of about 3 g. over a period of about 15 min. Near the end of the addition of lithium, the solution developed a blue color. Stirring was continued for an additional 30 min. during which time the blue coloration faded to a slate-gray color.

The reaction mixture was decomposed by the addition of 200 ml. of ethanol over a period of 20 min. and the solution then poured into 2 l. of ice water. The mixture was extracted with several portions of benzene, the benzene solutions washed with 5% sulfuric acid and water. The solvent was removed and the product distilled at atmospheric pressure through a 20″ column, b.p. 194–196°, n_D^{25} 1.4950–1.4970, yield 48 g. (71%).

9-Nitroso-10-chlorodecalin. A solution of 45 g. (0.33 mole) of mixed octalins, prepared above, and 75 g. (1 mole) of ethyl nitrite in 100 ml. of glacial acetic acid was allowed to react with 75 ml. of concentrated hydrochloric acid at −15° in the usual manner and after 2 hr. the blue crystalline solid was removed by filtration. The solid was recrystallized from acetone twice to yield 35–40 g. (50–60%), m.p. 91–92° (lit.[2] 92°).

The yield of this derivative when pure Δ^9-octalin was employed was 77%.

Δ^9-*Octalin.* In an all-glass apparatus were placed 30 g. (0.46 mole) of zinc dust and a solution of 35 g. (0.17 mole) of 9-nitroso-10-chlorodecalin in 300 ml. of dry ether and to the stirred mixture was added 6 ml. of concentrated hydrochloric acid over the period of 10 min. The stirring was continued for 12 hr., then an additional 30 g. portion of zinc dust and 6 ml. of hydrochloric acid was added. The mixture was allowed to stir for an additional 24 hr., the zinc dust removed by filtration and washed with ether. The combined filtrate and washing were washed with sodium bicarbonate and water and then dried. After removal of the solvent, the Δ^9-octalin was distilled at atmospheric pressure, b.p. 194–196°, n_D^{25} 1.4971, yield 13.8 g. (59%).

When 9.8 g. of the purified material was heated with 5 g. of phosphorus pentoxide under the usual conditions and the product distilled, the following fractions were obtained: (1) b.p. 193–194°, n_D^{25} 1.4910, yield 1.7 g.; (2) b.p. 194–195°, n_D^{25} 1.4930, yield 0.6 g.; (3) b.p. 195.0–195.5°, n_D^{25} 1.4960, yield 7.8 g.; (4) b.p. 195.5–196.0°, n_D^{25} 1.4965, yield 2.3 g.

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Crystallizable Polystyrene. III. A Comparison of Crystallinities of Polystyrenes Prepared Using Various Catalysts

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In preceding publications,[1–3] crystallizable polystyrene was prepared by the use of Alfin catalysts and alkali-metal derivatives of arylmethanes. It is the purpose of this paper to demonstrate the difference in crystallizability between polystyrenes made using Alfin-type catalysts and arylmethane–alkali-metal catalysts, and those prepared using a Ziegler–type polymerization system.

The isotactic polystyrenes, prepared using various catalysts, are listed in Table I in the order of increasing crystallizability. X-ray diffraction photographs of these polymers are presented in Fig. 1.

TABLE I

Crystallinity of Isotactic Polystyrenes

Catalyst	(η)	Yield, %	Figure Number
Alfin catalyst	2.98	77.0	1
Triphenylmethyl potassium	1.58	11.1	2
Modified Ziegler, Run 1 system	1.14	0.13	
Modified Ziegler, Run 2 system	4.42	72.0	3

The most striking difference between polystyrenes obtained from organo-alkali-metal catalysts and those obtained from a Ziegler-type catalyst, is the higher degree of crystallinity obtained in the latter case. The order of increasing crystallizability was found to be the following: Alfin, triphenylmethylpotassium, and Ziegler-catalyzed polystyrene. Although only very low yields were obtained at first, using the Ziegler system, it was discovered that, by modification of the Ziegler system, high yields of isotactic polystyrene were obtained. In attempts to repeat the method described in the Ziegler Australian Patent No. 14116, it was expedient to substitute trimethylaluminum for triethylaluminum. It was also necessary to run the reactions under atmospheric pressure. By employing these two changes, the catalyst prepared according to the reaction sequences described by Ziegler gave

(1) J. L. R. Williams, J. VanDenBerghe, W. J. Dulmage, and K. R. Dunham, *J. Am. Chem. Soc.*, **78**, 1260 (1956).

(2) J. L. R. Williams, J. VanDenBerghe, K. R. Dunham, and W. J. Dulmage, *J. Am. Chem. Soc.*, **79**, 1716 (1957).

(3) J. L. R. Williams, T. M. Laakso, and W. J. Dulmage, Part II, *J. Org. Chem.*, **23**, 638 (1958).

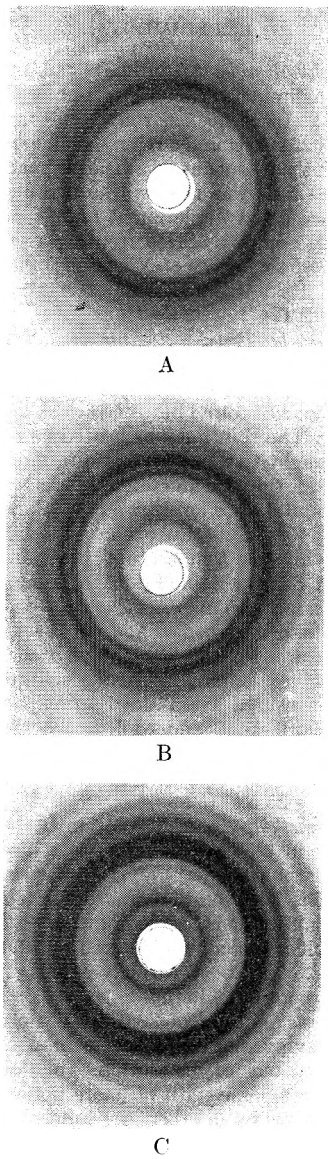

Fig. 1. X-ray diffraction photographs of polystyrenes (CuKα radiation). *A*. Alfin polystyrene crystallized by heating 14 hours in heptane at 90°. *B*. Triphenylmethylpotassium-catalyzed polystyrene crystallized by heating 14 hours in heptane at 90°. *C*. Modified-Ziegler-catalyzed polystyrene extracted and crystallized in boiling acetone

highly crystallizable polystyrene in very low yields. By use of a pressure bottle to contain the reaction system, good yields of highly crystallizable polystyrene were obtained, employing triisobutylaluminum-titanium tetrachloride as catalyst.

It appears that the organo-alkali-metal-catalyzed polystyrenes are block polymers consisting of interlinked atactic and isotactic regions. By extraction with methyl ethyl ketone, it is not possible to raise the crystallinity as high as is obtainable from the Ziegler-type polymer. This statement also applies to organo-alkali-metal-catalyzed polymer which has been degraded to inherent viscosities as low as 0.75. Such degradations release low-viscosity, amorphous polymer, which, after extraction, precipitation, and crystallization, has very low crystallinity.

In contrast, the Ziegler-type polystyrene lends itself readily to the fractionation of isotactic from the atactic materials, partly because the atactic polymers are mainly of low molecular weight and hence are easily extracted. When Ziegler-type polystyrene ($[\eta]=1.6$) and high-molecular-weight atactic polymer ($[\eta]=1.8$) were precipitated together from a dilute solution in benzene, extraction of the crystallized intimate mixture gave a high yield of isotactic polymer. This extracted residue was as highly crystalline as the polymer before dilution with atactic polystyrene and more highly crystalline than any extracted residue obtained from polystyrene which was polymerized with an organo-alkali-metal catalyst.

EXPERIMENTAL

Polymerizations.[4] Polystyrenes were prepared using Alfin-type catalyst and triphenylmethylpotassium, as previously described.[2,3] Modified Ziegler[5]-type polymerizations were carried out as follows:

Run 1. The apparatus consisted of a three-necked, one-liter flask equipped with a sintered glass disk in the bottom, high-speed, stainless-steel stirrer, reflux condenser, thermometer, dropping funnel, and nitrogen inlet tube. The reaction flask was heated in an oil bath.

A solution of 7.045 g. of trimethylaluminum in 70 ml. of heptane was placed in the flask and heated to 70° under an atmosphere of dry nitrogen. A solution of 7.6 g. of titanium tetrachloride in 20 ml. of heptane was added over a period of 10 min., with efficient stirring, during which time gas was evolved and a black precipitate formed. Heating was continued for 30 min. after the addition was complete and, using the porous glass disk, the precipitate was then filtered by means of nitrogen pressure upon the surface of the liquid. The precipitate was washed three times with a 2% solution of trimethylaluminum in heptane. The coarse precipitate was then suspended in 250 ml. of heptane containing 7.05 g. of trimethylaluminum. After the suspension was transferred (under nitrogen) to a one-liter, three-necked flask, the catalyst mixture was heated to 65°, and 150 g. (166 ml.) of freshly distilled styrene was added dropwise, with efficient stirring, over a 15-min. period. The polymerization mixture was then heated at 70–75° for 4 hr. The reaction mixture was cooled, poured into methanol, and the inorganic products were dissolved by the addition of hydrochloric acid. Two layers were formed; the flocculent product was present in the upper layer. After the precipitate was collected, it was purified by boiling in acetone containing hydrochloric acid. The polymer was filtered, and then washed several times with fresh acetone. The highly crystalline polymer had a melting point of 228° and an inherent viscosity of 1.14. The yield was 0.2 g. (0.13%). The crystallinity was extremely high.

Run 2. A 375-ml. pressure bottle was flushed with dry nitrogen and capped using a Neoprene-line, self-sealing cap. A solution of 5.7 g. of triisobutylaluminum, diluted with dry heptane to a total volume of 42.3 ml., was injected into the bottle by means of a hypodermic syringe. The bottle

(4) Trimethylaluminum and triisobutylaluminum were used in these experiments, whereas triethylaluminum was employed by Ziegler.[5] All-glass equipment was used rather than steel autoclaves.

(5) K. Ziegler, Australian Patent **14116**, example 44 (1955).

was immersed in a 70° water bath for 10 min. and a solution of 3.8 g. of titanium tetrachloride, diluted with dry heptane to a volume of 12.2 ml., was added in small amount over a 5-min. period, using a hypodermic syringe. The bottle was vented from time to time in order to relieve the pressure. The reaction bottle was then tumbled for 30 min. at 70°, after which time 42.3 ml. of triisobutylaluminum-heptane solution and 75 ml. of freshly distilled styrene were added. The bottle was then tumbled in a 70° water bath for 24 hr. After the bottle was cooled to room temperature, the contents were poured into methanol. Hydrochloric acid was added to dissolve the inorganic materials, and the mixture allowed to stand for 16 hr. The polymer was collected and then suspended in acetone containing hydrochloric acid. The polymer was washed by decantation several times with a fresh acetone and subsequently boiled in acetone for 18 hr., to give a 72% yield of polystyrene having an inherent viscosity of 4.42, a melting point of 230°, and extremely high crystallinity.

KODAK RESEARCH LABORATORIES
COMMUNICATION NO. 1922
ROCHESTER, N. Y.

An Improved Synthesis of 3-Methylpyrrole[1]

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The simple compound 3-methylpyrrole is only very poorly characterized in the chemical literature. Earlier methods of synthesis[2-7] gave either low yields, small amounts of impure material, or an inseparable mixture of isomers.

The present paper reports the synthesis of pure 3-methylpyrrole in 37.8% yield starting with potassium phthalimide by condensation of aminoacetone with diethyl oxalacetate and subsequent hydrolysis and decarboxylation of the product, 2-carboxy-3-carbethoxy-4-methylpyrrole, essentially by the method of Piloty and Hirsch.[2] Our contribution consists in the development of a new method for the *in situ* synthesis of aminoacetone (hydrolysis of *N*-acetonylphthalimide) and in the improvement of the subsequent steps, as well as in a more complete characterization of 3-methylpyrrole.

EXPERIMENTAL

N-Acetonylphthalimide. An intimate mixture of 250 g. of potassium phthalimide with 200 g. of 1-chloropropanone was added to a 2-l., three necked round bottomed flask fitted with a mechanical stirrer and a reflux condenser. The mixture was heated gently by means of a heating mantle until reaction began; the heat was then withdrawn and the reaction allowed to proceed to completion at room temperature. The solid product was recrystallized from water to yield 269 g. (98.2%) of colorless needles of *N*-acetonylphthalimide, m.p. 116.0–116.8°, 122.9–123.5° after recrystallization from water (reported[8] 124°).

2-Carboxy-3-carbethoxy-4-methylpyrrole. A solution made from 150 ml. of concentrated hydrochloric acid and 75 ml. of water was added to 50.0 g. of crude *N*-acetonylphthalimide in a 500-ml., one necked round bottomed flask fitted with a reflux condenser. The solution was heated at reflux for 4 hr., cooled and brought to *p*H 1.5 by addition of 30% aqueous sodium hydroxide solution and filtered to remove the phthalic acid that precipitated. The filtrate was then added slowly to a solution of 45 g. of diethyl oxalacetate sodium salt in 400 ml. of water while the temperature was maintained at 75° and the *p*H at 5 by periodic addition of small amounts of sodium hydroxide solution.

The mixture was then cooled and the precipitate removed by filtration. The *p*H of the filtrate was brought to 8 by the addition of further sodium hydroxide solution and the resulting solution heated at 75° for 30 min., reacidified with dilute hydrochloric acid, and cooled. Filtration afforded a second crop of 2-carboxy-3-carbethoxy-4-methylpyrrole to bring the total yield of product, m.p. 195.7–196.8° (reported[3] 196°), to 25.5 g. (52.8%).

3-Carboxy-4-methylpyrrole. A solution of 440 g. of potassium hydroxide in 1250 ml. of water was added to 67 g. of 2-carboxy-3-carbethoxy-4-methylpyrrole and the mixture refluxed for 24 hr. The solution was brought to *p*H 9 with concentrated sulfuric acid, cooled, and filtered. The filtrate was then acidified, cooled, and filtered to afford a quantitative yield (42.5 g.) of 3-carboxy-4-methylpyrrole, m.p. 152.6–153.7° (reported[3] 149°).

3-Methylpyrrole. A total of 22.0 g. of finely powdered 3-carboxy-4-methylpyrrole was placed in a 200-ml. round bottomed flask fitted for distillation. The flask was heated gently with a free flame until no more liquid distilled. The distillate was taken up in ether, the solution dried over anhydrous magnesium sulfate and redistilled to yield 10.6 g. (73.1%) of pure 3-methylpyrrole, b.p. 142–143° (740 mm.) n_D^{20} 1.4970, n_D^{25} 1.4949.

Anal. Calcd. for C_5H_7N: C, 74.0; H, 8.7; N, 17.3. Found: C, 74.0; H, 8.8; N, 17.3.

The absorption bands in the infrared spectra of 3-methylpyrrole and 2-methylpyrrole[9] are compared in Table I and the respective infrared spectra of 12.25% solutions in chloroform taken with a Perkin Elmer Model 21 double beam spectrophotometer in 0.05 mm. sodium chloride cells are shown in Figs. 1 and 2.

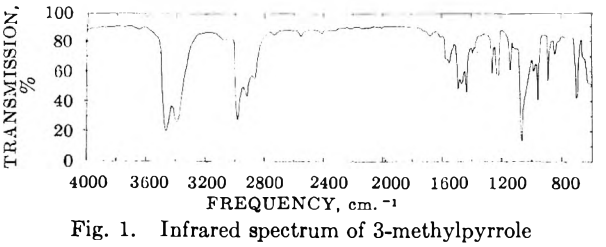

Fig. 1. Infrared spectrum of 3-methylpyrrole

(1) This investigation was performed as a part of American Petroleum Institute Research Project 52 on *Nitrogen Constituents of Petroleum*, which is conducted at the University of Kansas in Lawrence, Kan., and the Bureau of Mines Experiment Stations in Laramie, Wyo., and Bartlesville, Okla.

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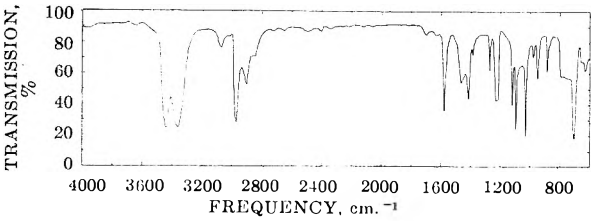

Fig. 2. Infrared spectrum of 2-methylpyrrole

TABLE I

ABSORPTION BANDS IN INFRARED SPECTRA OF 3-METHYLPYRROLE AND 2-METHYLPYRROLE[a]

3-Methylpyrrole	2-Methylpyrrole	3-Methylpyrrole	2-Methylpyrrole
3462 vs	3441 vs	1390 vw	1386 vw
3390 vs	3362 vs	1375 vw	1375
3080 sh	3072 w	1259 m	1259
2981 vs	2971 vs	1218[b] m	1230[b] s
2915 s	2904 m	1139 m	1130 s
2862 m	2850 w (sh)	1097[b]	1097[b] vs
2730 vw	2730	1061 vs	1061
2550 vw	2550	1030[b]	1030[b] vs
1700	1700 vw	980 w	980 w
1672 vw	1672	956 m	951 m
1635	1635 vw	889 m	889 m
1570[b] w	1577[b] s–vs	879	879 sh
1550[b] w–m	1550[b]	790[b]	790[b] m
1490[b] m–s	1490[b]	700 s	704 vs
1463 m	1463 m	660	660 sh
1432 m–s	1418 m–s	633	633 w

[a] Values are frequencies in cm.⁻¹; s = strong, m = medium, w = weak, vs = very strong, sh = shoulder. [b] Principal differences.

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Preparation of *cis*-2-Hydrocycyclohexaneacetic Acid Lactone

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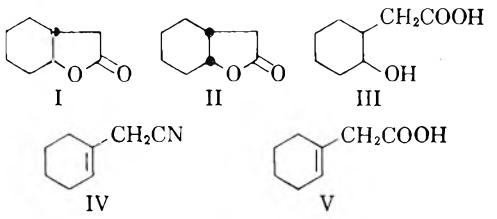
The *trans*-lactone (I) of 2-hydroxycyclohexaneacetic acid is easily obtainable from diethyl sodiomalonate and cyclohexene oxide. However, the *cis*-lactone (II) has only been obtained indirectly by hydrolysis of I to the *trans*-acid (III), followed by oxidation to the corresponding ketoacid and catalytic hydrogenation to a mixture of the acids III, containing 84% of the *cis*-isomer. The latter lactonized spontaneously to II. The over-all yield of II, based on cyclohexene oxide, was 38%.[1]

It has now been found that II is obtained in about 30% yield by one-step reaction of the readily accessible 1-cyclohexene-1-acetonitrile[2] (IV) with concentrated hydrochloric or hydrobromic acid in boiling glacial acetic acid. The determination of the composition of the lactone obtained was based on the fact observed by Newman and Vanderwerf[1] that I yields on dissolution in aqueous sodium hydroxide and subsequent acidification the *trans*-acid III, while the *cis*-acid III, obtained under these conditions from II, cyclizes spontaneously again to II.



I II III IV V

The mechanism of this stereospecific reaction very probably does not consist of initial hydration of the double bond and subsequent attack of the hydroxy group on the nitrile triple bond. In this case it would have to lead to a mixture of I and II and should not markedly depend on the nature of the acid employed. In fact sulfuric acid, for example, does not bring about the conversion of IV to II. The first step in the production of the lactone II is the formation of the unsaturated acid (V); it can be isolated when the reaction is interrupted after a shorter time than that required for the formation of the lactone. The hydrolysis of the nitrile function is obviously not a simple acid-catalyzed reaction, but is brought about by an addition of the acid to the C≡N bond and is influenced also by the anion of the acid. Therefore, the order of the rates of the reaction of IV with the acids employed is: hydrobromic> hydrochloric> sulfuric acid; this is also the order of the nucleophilicities of the anions.

The cyclization step, which follows the formation of the acid V, is not the rate controlling one, since the acid V is cyclized smoothly in the presence of either hydrobromic or sulfuric acid.

EXPERIMENTAL

Reaction of hydrobromic acid with 1-cyclohexene-1-acetonitrile IV. *General procedure.* To 20 g. of IV in 80 ml. of glacial acetic acid, 140 ml. of concentrated hydrobromic acid was added and the mixture was refluxed for the desired period of time, after which water was added and the product extracted with benzene. The benzene layer was washed with 5% aqueous sodium carbonate solution. The acidic products, obtained by acidification of the washings, were extracted with benzene and distilled. 1-Cyclohexene-1-acetic acid (V) distills at 155–158° (20 mm.) and melts at 37°.[3] Some bromine-containing acids were also observed after longer reaction periods. They boiled at 170–190° (20 mm.), but have not been obtained in pure form.

The *neutral products* remaining in the benzene layer can be separated by fractionation. The nitrile IV distils at 120° (20 mm.); the lactone II boils at 145–148° (20 mm.).

The obtained lactone consisted of the *cis*-product II. In one case only was a small amount of the *trans*-isomer I found.

In order to determine the content of I and II in the lactone, the *neutral products* obtained after evaporating

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(3) O. Wallach, *Ann.*, **343**, 51 (1905).

the benzene solution were stirred with warm 10% aqueous sodium hydroxide solution for 15 min. and extracted with benzene, which removed the unchanged nitrile IV. The alkaline solution was acidified with cooling, and the oil which separated extracted with benzene. From the extract, the *trans*-acid could be removed by means of 5% aqueous sodium carbonate solution, while the *cis*-lactone II was obtained by distillation of the benzene solution. B.p. 145–148° (20 mm.).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.6; H, 8.6. Found: C, 68.6; H, 8.7.

The *trans*-acid, eventually obtained by acidification melts at 106°.[1]

The results of the experiments are summarized in Table I.

TABLE I

ACID HYDROLYSIS OF THE NITRILE IV

Product (in % of theory)	Hydrobromic Acid after 2 hr.	4 hr.	7 hr.	13 hr.	Hydrochloric Acid after 2 hr.	4 hr.	10 hr.	Sulfuric Acid after 4 hr.	10 hr.
Lactones[a]			23	24			22	2	5
cis-Lactone (II)	15	30			8	24			
trans-III		4							
V	26		10		30	15			
Acid m.p. 117°								1	8
Starting material (IV)	5				30	8		73	
Unsaturated amides[b]									
Acids containing bromine			13	15					

[a] Total amount of lactones, when no separation of the isomers was carried out. [b] See text.

Reaction of sulfuric acid with IV. To 20 g. of IV in 150 ml. of acetic acid, 100 ml. of 10% sulfuric acid was added and the reaction mixture was treated as above. In this case, the neutral product had m.p. 135–152° and showed the same elementary analysis as the amide of V.[4]

In the acidic fraction a product m.p. 117° was found.

Reaction of 1-cyclohexene-1-acetic acid (V) *with sulfuric acid.* To 4.5 g. of the acid V in 35 ml. of glacial acetic acid, 25 ml. of 50% sulfuric acid was added and the mixture was refluxed for 4 hr. Water was added and the product worked up as usual. Distillation of the benzene layer gave 2.5 g. (55%) of the *cis*-lactone II, b.p. 140–150° (20 mm.). An unidentified acidic product (1 g.), b.p. 180–200° (20 mm.), was also found.

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Preparation of 4-Carboxy-1,2-cyclohexanedione Dioxime[1,2]

CHARLES V. BANKS, J. P. LAPLANTE, AND JOHN J. RICHARD

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In an effort to find a *vic*-dioxime which was water soluble and still possessed the desired properties which would make it useful as an analytical reagent for nickel and palladium,[3] and for the study of the complexes formed between nickel and the *vic*-dioxime in basic solution,[4–13] 4-carboxy-1,2-cyclohexanedionedioxime was prepared in this Laboratory.

The synthesis of 4-carboxy-1,2-cyclohexanedionedioxime involves the following steps: the high pressure hydrogenation of ethyl-4-hydroxybenzoate to 4-ethoxycarbonylcyclohexanol, the oxidation of this alcohol by the acid-chromate method to 4-ethoxycarbonylcyclohexanone, the selenium dioxide oxidation of the monoketone to 4-ethoxycarbonyl-1,2-cyclohexanedione, the oximation of the dione to 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime, and hydrolysis of this dioxime to the desired compound, 4-carboxy-1,2-cyclohexanedionedioxime.

Aqueous oximation of 4-ethoxycarbonyl-1,2-cyclohexanedione using potassium hydroxide and hydroxylammonium chloride gave as the major product 4-hydroxyaminocarbonyl-1,2-cyclohexanedionedioxime rather than 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime. 4-Hydroxyaminocarbonyl-1,2-cyclohexanedionedioxime can also be conveniently prepared from 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime.

The pK values were determined for the three acidic hydrogens of 4-carboxy-1,2-cyclohexanedionedioxime and the following results were obtained: $pK_1 = 4.85$, $pK_2 = 10.45$ and $pK_3 = 12.37$.

EXPERIMENTAL

4-Ethoxycarbonylcyclohexanol. 4-Ethoxycarbonylcyclohexanol has been prepared by Ungnade and Morriss.[14] Equally satisfactory results were obtained by the following procedure. One hundred grams of ethyl-4-hydroxybenzoate and 15 g. of a 2% palladium catalyst[15] on a strontium car-

(1) No. XX in a series on "Chemistry of the *vic*-Dioximes." Previous paper in this series is No. XIX, *J. Org. Chem.*, **21**, 815 (1956).

(2) Contribution No. 583; work was performed in the Ames Laboratory of the U. S. Atomic Energy Commission.

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bonate support were suspended in 150 ml. of purified dioxane, and the material was reduced at a hydrogen pressure of 1800 p.s.i. at 150° for 4 hr. in a Parr high-pressure apparatus. The reaction mixture was filtered, the dioxane removed by distillation and the 4-ethoxycarbonylcyclohexanol was vacuum-distilled through a 50-cm. Vigreux column. Yield of 4-ethoxycarbonylcyclohexanol, 80%; b.p. 115–123° (4 mm.); n_D^{20} 1.4635.

4-Ethoxycarbonylcyclohexanone. 4-Ethoxycarbonylcyclohexanol was oxidized by the acid-dichromate method,[16] but because of possible hydrolysis of the ester grouping, the usual procedure was slightly modified in that the temperature was not allowed to rise above 35°. The crude 4-ethoxycarbonylcyclohexanone was vacuum-distilled through a 50-cm. Vigreux column and the product was collected. Yield of 4-ethoxycarbonylcyclohexanone, 65%; b.p. 112–118° (4 mm.); n_D^{25} 1.4594.

4-Ethoxycarbonyl-1,2-cyclohexanedione. The 4-ethoxycarbonylcyclohexanone was oxidized with alcoholic selenium dioxide to give the corresponding diketone. The method reported by Riley, Morley, and Friend[17] as modified by Hach, Banks, and Diehl[18] was employed. The reaction mixture was filtered and fractionated through a 50-cm. Vigreux column under reduced pressure. The dione is very unstable towards prolonged heating and the distillation should be completed as rapidly as possible. Yield of 4-ethoxycarbonyl-1,2-cyclohexanedione, 48%; b.p. 120–135° (2 mm.); n_D^{20} 1.4862.

4-Ethoxycarbonyl-1,2-cyclohexanedionedioxime. 4-Ethoxycarbonyl-1,2-cyclohexanedione was oximated by a method very similar to that of Bachmann and Boatner.[19] One-half mole of the dione, 2 moles of hydroxylammonium chloride, 4 moles of pyridine, and 600 ml. of absolute alcohol were refluxed for 35 min. on a steam bath. After most of the pyridine had evaporated, the oily mixture was poured into an equal volume of cold water to precipitate the crude 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime. This material was dried and recrystallized twice from ethyl acetate. Yield of 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime, 55%; m.p. 167°.

Analytical samples were obtained by dissolving 1 g. of the ester in 50 ml. of absolute ethanol and passing the solution through a column 10 cm. in length and 2.5 cm. in diameter packed with Woelm basic alumina. Ethanol was used as the eluant. The 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime was precipitated from the ethanol by the addition of petroleum ether, filtered, and dried at 110° for 1 hr.

Anal. Calcd. for $C_9H_{14}N_2O_4$: N, 13.08%. Found: N, 12.97%; 13.15%.

4-Hydroxyaminocarbonyl-1,2-cyclohexanedionedioxime. 4-Hydroxyaminocarbonyl-1,2-cyclohexanedionedioxime can be prepared from 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime by using the synthesis given for benzohydroxamic acid.[20] This compound gave a red precipitate with nickel while cupric acetate produced a greenish-blue color characteristic of hydroxamic acids. It was observed that this hydroxamic acid was hydrolyzed readily by aqueous acid solution, which is in agreement with the information reported in the review paper by Yale.[21] Yield of 4-hydroxyaminocarbonyl-1,2-cyclohexanedionedioxime 60%; m.p. 152°.

Anal. Calcd. for $C_7H_{11}N_3O_4$: N, 21.00%. Found: N, 21.10%; 20.81%.

4-Carboxy-1,2-cyclohexanedionedioxime. 4-Carboxy-1,2-cyclohexanedionedioxime was obtained by hydrolysis of 4-ethoxycarbonyl-1,2-cyclohexanedionedioxime. This was accomplished by heating on a steam bath for 1 hr. a mixture of 0.1 mole of the ester, 0.15 mole of potassium hydroxide, and 125 ml. of water. After cooling, the reaction mixture was acidified to *p*H 1–2. The precipitated acid was filtered and dried. More acid can be obtained by extraction of the hydrolysis mixture with diethyl ether. The acid was recrystallized by dissolving in a minimum amount of hot dioxane, adding petroleum ether to incipient cloudiness, cooling, and filtering. The acid had a purity of 95% based on micro Dumas nitrogen determinations and titration of the carboxy hydrogen.

Further purification can be obtained by dissolving approximately 2 g. of the acid in 50 ml. of dioxane and passing the solution, while hot, through a column 10 cm. in length and 2.5 cm. in diameter which was packed with a 1:1 mixture of acidic and basic Woelm alumina. This procedure was repeated twice and a very pure compound was obtained, as indicated by titration of the acid which gave a molecular weight of 186.16; theoretical is 186.17. Yield of 4-carboxy-1,2-cyclohexanedionedioxime, 50%; m.p. 218–220° with decomposition.

Anal. Calcd. for $C_7H_{10}N_2O_4$: N, 15.05%. Found: N, 15.08%; 15.04%.

pK Determinations. The molar dissociation constants for 4-carboxy-1,2-cyclohexanedionedioxime were determined by the following methods. The pK_1' for the carboxy hydrogen was determined by direct titration with 0.1*N* potassium hydroxide after having added a known excess of standardized 0.1*N* hydrochloric acid. A value of 4.75 (μ = 0.100) was found. Conversion to the thermodynamic constant, pK_1, by application of the Debye and Hückel theory, gave a value of 4.85.

The method of Banks and Carlson[22] was used to determine the *p*K values of the oxime hydrogens. The average value found for four determinations of pK_2' was 10.44 (μ = 0.01) and for two determinations of pK_3' was 12.31 (μ = 0.06). Conversion to the thermodynamic constants gave 10.45 for pK_2 and 12.37 for pK_3.

Due to the hydrolysis of 4-hydroxyaminocarbonyl-1,2-cyclohexanedionedioxime the *p*K values were not determined.

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Reactivity Ratios of Trifluoromethyl-substituted Styrenes with Methyl Methacrylate and Styrene

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To find the effect of substitution of the trifluoromethyl group on the polymerization reactivity of styrene, the reactivity ratios of 3-

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TABLE I

REACTIVITY RATIO DETERMINATIONS

M_1	r_1	M_2	r_2
Styrene	.70±.05	3-Trifluoromethylstyrene	1.05±.05
Methyl methacrylate	.60±.10	3-Trifluoromethylstyrene	0.98±.15
Styrene	.45±.05	2,5-bis(Trifluoromethyl)styrene	1.15±.08
Methyl methacrylate	.57±.07	2,5-bis(Trifluoromethyl)-styrene)	1.35±.05

The "r" values of these substituted styrenes are similar to those for halogen-substituted styrenes. Since the reactivity ratio is a measure of the tendency of one monomer to add to itself or to the comonomer, the results show that the substituted styrenes add to their own radical slightly faster than they add to the comonomer radical and that substitution of a second trifluoromethyl group increases this tendency.

Using the Price-Alfrey scheme with revised Q and e styrene and methyl methacrylate, the reactivity of 3-trifluoromethylstyrene, Q, and the

TABLE II

REACTIVITY RATIO DETERMINATION WITH METHYL METHACRYLATE

Mole fraction[a]	$\frac{M_1}{M_2}$	Conversion, %	Analysis, %F	Mole fraction[b]	$\frac{M_2}{M_1}$
		3-Trifluoromethylstyrene			
0.100	9.03	6.3	7.62	0.148	0.174
0.252	2.97	6.0	14.24	0.305	0.439
0.400	1.50	4.5	19.54	0.455	0.837
0.498	1.01	5.2	22.52	0.552	1.234
0.600	0.67	6.0	22.50	0.660	1.943
		2,5-Bis(trifluoromethyl)styrene			
0.249	3.01	2.6	26.59	0.347	0.531
0.400	1.50	8.6	34.18	0.517	1.07
0.500	1.00	9.5	37.98	0.625	1.66
0.599	0.67	9.3	39.88	0.686	2.19
0.769	0.30	9.8	43.68	0.827	4.79

[a] Fluorine-containing styrene in charge. [b] Fluorine-containing styrene in polymer.

TABLE III

REACTIVITY RATIO DETERMINATION WITH STYRENE

Mole Fraction[a]	$\frac{M_1}{M_2}$	Conversion, %	Analysis, %F	Mole Fraction[b]	$\frac{M_2}{M_1}$
		3-Trifluoromethylstyrene			
0.103	8.75	7.4	6.62	0.131	0.151
0.253	2.95	6.3	14.24	0.313	0.457
0.402	1.49	7.0	19.21	0.455	0.836
0.500	1.00	6.4	22.19	0.551	1.227
0.599	0.67	8.6	24.67	0.639	1.767
		2,5-Bis(trifluoromethyl)styrene			
0.100	8.98	9.4	17.80	0.206	0.260
0.250	3.00	9.0	27.06	0.365	0.574
0.402	1.49	8.5	36.55	0.516	1.065
0.500	1.00	6.4	38.70	0.592	1.452

[a] Fluorine-containing styrene in charge. [b] Fluorine-containing styrene in polymer.

trifluoromethylstyrene and 2,5-bis(trifluoromethyl)-styrene with methyl methacrylate and styrene were determined by the method of Mayo and Lewis.[2] Polymerizations were run in bulk and the composition of the resultant polymers was determined by fluorine analysis. The error in the "r" values was estimated by assuming that the maximum error in elemental analysis (about ±0.25%) is the primary limiting factor.[3] The results are summarized in Table I.

polarity, e, were calculated to be 0.92 and −0.28 respectively. Values of Q = 1.14 and e = −.04 were calculated for 2,5-bis(trifluoromethyl)styrene.

EXPERIMENTAL

Monomers. Commercial samples of styrene and methyl methacrylate were redistilled before use. The trifluoromethyl styrenes were prepared by Dr. E. T. McBee.[4]

(2) F. R. Mayo and F. M. Lewis, *J. Am. Chem. Soc.*, 66, 1594 (1944).

(3) T. Alfrey, Jr., and H. Mark, *Copolymerization, High Polymers*, Vol. VIII, Interscience, New York (1952).

Reactivity ratio determinations. Polymerization was carried out in bulk at 60° using 1.0% benzoyl peroxide initiator. The polymer was precipitated in methanol and unreacted monomer was extracted by low-boiling petroleum ether in a Soxhlet extractor for 6 hr. For further purification the polymer was twice reprecipitated from benzene or trifluoromethylbenzene. The conversion in these reactivity ratio studies were of the order of 5–10% and never more than 10%. The experimental data are summarized in Tables II and III.

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(4) This work was supported by the United States Air Force under contract and monitored by the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

para-Nitrobenzyl Nitrite[1]

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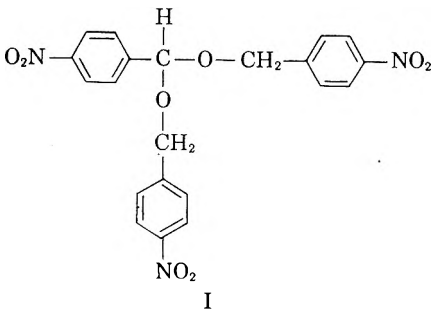
Received January 24, 1958

In the course of another study it became necessary to know something of the chemical properties of *p*-nitrobenzyl nitrite, a compound first prepared in 1955.[2]

p-Nitrobenzyl nitrite is a yellow liquid which has previously been reported[2] to decompose to a light yellow solid (uncharacterized) on standing overnight exposed to the atmosphere, in the dark, at room temperature. In the present study, the nitrite ester was protected from the atmosphere and allowed to decompose at room temperature in the dark; four days were required for complete solidification. During this time a colorless gas, which turned brown on contact with the air, and which attacked mercury, was evolved. The resulting light yellow solid was easily separated into two components: *p*-nitrobenzaldehyde (24% yield), and the acetal (I) of *p*-nitrobenzaldehyde with *p*-nitrobenzyl alcohol (72% yield). The colorless gas is presumably nitric oxide.



I

The formation of an acetal in the thermal decomposition of a nitrite ester is, to our knowledge, unprecedented. Another interesting feature is the relatively great instability of *p*-nitrobenzyl nitrite. While it is not difficult to imagine why *p*-nitrobenzaldehyde should go over to the acetal rather readily, it is less than obvious why *p*-nitrobenzyl nitrite is so unstable.

(1) This work was supported by a grant from the Explosives Department of E. I. du Pont de Nemours and Co., Inc.

(2) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, 77, 6269 (1955).

EXPERIMENTAL[3]

Decomposition of p-nitrobenzyl nitrite. *p*-Nitrobenzyl nitrite was prepared by the previously reported method[2] except that purification was accomplished by molecular distillation at *ca.* 10^{-3} mm. and room temperature; the distillate was kept at Dry Ice temperature as it was being collected. A 6.4-g. (0.035 mole) sample, n^{20}_D 1.5498; m.p. 12.5°, was protected from the atmosphere by a mercury valve and allowed to stand in the dark at room temperature. Sometime during the first 12 hr. the evolution of a colorless gas, which attacks mercury and which turns brown on contact with air, commenced. After 4 days all the liquid had disappeared and in its place a pale yellow solid, 5.2 g., m.p. 105–155° remained.

Digestion of this solid with refluxing acetone gave, upon cooling, the acetal (I), 3.9 g. (.0088 mole), m.p. 209–210° (72% yield). Evaporation of the acetone left 1.3 g. (0.009 mole, 24% yield) of *p*-nitrobenzaldehyde, m.p. 102–104°; recrystallization gave m.p. 105–106°, mixed m.p. with an authentic sample of m.p. 105–106°, was undepressed.

The dinitrophenylhydrazone prepared from the aldehyde had m.p. 318° (dec.); a mixed m.p. determination with the dinitrophenylhydrazone of authentic *p*-nitrobenzaldehyde, m.p. 318° (dec.), showed no depression.

Characterization of acetal (I). This chalk white solid, m.p. 209–210°, was insoluble in water, ethyl ether, and benzene and was slightly soluble in acetone, dioxane, and ethyl acetate. Recrystallization from acetone raised the m.p. of I to 210–211°. I does not react with aqueous potassium permanganate or dinitrophenylhydrazine reagent. It dissolves in cold concentrated sulfuric acid to give a colorless solution which, when poured on to ice gave straw yellow crystals, m.p. 100–102°. Recrystallization from water raised the m.p. to 105–106°; a mixed m.p. with authentic *p*-nitrobenzaldehyde, m.p. 105–106°, was undepressed. The dinitrophenylhydrazone had m.p. 318° (dec.), and a mixed m.p. with authentic dinitrophenyl hydrazone m.p. 318°, was undepressed.

Hydrolysis of 0.3 g. of the acetal (I) was also accomplished by heating under reflux for 4 hr. in 35 ml. of 43% aqueous dioxane containing 5 drops of concentrated hydrochloric acid. The resulting solution was cooled to room temperature and treated with benzoyl chloride and 10% aqueous sodium hydroxide; this gave *p*-nitrobenzyl benzoate m.p. 89–92°. Recrystallization from ethanol raised the m.p. to 92–93°. A mixed m.p. with an authentic sample of *p*-nitrobenzyl benzoate (m.p. 91–93°) gave m.p. 91–93°.

Anal. Calcd. for $C_{21}H_{17}N_3O_8$: C, 57.6; H, 3.90; N, 9.56. Found: C, 57.6; H, 3.77; N, 9.76.

Synthesis of the acetal of p-nitrobenzaldehyde and p-nitrobenzyl alcohol (I). *p*-Nitrobenzyl alcohol, 1.0 g. (0.0065 mole), and *p*-nitrobenzaldehyde, 0.5 g. (0.0033 mole), were dissolved in 50 ml. of dry benzene. One drop of 85% phosphoric acid was added and the benzene-water azeotrope was slowly distilled out; from time to time dry benzene was added to maintain the volume between 15 and 50 ml. The distillation was conducted for 16 hr. during which time 85 ml. of benzene distilled.

The precipitate which formed, even in the hot solution, was isolated by cooling the mixture to room temperature and filtering; 1.14 g. (80% yield), m.p. 204–210°. Recrystal-

(3) Microanalyses by Dr. C. S. Yeh and Mrs. S. Margerum of this department.

lization of 0.26 g. from acetone gave 0.22 g., m.p. 210–211°. A mixed melting point with the acetal obtained from the decomposition of *p*-nitrobenzyl nitrite gave no depression.

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Allylic Chlorides. XXV. The Reaction of 1,1,3-Trichloro-1-propene and 1,1-Dibromo-3-chloro-1-propene with Potassium Iodide in Acetone[1]

LEWIS F. HATCH AND SHIH-HSI CHU

Received January 30, 1958

The preparation and properties of 1,1,3-trichloro-1-propene and 1,1-dibromo-3-chloro-1-propene have been reported recently.[1] It was noted that the reaction of the 1,1-dihalo-3-chloro-1-propenes with potassium iodide, while giving the expected 1,1-dihalo-3-iodo-1-propenes, did not yield kinetic data of value at 20°.

Kinetic data have now been obtained for this reaction with 1,1,3-trichloro-1-propene at 0°, 5°, and 10° (Table I). From these data the energy of activation for the reaction was calculated by use of the Arrhenius equation to be 12 kcal./mole. The straight line relationship between ln k and 1/T indicated that k at 20° would be *ca.* 49. This figure represents a relative reactivity for 1,1,3-trichloro-1-propene of *ca.* 98 (allyl chloride as 1.00 with k = 0.502). When both 1,1-substituents are CH_3- the relative reactivity is 28.[2]

TABLE I

REACTION OF 1,1,3-TRICHLORO-1-PROPENE WITH POTASSIUM IODIDE IN ACETONE

Temperature	Time, hr.	% Reacted	k, hr.$^{-1}$ mole^{-1} l.	Average
0.0°	0.50	59.2	9.64	
	0.63	67.2	9.56	
	0.78	74.0	9.50	
	0.87	76.8	9.36	
	1.08	82.7	9.07	9.42 ± 0.17
5.0°	0.25	51.5	15.6	
	0.37	65.2	15.6	
	0.47	73.3	15.4	
	0.57	79.1	15.3	
	0.62	80.9	14.8	15.3 ± 0.2
10.0°	0.16	48.5	21.3	
	0.28	67.1	21.3	
	0.35	74.2	21.5	
	0.44	81.4	21.3	
	0.50	83.8	20.4	21.2 ± 0.2

An attempt was made to obtain similar data for 1,1-dibromo-3-chloro-1-propene but the reaction was too fast at −10° to give acceptable kinetic data. Three points were obtained which gave an average k value of 151 ± 3.

The marked increase in reactivity in going from chlorine to bromine in the number 1 position has been noted previously[3] and ascribed to steric effects related to the size of the bromine atom. Apparently steric, inductive, and resonance effects all influence the reactivity of the allylic chlorine atom and this makes it difficult to relate cause and effect.[4]

EXPERIMENTAL

1,1,3-Trichloro-1-propene. 1,1,3-Trichloro-1-propane was prepared from 1,1-dichloro-1-propene by bromination using *N*-bromosuccinimide, hydrolysis of the 3-bromo-1,1-dichloro-1-propene to 3,3-dichloro-2-propen-1-ol and conversion of the alcohol to the trichloride using phosphorus trichloride in dry pyridine in a manner similar to that described previously.[1] B.p. 59° (50 mm.); n_D^{25} 1.4931 [lit.[1] b.p. 59.5° (50 mm.); n_D^{25} 1.4930].

1,1-Dibromo-3-chloro-1-propene. This compound was prepared from 1,1-dibromo-1-propene (0.25 mole) by reaction with *N*-chlorosuccinimide (0.25 mole) at 70° for 8 hr. in the presence of benzoyl peroxide (10 g.), using carbon tetrachloride as the solvent. A 47% yield of 1,1-dibromo-3-chloro-1-propene was obtained and it had the following physical constants: b.p. 37–38° (1.0 mm.); n_D^{25} 1.5620 [lit.[1] b.p. 35.5–36° (0.6 mm.); n_D^{25} 1.5634].

Reaction of 1,1,3-trichloro-1-propene with potassium iodide in acetone at 0°, 5° and 10°. The procedure used was similar to that described previously.[5] With the usual modified second-order rate equation, the plot of log 5-Z/(5)(1-Z) *vs.* time where Z is the fraction of potassium iodide having reacted in time t, gave a straight line between *ca.* 50 and 80% reacted at 0°, 5° and 10°. The rates at 0° and 5° showed some drift. The data are presented in Table I.

Reaction of 1,1-dibromo-3-chloro-1-propene with potassium iodide in acetone at −10°. Experimental difficulties prevented the obtaining of reliable kinetic data for this reaction. The following data are approximate.

Time, hr.	0.067	0.083	0.100
Reacted, %	85.	88.	93.
k, hr.$^{-1}$ mole^{-1} l.	159	146	149
Av. k		151 ± 3	

It is assumed that the vinyl bromine atoms have not reacted.[3]

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(2) L. F. Hatch and L. S. Gerhardt, *J. Am. Chem. Soc.*, **71**, 1679 (1949).

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(5) L. F. Hatch, L. B. Gordon, and J. J. Russ, *J. Am. Chem. Soc.*, **70**, 1093 (1948).

Solvolysis of Diarylcarbinyl Chlorides

J. Packer, J. Vaughan and A. F. Wilson

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In connection with studies on naphthalene reactivity, we were following the solvolysis of naphthylphenylcarbinyl chlorides at the time of publication of the important work of Brown and Okamoto[1,2] on σ^+ values. It then seemed logical to expand our solvolytic studies to obtain σ^+ figures for comparison with those of Brown and Okamoto.

TABLE I

Solvolysis of $ArCH(C_6H_5)Cl$

R	$k \times 10^5$ (sec.$^{-1}$) 5°	10°	15°	25°	35°	45°	55°	65°	75°
1-Naphthyl	4.06	7.83	15.2	49.6					
I	4.10	8.11	15.2	47.6					
	4.01	8.17		48.8					
				49.1					
2-Naphthyl	3.24	6.12	12.2	40.6					
II	3.21	6.04	11.6	40.4					
		6.06	11.6	41.4					
		6.15	10.8						
m-Tolyl				13.7					
III				13.7					
Phenyl			1.49	5.45[a]	17.4	51.8			
IV			1.54	5.38	17.8	53.1			
				5.34	18.1	49.4			
						51.3			
m-Bromophenyl				0.131		1.58		14.0	
V								13.9	
m-Chlorophenyl				0.121		1.55		13.1	
VI								12.5	
m-Nitrophenyl				0.0103[b]		0.123	0.366	1.10	2.86
VII						0.118		1.03	2.78

[a] *Cf.* k = 5.30,[4] 4.43.[5] [b] Obtained by extrapolating the Arrhenius plot.

Deno and Evans[3] have recently compared independently determined values for these parameters and the limited data available to them on arylphenylcarbinyl chloride ethanolysis are extended by the results now reported.

Hughes, Ingold, and Taher[4] followed the ethanolysis of certain phenyl-*p*-alkylphenylcarbinyl chlorides at 25°. Norris and co-workers[5,6] also reported rate data for a number of compounds, but they included only two *meta* substituents, and to obtain an accurate ρ value without resorting to Brown's σ^+ values, more *meta*-substituted compounds were required for study.

(1) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, 79, 1913 (1957).

(2) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, 22, 485 (1957).

(3) N. C. Deno and W. L. Evans, *J. Am. Chem. Soc.*, 79, 5804 (1957).

(4) E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 949 (1940).

(5) J. F. Norris and C. Banta, *J. Am. Chem. Soc.*, 50, 1804 (1928).

(6) J. F. Norris and J. T. Blake, *J. Am. Chem. Soc.*, 50, 1808 (1928).

EXPERIMENTAL

Of the carbinyl chlorides listed in Table I, compounds I, II, III, and IV were prepared by the action of dry hydrogen chloride on the parent carbinols. In preparing the less reactive carbinyl chlorides V, VI, and VII, thionyl chloride replaced hydrogen chloride. All the parent carbinols were prepared by one of two standard methods depending on the commercial availability of the appropriately substituted benzaldehyde or benzoic acid. Carbinols prepared by the action of phenylmagnesium bromide on an aldehyde were obtained in 40–50% yield. Carbinols prepared from the relevant acid *via* a substituted benzophenone were obtained in overall yields of 55–65%. Reduction of phenyl *m*-nitrobenzophenone was effected by a Meerwein-Poundorf-Verley reduction, as compared with the zinc/alkali method adopted in other cases. Data on the carbinyl chlorides, together with analyses where appropriate, are as follows:

I, m.p. 58°.

II, m.p. 74.8°.

III, b.p. 119°/1 mm.; n_D^{20} 1.5958.

Anal. Calcd. for $C_{14}H_{13}Cl$: C, 77.59; H, 6.05; Cl, 16.36. Found: C, 77.78; H, 6.00; Cl, 16.37.

IV, b.p. 134°/4 mm.

V, b.p. 133°/1 mm.; n_D^{20} 1.6180.

Anal. Calcd. for $C_{13}H_{10}BrCl$: C, 55.45; H, 3.58; Br, 28.38; Cl, 12.59. Found: C, 55.70; H, 3.50; Br, 27.95; Cl, 12.39.

VI, b.p. 126°/1 mm.

VII, b.p. 152°/1 mm.; n_D^{20} 1.6112.

Anal. Calcd. for $C_{13}H_{10}O_2NCl$: C, 63.04; H, 4.07; N, 5.66; Cl, 14.32. Found: C, 63.14; H, 3.94; N, 5.50; Cl, 14.27.

Phenyl *m*-nitrophenylcarbinol melted at 65.5°.

Anal. Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.3±; H, 4.62; N, 6.20.

The titration method of the earlier workers was adopted in following the solvolyses in ethanol.

Results. First-order rate constants and derived Arrhenius data are given in Tables I and II. Unimolecular solvolysis was checked by ethoxide additions, which were accompanied by unchanged reaction rates except with higher concentrations approaching that of the carbinyl chloride (*ca.* 0.01*M*).

Rate increases in the latter instances were probably the result of appreciable increases in ionizing power of the solvent, to which the S_N1 reaction is very sensitive.

TABLE II

ARRHENIUS PARAMETERS AND DERIVED DATA

Compound	E_a kcal. mole^{-1} (±0.20)	$\log_{10} A$ (±0.1)	$\Delta\Delta H^+$ kcal. mole^{-1}	$T\Delta\Delta S^+_{25°}$ kcal. mole^{-1}
I	20.45	11.67	−1.01	0.30
II	21.04	12.01	−0.43	0.76
IV	21.47	11.45	(0.00)	(0.00)
V	23.38	11.24	1.91	−0.29
VI	23.32	11.17	1.85	−0.38
VII	23.20	10.00	1.73	−1.97

In calculating ρ for the reaction, only *meta* substituent data were used and the linear plot of $\log_{10} k_{25°}$ *versus* σ was fully satisfactory. Relevant information on the plot is given by the figures: $\rho = -4.030$; r = 0.996; s = 0.14; n = 5, where the symbols have their standard significance.[7]

Where comparison is possible, the rate constants of Hughes, Ingold, and Taher are consistently higher than those of Norris by a reasonably constant difference which has been commented upon by the first-named group. The value now reported for diphenylcarbinyl chloride agrees closely with that of Hughes *et al.* and a "correction" factor has been applied to the results of Norris to make them comparable with the data of Hughes and of the present work. Results then lead to the figures in Table III.

TABLE III

σ^+ PARAMETERS

Substituent	$k_{25°} \times 10^5$ (sec.$^{-1}$)	σ^+ (Present Work)	σ^+ (Okamoto & Brown)
m-NO_2	0.0103[a]		
m-Cl	0.124[a]		
m-Br	0.132[a]		
m-CH_3	13.7[a]		
H	5.41[a]		
3:4-C_6H_4	40.3[a]	−0.207	−0.132
p-CH_3	123.0[b]	−0.327	−0.306
p-C_2H_5	120.0[b]	−0.324	−0.291
p-iso-C_3H_7	106.0[b]	−0.311	−0.276
p-tert-C_4H_9	98.7[b]	−0.303	−0.250
p-Cl	1.48[c]	−0.158	−0.112
p-Br	1.23[c]	−0.179	−0.148
p-OC_6H_5	1170.0[c]	−0.555	−0.63[d]
p-C_6H_5	50.2[c]	−0.218	−0.12[d]

[a] Present work. [b] Ref. 4. [c] Refs. 5 and 6. [d] See ref. 3.

Agreement between the last two columns is seen to be good. The effect of the 3:4 C_6H_5 substituent in a number of reactions is currently being reviewed by us and comment on this substituent is at present withheld.

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(7) H. H. Jaffé, *Chem. Revs.*, 53, 191 (1953).

Reactions of Some Organochlorosilanes in Acetone

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Received February 4, 1958

The author wishes to report on the conversion of some organochlorosilanes to siloxanes in acetone. When solutions of organochlorosilanes in acetone are allowed to stand at room temperature for extended periods, conversion to organopolysiloxanes occurs, all of the silicon-chlorine bonds being replaced by silicon-oxygen bonds.

EXPERIMENTAL

Reagents and general procedure. Silicon tetrachloride (hereafter called STC), methyltrichlorosilane (MTS), dimethyldichlorosilane (DDS), diphenyldichlorosilane (DPDS) provided in purified grades by the Shin-etsu Chemical Industrial Company were used. Acetone was purified according to the ordinary method; titration with Karl Fischer reagent showed 0.2% (mean) water content. Each solution of the chlorosilane in acetone was enclosed in a Pyrex glass tube of 2 cm. in diameter and 15 cm. in length and allowed to stand at room temperature. After several days, the solution developed a yellowish color which became dark gradually. Ultimately it turned dark red, nearly black, and at the same time the corresponding polysiloxane was formed. The time required for these changes, and the character of polysiloxane finally formed, varied with the concentration and with the chemical identity of the chlorosilane used, but much more with the water content of acetone used. For example, the addition of a small amount of water (or methanol) to the initial mixture promoted the coloration and the formation of polysiloxanes remarkably.

The reactions of individual silanes in acetone thus observed are described below.

STC, MTS. Each of them shows an entirely similar reaction in acetone; solutions in acetone finally form dark red gels. Especially when the solution consists of 1 mole of silane and 3–5 moles of acetone, the whole mixture solidifies, transforming into a dark red, brittle gel. The reaction takes a period of 3 or 4 weeks. In a previous publication,[1] this red gel was described as an addition compound of STC and acetone, but no information about its structure or composition was given.

The author now concludes that these red gels are polysiloxane $(SiO_2)_n$ and methylpolysiloxane $(CH_3SiO_{1.5})_n$, respectively. For evidence, the gel was decolorized gradually on being extracted with fresh acetone, ultimately turned to white and translucent, while acetone acquired a deep red color and emitted a characteristic terpene-like odor. The X-ray powder pattern for white gels showed broad halos

(1) W. R. Trost, *Nature*, 169, 289 (1952).

at 3.90 Å (for gel from STC), at 4.09 Å (for gel from MTS) respectively, in good agreement with those of two polysiloxanes prepared by direct hydrolysis of STC and of MTS.

Anal. For STC gel (Calcd. for $n SiO_2$: Si, 46.75; Found: Si, 46.54), for MTS gel (Calcd. for $n CH_3SiO_{1.5}$: Si, 41.85; Found: Si, 41.57). No chlorine was detected by an argentometric titration carried out after ignition with sodium peroxide.

On shaking the red acetone with 5% sodium hydroxide solution, a deep red oily layer was separated at the top, from which mesityl oxide (b.p. 131°/760 mm., d_D^{25} 0.8535) was isolated; the distillation residue was a tar-like, black material from which no pure substances were isolated hitherto. It is considered to be a high order condensation product of acetone.

DDS. From DDS solution in acetone, when it contained not less than 5 moles of acetone per 1 mole of DDS, a colorless transparent oily layer separated at the bottom after standing for about 2 weeks. Fractional distillation under atmospheric pressure showed that it consisted of hexamethylcyclotrisiloxane (b.p. 134°/760 mm.), octamethylcyclotetrasiloxane (b.p. 175°/760 mm., n_D^{25} 1.3966) as the main products, and of higher polymers of dimethylsiloxane. The polymer fraction was very difficult to purify, because it gave no distillate below 200° under 2 mm. and its molecular weight changed (measured cryoscopically in benzene) on heating.

DPDS. From DPDS solution in acetone, hexaphenylcyclotrisiloxane (hereafter called trimer) crystallized upon standing. From a solution of suitable composition (*e.g.* DPDS, 8 g.; acetone, 25 g.; chloroform, 5 g.), trimer was obtained as large hexagonal plates of 5–10 mm. in width. Thorough investigations[2] on the relation between mixing ratio and yield of trimer, have been made recently in this laboratory. Properties of trimer produced here are as follows: m.p. 189°, d_4^{25} 1.23, mol. wt. 579–609 (in benzene).

Anal. Calcd. for $C_{36}H_{30}Si_3O_3$: Si, 14.16; C, 72.68; H, 5.09. Found: Si, 14.06; C, 72.77; H, 4.83.

The X-ray powder pattern data are in complete agreement with those given by Hyde[3] as type I_3 (trimer in orthorhombic system).

When non-purified acetone was used, the trimer was obtained much sooner (2 or 3 days after mixing, with the yield of 80% max.). These results would suggest that this "acetone method" is a convenient method for preparation of the trimer which is usually synthesized after the method of Burkhard.[4]

Reaction of other ketones. The author confirmed the statement by Rochow and Gingold[5] that acetophenone did not react with any of the chlorosilanes. Methyl ethyl ketone was found to react with chlorosilanes used here in just the same manner of acetone, except that the siloxane formation was far slower and the color developed was a dark somewhat greenish red.

Acknowledgment. The helpful discussions with Dr. F. Hirata, in whose laboratory this work was carried out, and the generous supply of silanes by the Shin-etsu Chemical Industrial Company are greatly appreciated.

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(2) T. Takiguchi, *J. Chem. Soc. Japan* (*Ind. Chem. Sect.*), **61**, 478 (1958).

(3) J. F. Hyde, L. K. Frevel, H. S. Nutting, P. S. Petrie, and M. A. Purcell, *J. Am. Chem. Soc.*, **69**, 488 (1947).

(4) C. A. Burkhard, *J. Am. Chem. Soc.*, **67**, 2173 (1945).

(5) E. G. Rochow, K. Gingold, *J. Am. Chem. Soc.*, **76**, 4852 (1954).

Dicyclopropylmercury and Divinylmercury

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In the course of an investigation of the electrophilic cleavage of dialkylmercury compounds, two new mercury compounds, dicyclopropyl- and divinyl-mercury, were prepared in good yield by the action of mercuric chloride on the corresponding Grignard reagent in tetrahydrofuran.

It might be expected that since dialkylmercury compounds in general, with the exception of dimethylmercury, decompose on standing to give hydrocarbons and metallic mercury,[2] these compounds would exhibit considerable instability. However, dicyclopropylmercury stood for several weeks at room temperature exposed to sunlight without giving noticeable evidence of decomposition, while during the same period of time di-*n*-propylmercury showed considerable decomposition. Divinylmercury can be stored in the cold for several weeks without apparent decomposition, although over the same period of time at room temperature some deposition of mercury is detectable. It should be noted that although no previous preparation of divinylmercury has been reported, a series of substituted vinylmercury compounds were prepared and studied by Nesmeyanov and co-workers,[3] and the vinylmercuric halides were recently prepared by reaction of tetravinyltin with the corresponding mercuric halides.[4]

The identities of the two compounds were established by their infrared spectra and carbon-hydrogen analysis. The spectrum of dicyclopropylmercury resembles that of cyclopropyl bromide[5] with strong absorptions at 809, 880, 1030, and 2990 cm.$^{-1}$. The spectrum of divinylmercury shows four strong absorptions at 938, 1010, 1250, and 2980 cm.$^{-1}$, and two medium adsorptions at 1400 and 3040 cm.$^{-1}$. The absorption peaks at 2980 and 3040 cm.$^{-1}$ are attributed to CH stretching vibrations, those at 938 and 1010 cm.$^{-1}$ to CH_2 and CH out-of-plane deformation vibrations, and that at 1400 cm.$^{-1}$ to a CH_2 in-plane deformation vibration. The medium absorption peak at 1250 cm.$^{-1}$ is unaccounted for and appears also in the spectrum of dicyclopropylmercury.

This method of preparing the dialkylmercuries involving the addition of a tetrahydrofuran solution of mercuric chloride to a tetrahydrofuran solu-

(1) Fulbright Fellow, University of Paris, France (1956–57).

(2) Rochow, Hurd, and Lewis, *The Chemistry of Organometallic Compounds*, John H. Wiley and Sons, Inc., New York, 1957, p. 117.

(3) A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **I**, 158 (1957).

(4) D. Seyferth, *J. Org. Chem.*, **22**, 478 (1957).

(5) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951).

tion of the Grignard reagent is a general one, and seems to be much superior to their preparation in ether. Mercuric chloride is but slightly soluble in ether and is inclined to cake in the reaction mixture,[6] while 100 g. of mercuric chloride can readily be dissolved in 100 ml. of tetrahydrofuran. Furthermore, prolonged periods of heating to obtain satisfactory yields[7] are no longer necessary. In several attempts to prepare di-*n*-propylmercury in good yield in ether after the improved method of Gilman and Brown,[8] the highest yield obtained was 57%. Marvel and Gould[6] report a 51% yield of this compound in ether solution. A single trial using tetrahydrofuran gave a 75% yield of the di-*n*-propylmercury.

EXPERIMENTAL

All reactions were carried out under an atmosphere of dry nitrogen. The tetrahydrofuran employed was predried over sodium hydroxide pellets and distilled from sodium wire.

Dicyclopropylmercury. Cyclopropylmagnesium bromide was prepared in tetrahydrofuran from magnesium turnings and cyclopropyl bromide, which was made according to the method of Roberts and Chambers.[9] To 4.6 g. (0.19 mole) of magnesium in a 250 ml. 3-necked flask equipped with stirrer, water-cooled condenser, thermometer, and dropping funnel was added just enough tetrahydrofuran to cover the surface of the magnesium and approximately 3 ml. of cyclopropyl bromide. Reaction was thoroughly initiated by heating the solution to reflux for several minutes. The remaining 0.19 mole of cyclopropyl bromide, dissolved in 100 ml. of tetrahydrofuran, was added over a period of 1 hr. with the temperature of the reaction being held at 15–20° with an ice water bath to prevent coupling. Reaction was completed by heating the solution to between 50–60° for 1 hr.

To this Grignard solution was added dropwise with stirring a solution of 20.6 g. of mercuric chloride (80% of theory) in 50 ml. of tetrahydrofuran. After the addition was completed the solution was gently refluxed overnight. At the end of this time the solution was cooled and hydrolyzed with 50 ml. of water. Stirring was continued during the entire heating and hydrolysis. The liquid was separated from the pasty precipitate by suction filtration, the organic layer extracted with ether, washed with several portions of water, and dried over anhydrous magnesium sulfate. After preliminary stripping off of the organic solvent at atmospheric pressure using a water bath, the remaining liquid was transferred to a small distillation flask and vacuum distilled. 13.7 g. of dicyclopropylmercury was obtained (64% of theory), b.p. 110–112° at 18 mm.

Anal. Calcd. for $C_6H_{10}Hg$: C, 25.49; H, 3.57. Found: C, 25.56; H, 3.72.

Divinylmercury. Vinylmagnesium bromide was prepared from 30.4 g. (1.25 mole) of magnesium turnings and excess vinyl bromide in 500 ml. of tetrahydrofuran according to the method of Normant.[10] To the Grignard solution in a 2-l. flask equipped as previously described was added dropwise a solution of 136 g. of mercuric chloride (80% of theory) in 200 ml. of tetrahydrofuran. Addition was accomplished over a period of 1 hr. with stirring at a temperature of about 60°. After completion of addition the solution was heated for 1 hr. with stirring at 60° with an infrared lamp. The solution was then allowed to cool, and the remaining Grignard decomposed by hydrolysis with 250 ml. of water. Work-up proceeded as before with the exception that the organic solvent was separated from the rather volatile divinylmercury by use of a Rinco Rotary Evaporator. Using a water aspirator and a water bath at 30° the solvent came off at about 20 mm. The evaporation was discontinued when the pressure fell abruptly to 12–14 mm. The remaining liquid was distilled under vacuum through a 10 cm. Vigreux column by use of a water bath. 76.8 g. of divinylmercury (60% of theory) was obtained, b.p. 48–50° at 14 mm.

Anal. Calcd. for C_4H_6Hg: C, 18.86; H, 2.38. Found: C, 18.81; H, 2.58.

Because of its volatility, divinylmercury should be handled with extreme care in a good hood, as the dangerous toxicity of organomercury compounds is well known.[11] Divinylmercury readily decolorizes potassium permanganate solution while dicyclopropylmercury does not.

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(6) C. S. Marvel and V. L. Gould, *J. Am. Chem. Soc.*, **44**, 153 (1922).

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(10) H. Normant, *Bull. soc. chim. France*, 728 (1957).

(11) Sax, *Handbook of Dangerous Materials*, Reinhold Publishing Corp., 1951, p. 236.

Use of Chlorides in the Preparation of Organic Sulfides

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The reaction of alkyl bromides or iodides with sodium sulfide to give organic sulfides is well known.[2] Alkyl chlorides, though frequently more readily available than the bromides or iodides, are seldom employed.

Our research activities required a sample of bis-(2-ethylhexyl) sulfide. Since this material does not appear to be listed in the literature, we sought a method of preparation, preferably one suitable for scaling up, and which utilized commercially available intermediates. Since 2-ethylhxeyl bromide and iodide were not readily available, the usual method of allowing an alkyl bromide or iodide to react with sodium sulfide in aqueous or alcoholic solution was not applicable.[3] The reaction of 2-ethylhexyl

(1) Present address: Ethyl Corp., Baton Rouge, La.

(2) See (*a*) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951); and (*b*) R. W. Bost and M. W. Conn, *Org. Syntheses*, **Coll. Vol. II**, 547 (1943).

chloride with sodium sulfide was inviting if suitable conditions could be found for causing it to take place. As expected, this reaction was very slow in aqueous or alcoholic solution. The use of ethylene glycol as a solvent gave a much more satisfactory procedure (see Experimental). The yield of bis-(2-ethylhexyl) sulfide from such a run was 76%.

As a further check on the usefulness of ethylene glycol as a solvent in the reaction of an organic chloride with sodium sulfide, a run was carried out employing 1,4-dichlorobutane. This reaction proceeded smoothly giving a 67% yield of tetramethylene sulfide.

Though our examples illustrating the usefulness of ethylene glycol as a solvent in the preparation of organic sulfides are limited, it appears likely that the method is of general applicability. Since we do not plan further investigation along this line, we feel it is desirable that we report our results for those who may find the method of interest.

EXPERIMENTAL

The starting materials were obtained from commercial sources and were used without purification. Boiling points are uncorrected. Fractionations were carried out through an 80-cm. Podbielniak-type column similar to that described by Cason and Rapoport.[4]

Bis(2-ethylhexyl) sulfide. A two-phase mixture of 74.3 g. (0.5 mole) of 2-ethylhexyl chloride, 60 g. (0.25 mole) of sodium sulfide nonahydrate, and 200 ml. of ethylene glycol was maintained at the boiling point (about 135°) under reflux for 24 hr. The course of the reaction was followed by removing a small sample of the upper phase from time to time to time and checking its refractive index. This property showed a moderately rapid increase during the early stages but had essentially ceased changing at the end of the heating period. At this point the upper layer was separated, washed twice with water, and dried over calcium chloride. Fractionation gave a forerun of about 10 g. of 2-ethylhexyl chloride, followed by 49 g. (76%) of nearly colorless product at 178–179° (23 mm.), n_D^{25} 1.4622.[5]

Anal. Calcd. for $C_{16}H_{34}S$: C, 74.34, H, 13.26, S, 12.40. Found: C, 74.46, H, 13.09, S, 12.24.

On a similar run to that described above, except that 200 ml. of ethanol was used in the place of the ethylene glycol, it was observed that the ethanol remained primarily in the upper phase with the alkyl chloride at the start of the reaction. As the reaction proceeded (reflux temperature, about 80°), the lower phase increased in volume and salts separated out, giving some tendency to bump. After a 24-hr. reflux period the reaction was worked up essentially as described above. Fractionation gave a forerun followed by 46 g. (71%) of bis(2-ethylhexyl) sulfide at 162–163° (12 mm.).

Tetramethylene sulfide. A mixture of 127 g. (1 mole) of 1,4-dichlorobutane and 240 g. (1 mole) of sodium sulfide nonahydrate was heated under reflux for 7 hr. The refractive index of the upper layer increased from n_D^{20} 1.4552 to n_D^{20} 1.4560 during this time, indicating very little reaction. At this point, 100 ml. of ethylene glycol was added and heating was continued for 16 hr. The refractive index of the upper layer (which was unchanged by the addition of the ethylene glycol since this component went into the lower phase) increased rapidly during this time to a final value of n_D^{20} 1.5038. At this point the upper layer was separated, washed twice with 20% sodium chloride solution, and dried over calcium chloride. Fractionation gave a yield of 59 g. (67%) of tetramethylene sulfide at 120–121°, n_D^{20} 1.5043 (lit.,[6] b.p. 121.2°, n_D^{20} 1.5047).

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(3) Since 2-ethylhexanol is commercially available, the method of preparation of sulfides utilized by F. Drahowzal and D. Klamann [*Monatsh.*, **82**, 970 (1951)] involving the reaction of an alkyl-4-toluenesulfonate with sodium sulfide was seriously considered. However, this would have involved the preparation of 2-ethylhexyl-4-toluenesulfonate as an intermediate, and was abandoned in favor of the direct reaction of the alkyl chloride with sodium sulfide.

(4) J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1950, p. 238.

(5) On one run similar to that described here, except that no ethylene glycol was added, many hours of refluxing gave very little reaction. Fractionation of the top phase gave a recovery of 75% of the 2-ethylhexyl chloride and revealed no significant amount of the desired sulfide. A small forerun was not identified. When ethylene glycol was added to the run described above, it dissolved essentially completely in the sodium sulfide nonahydrate phase, giving a higher reflux temperature and possibly increasing the amount of alkyl chloride which dissolved in this phase.

(6) E. V. Whitehead, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3632 (1951) made use of the dibromide in the preparation of this compound.

The Polymerization and Cyclization of Allyldimethylsilane

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Mironov and Petrov have recently described[1] the synthesis and polymerization of certain silanes containing an unsaturated organic group and hydrogen joined to the same silicon atom. They reported, however, that they were unable to cause the polymerization of allyldimethylsilane under their experimental conditions (refluxing in the presence of 15% platinized carbon). We wish to report that we have successfully polymerized this monomer as well as effected the formation of a cyclic dimer from it.

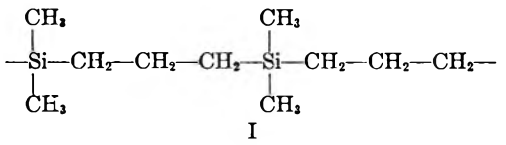
Allyldimethylsilane was synthesized under high dilution conditions by a Grignard reaction, starting from dimethylchlorosilane, allyl bromide, and magnesium. The resulting monomer was heated under reflux, in the absence of solvent, with a 0.06% platinum-on-carbon catalyst.[2] Polymerization proceeded smoothly to yield a colorless, moderately viscous liquid, similar in appearance to the di-

(1) V. F. Mironov and A. D. Petrov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 383 (1957).

(2) G. H. Wagner (to Union Carbide and Carbon Corp.), U. S. Patent 2,637,738, May 5, 1953.

methylvinyl- and diethylvinyl- silane polymers described earlier.[3] In contrast with the previous results, the concurrent formation of a cyclic dimer was not observed.

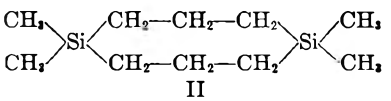
The structure of the new polymer was established by means of nuclear magnetic resonance spectral analysis, which showed that the silicon atoms in the main chain are joined through trimethylene bridges (I). In the NMR spectrum there was found a low,



I

broad pattern of five lines caused by spin-spin coupling of the protons of the central methylene group in each bridge with the four protons of the two adjacent methylene groups. At slightly higher field there was also observed another resonance peak, which was attributed to methylene attached to silicon, and which was split into a triplet because of coupling with the protons of the central methylene group.

Since ring formation was not found to occur in the first experiment, a second reaction was conducted in the presence of toluene as a solvent in an effort to promote cyclization. Allyldimethylsilane polymer was formed as before, but in addition, a small amount of a crystalline material was isolated from the reaction mixture. The solid was identified as a cyclic dimer of allyldimethylsilane on the basis of elemental analysis, molecular weight determination, and a negative test for the Si-H function. The final proof of structure was by NMR analysis and was based on the same reasoning as that applied to the polymer, because it involved showing that the ring silicon atoms are connected through trimethylene bridges. The cyclic compound is therefore 1,1,5,5-tetramethyl-1,5-disilacyclo-octane (II), and



II

as such it represents the first reported example of the 1,5-disilacyclo-octane ring system.

EXPERIMENTAL[4-6]

Allyldimethylsilane. A stirred slurry of 387.7 g. (15.95 gram atoms) of 70–80 mesh magnesium in 1250 ml. of dry ether was heated under vigorous reflux, while a mixture of 322.0 g. (2.66 moles) of allyl bromide and 251.7 g. (2.66 moles) of dimethylchlorosilane containing a trace of iodine was added dropwise through a high dilution apparatus.[7] The addition required 57 hr., following which the reaction mixture was stirred for an additional 15 hr. without external heating. An argon atmosphere was maintained throughout. The solid magnesium salts were removed by filtration and washed on the funnel with ether. The combined filtrate and ether washings were washed neutral with five 100-ml. portions of water, then dried over anhydrous sodium sulfate. Following the removal of solvent, the liquid residue was fractionated at atmospheric pressure to afford allyldimethylsilane, b.p. 69–70° (750 mm.), n_D^{25} 1.4042, yield 128.1 g. (48.0%). An analytical sample exhibited the following properties: b.p. 69.1° (750 mm.), n_D^{25} 1.4029, d_4^{25} 0.7046 (reported[1] b.p. 69° (755 mm.), n_D^{20} 1.4075, d_4^{20} 0.7086).

Anal. Calcd. for $C_5H_{12}Si$: C, 59.91; H, 12.07; MR_D, 34.63. Found: C, 59.88; H, 12.10; MR_D, 34.71.

Polymerization of allyldimethylsilane. A mixture of 21.6 g. (0.216 mole) of allyldimethylsilane and 0.22 g. of a 0.06% platinum-on-carbon catalyst was heated under reflux for 31 hr., during which time the reaction temperature rose from 67 to 153.5°. The polymer mass was allowed to cool to room temperature, ether was added, and the catalyst was removed by filtration. Following the removal of solvent from the combined filtrate and ether washings, the liquid residue was heated to 200° (20.5 mm.), then to 175° (0.28–0.32 mm.), but no volatile materials of any kind could be obtained. The cooled residue was filtered twice to effect clarification. The allyldimethylsilane polymer so obtained was a clear, colorless, moderately viscous liquid, n_D^{25} 1.4712, d_4^{25} 0.8549, yield 19.8 g. (91.7%).

Anal. Calcd. for $(C_5H_{12}Si)_x$: C, 59.91; H, 12.07; R_D, 0.3270. Found: C, 59.73; H, 11.87; mol. wt. (cryoscopic, in benzene), 1300; R_D, 0.3271.

Polymerization and cyclization of allyldimethylsilane. To 20.0 g. (0.200 mole) of allyldimethylsilane was added 0.20 g. of the Wagner platinum-on-carbon catalyst and 300 ml. of toluene. The mixture was heated under reflux for 72 hr., following which it was allowed to cool to room temperature, filtered to remove catalyst, then distilled to remove solvent. The solid and liquid components of the cooled distillation residue were separated by filtration. The filtrate consisted of clear, colorless, allyldimethylsilane polymer, n_D^{25} 1.4758, yield 15.6 g. (78.0%).

Anal. Found: Mol. wt. (cryoscopic, in benzene), 1160.

The solid substance remaining on the funnel was recrystallized repeatedly from ethanol to afford partially purified 1,1,5,5-tetramethyl-1,5-disilacyclo-octane (white needles), yield 0.6 g. (3.0%). An analytical sample, obtained by vacuum sublimation, exhibited m.p. 109.5–110.5° and gave a negative test for Si-H with ethanolic sodium ethoxide.

Anal. Calcd. for $C_{10}H_{24}Si_2$: C, 59.91; H, 12.07; mol. wt., 200. Found: C, 59.90; H, 11.90; mol. wt. (Rast), 220.

Nuclear magnetic resonance spectra. The nuclear magnetic resonance spectra were determined using the Varian Associates High Resolution Spectrometer (V-4300B), operated at 40 mc. and 9394.7 gauss.

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(3) J. W. Curry, *J. Am. Chem. Soc.*, 78, 1686 (1956).

(4) Elemental analyses were performed by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif.

(5) Boiling and melting points are uncorrected.

(6) Calculated molar and specific refractivities were computed from bond refractivity values listed in the following references: A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *Chem. & Ind. (London)*, 358 (1950), and A. I. Vogel, W. T. Cresswell, and J. Leicester, *J. Phys. Chem.*, 58, 174 (1954).

(7) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, 74, 1704 (1952).

A Novel Preparation of Isonitriles[1]

W. R. Hertler and E. J. Corey

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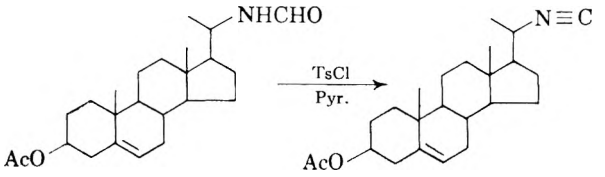
In connection with other studies it was found that a formamide which was treated with *p*-toluenesulfonyl chloride and pyridine was dehydrated to an isonitrile according to the equation

$$R{-}NHC{=}O + 2C_5H_5N + ArSO_2Cl \longrightarrow R{-}N{\equiv}C + 2C_5H_5N\overset{+}{H} + ArSO_3^- + Cl^-$$

The reaction appears to be quite general as is indicated by three diverse examples described herein from the aliphatic, alicyclic, and aromatic series. The practicality of the new method is obvious both from the ready availability of the required formamides and the simplicity of the procedure involved (see Experimental). The previously known general routes to isocyanides[2] involve (1) reaction of silver cyanide with alkyl halides and (2) reaction of primary amines with chloroform and alkali. It had previously been observed that pyrolysis of formamides gives trace amounts of isonitriles.[3]

When *N*-formyl-*p*-xylidine was treated with excess *p*-toluenesulfonyl chloride in pyridine a green color developed, and a 50% yield of 2,5-dimethylbenzoisonitrile was obtained after distillation. Similarly, 3β-acetoxy-20α-formamidopregnene-5 was converted to 3β-acetoxy-20α-isocyanopregnene-5 in 84% yield. The alicyclic formamide, 3α-formamidocholestane, was likewise dehydrated to 3β-isocyanocholestane in 93% yield.



The infrared absorption spectra of each of these isonitriles displayed a characteristic strong band at 2120–2140 cm.$^{-1}$

EXPERIMENTAL[4]

2,5-Dimethylbenzoisonitrile. *N*-Formyl-*p*-xylidine (7.46 g., 0.05 mole) and 13.3 g. (0.07 mole) of *p*-toluenesulfonyl chloride were dissolved in 40 ml. of pyridine, and the resulting orange-red solution was allowed to stand at room temperature. After one hour the solution had become green, and after 1.5 hr. the solution was cooled and treated with chipped ice and then poured into ice water. The product was extracted with ether, and the ethereal solution was washed three times with cold water and then dried over sodium sulfate. Most of the solvent was removed at atmospheric pressure, and the residue was distilled through a 20-cm. Holzmann column to give 3.305 g. (50%) of 2,5-dimethylbenzoisonitrile, b.p. 87.5–90° at 12 mm. (lit.,[5] b.p. 79–82° at 20 mm., 99° at 32 mm.).

3β-Acetoxy-20α-formamidopregnene-5. Acetoxybisnorcholenic acid (50 g.) was converted to a 3β-acetoxy-20α-aminopregnene-5 acetate by the procedure of Julian,[6] and the crude acetate was refluxed with 130 ml. of formic acid (98–100%) and 110 ml. of acetic anhydride for 5 hr. Then the solution was diluted with ice water and extracted with methylene chloride. The organic layer was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* leaving a tan residue which on crystallization from acetone gave 37.6 g. (75%) white amorphous solid, m.p. 191–195°. Repeated crystallization from acetone gave fine needles, m.p. 191–193°, $[\alpha]_D^{26}$ −66° (chf., c, 2.8).

Anal. Calcd. for $C_{24}H_{37}NO_3$: C, 74.38: H, 9.63. Found: C, 74.32; H, 9.87.

3β-Acetoxy-20α-isocyanopregnene-5. 3β-Acetoxy-20α-formamidopregnene-5 (150 mg., 0.387 mmole.) was dissolved in 2.5 ml. of pyridine, and to this was added 95 mg. (0.5 mmole.) of *p*-toluenesulfonyl chloride. After standing for 1.5 hr. at room temperature the solution was treated with a few chips of ice and poured into ice water. The product was extracted with ether-pentane, washed with water, and dried over sodium sulfate. Evaporation of the solvent gave a white crystalline residue which on crystallization from hexane gave 119.3 mg. (84%) of 3β-acetoxy-20α-isocyanopregnene-5, m.p. 144–151°. Further crystallization from hexane gave prismatic needles, m.p. 149–150°, $[\alpha]_D^{26}$ −48° (chf., c, 1.2).

Anal. Calcd. for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55. Found: C, 78.11; H, 9.62.

3α-Formamidocholestane. The following procedure was used for the preparation of 3α-aminocholestane and was found to give a purer product than the published methods:[7,8] Cholestanyl *p*-toluenesulfonate (11.28 g., 20.8 mmole.) was added in one portion to a stirred slurry of 40 g. of sodium azide in 300 ml. of dry dimethylsulfoxide, and the mixture was heated at 83–84° with stirring for 5.5 hr. The mixture was cooled, poured into ice water, and extracted with ether-pentane. The organic layer was washed three times with water and dried over sodium sulfate. Removal of solvent *in vacuo* gave a sirupy residue which was dissolved in 190 ml. of dry ether, and to this was added 3.6 g. of lithium aluminum hydride. The resulting slurry was stirred at room temperature for 11 hr. and then cautiously treated with water. The precipitate was removed and washed with ether. The combined washings and filtrate were dried over sodium sulfate. Dry hydrogen chloride was passed into the ethereal solution, and the precipitated amine hydrochloride was filtered off and washed thoroughly with ether. The filter cake, which weighed 7 g., was stirred for 0.5 hr. with concentrated ammonium hydroxide and pentane. The pentane layer was separated and dried over sodium sulfate. The solvent was evaporated, and the white crystalline residue was recrystallized from methanol to give 5.263 g. (65%) of 3α-aminocholestane, m.p. 104.5–105.5°, $[\alpha]_D^{26}$ 27° (chf., c, 1.1), (lit., m.p. 87–88°,[7] 89°,[8] $[\alpha]_D$ 27°).[7]

Anal. Calcd. for $C_{27}H_{49}N$: C, 83.65; H, 12.74; N, 3.61. Found: C, 83.59; H, 12.90; N, 3.61.

(1) This investigation was supported by fellowship AF-7544 from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) J. Houben, *Die Methoden der Org. Chem.*, 3rd ed. Georg Thieme, Liepzig, 1941, vol. 4, p. 29.

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(4) All melting points are corrected, and boiling points are uncorrected.

(5) J. Ploquin, *Bull. soc. chim. France*, 901 (1947).

(6) P. L. Julian, E. W. Meyer, and H. C. Printy, *J. Am. Chem. Soc.*, 70, 887 (1948).

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3α-Aminocholestane (2 g., 5.16 mmole.) was refluxed with 15 ml. of formic acid and 10 ml. of acetic anhydride for 12 hr. The solution was cooled, diluted with water, treated with about one half equivalent of 10% sodium hydroxide solution, and extracted with methylene chloride. The methylene chloride solution was washed with water and dried over sodium sulfate. Removal of solvent and crystallization of the residue from acetone gave 1.842 g. (86%) of feathery needles, m.p. 179–181°. Repeated crystallization from acetone gave 3α-formamidocholestane, m.p. 188–189°, $[\alpha]_D^{16}$ 35.6° (chf., c, 2.2).

Anal. Calcd. for $C_{28}H_{49}NO$: C, 80.90; H, 11.88; N, 3.37. Found: C, 81.02; H, 11.82; N, 3.27.

3α-Isocyanocholestane. 3α-Formamidocholestane (500 mg., 1.2 mmole.) was covered with 10 ml. of dry pyridine, and 382 mg. (2 mmole.) *p*-toluenesulfonyl chloride was added. The resulting orange solution was allowed to stand for 1.5 hr. at room temperature, cooled, treated with ice, and poured into ice water. The product was extracted with ether, washed twice with water, and dried over sodium sulfate. Removal of solvent and crystallization of the pink residue from acetone gave 442.6 mg. (93%) of flat needles, m.p. 139–141°. Further crystallization from acetone gave 3α-isocyanocholestane, m.p. 141–143°, $[\alpha]_D^{16}$ 27° (chf., c, 1.6).

Anal. Calcd. for $C_{28}H_{47}N$: C, 84.56; H, 11.91; N, 3.53. Found: C, 84.67; H, 11.89; N, 3.47.

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Action of Primary Aliphatic Amines on 2-Methyl-1,4-α-naphthopyrone

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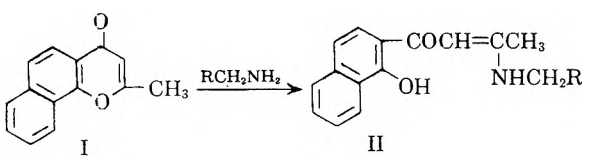
Received February 24, 1958

The action of alcoholic ammonia on 2-methyl-1,4-α-naphthopyrone has been studied by Wittig and Blumenthal.[1] Recently Musante and Stener[2] have studied the action of primary aliphatic amines on the 2-methylchromone derivative Khellin. Both groups of researchers agree that the reaction products are 2-(β-aminocrotonyl)phenols (type II).

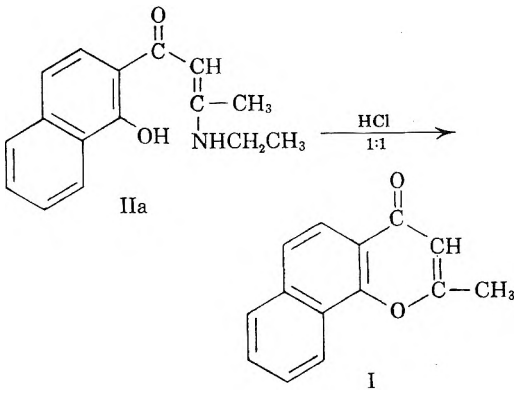
The author has investigated the action of ethylamine, butylamine, and benzylamine on 2-methyl-1,4-α-naphthopyrone(I), and believes that the reaction products are the 2-(β-aminocrotonyl)-1-naphthol derivatives IIa, IIb, and IIc.



I II

a: R = CH_3
b: R = $CH_2CH_2CH_3$
c: R = C_6H_5

The alcoholic solution of these substances gives a green color with alcoholic ferric chloride solution. This fact indicates that they contain a free phenolic hydroxyl group. When IIa was refluxed with dilute hydrochloric acid (1:1), 2-methyl-1,4-α-naphthopyrone (I) was obtained on cooling. The hydrolysis of IIb with aqueous alkali yielded 1-hydroxy-2-naphthoic acid.



EXPERIMENTAL

2-(β-Ethylaminocrotonyl)-1-naphthol IIa. 2-Methyl-1,4-α-naphthopyrone[3] (2 g.) was heated under reflux with two ml. of ethylamine solution in 20 ml. of ethyl alcohol on a steam bath for 3 hr. The deep yellow crystalline solid that precipitated on cooling was filtered off and crystallized from petroleum ether (b.p. 80–100°); m.p. 126°; yield 1.9 g. It has a green fluorescence and is insoluble in aqueous sodium hydroxide solution (10%). It gives a green color with alcoholic ferric chloride solution and a red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5. Found: C, 75.2; H, 6.7; N, 5.4.

2-(β-Butylaminocrotonyl)-1-naphthol IIb was obtained from 2-methyl-1,4-α-naphthopyrone (2 g.) and butylamine (2 ml.). This compound was crystallized from petroleum ether (b.p. 80–100°) as deep yellow crystals with green fluorescence, m.p. 106°; yield 1.8 g. It dissolved in concentrated sulfuric acid with an orange color and was insoluble in cold alkali. Its alcoholic solution gave a color reaction with ferric chloride solution (deep green).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.4; N, 5.0. Found: C, 76.6; H, 7.5; N, 4.8.

2-(β-Benzylaminocrotonyl)-1-naphthol IIc. The same procedure was followed with benzylamine. This compound was crystallized from petroleum ether (b.p. 80–100°), as deep yellow crystals with green fluorescence, m.p. 136°; yield 80%. It gives a red-orange color on treatment with concentrated sulfuric acid and a deep green color with ferric chloride solution.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.5; H, 6.0; N, 4.4. Found: C, 79.6; H, 6.1; N, 4.5.

Action of hydrochloric acid on IIa. Half a gram of IIa was heated under reflux with 25 ml. of dilute hydrochloric acid (1:1) for 0.5 hr. The colorless crystalline solid that separated on cooling was filtered off and proved, by melting point and mixture melting point (178°), and the deep violet color reaction[4] on adding alkali to its solution in dioxane containing *m*-dinitrobenzene, to be 2-methyl-1,4-α-naphthopyrone.

Hydrolysis of IIb *with alkali.* IIb (0.5 g.) and aqueous sodium hydroxide solution (5%, 25 ml.) was heated under reflux for 2 hr. The filtrate was acidified with dilute hydro-

(1) G. Wittig and H. Blumenthal, *Ber.*, **60**, 1085 (1927).
(2) C. Musante and A. Stener, *Gazz. chim. ital.*, **86**, 297 (1956).
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chloric acid. The precipitate was filtered off and identified as 1-hydroxy-2-naphthoic acid (m.p. and mixture m.p. 190°) and the green color with alcoholic ferric chloride solution).

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Synthesis of Some α- and β-(6-Purinylthio)carboxylic Acids

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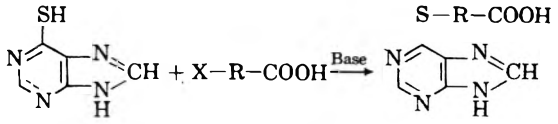
A number of 6-alkyl- and 6-(ω-phenylalkyl)-thiopurines have been found to possess biological activity (in several assay systems) comparable to the corresponding 6-(substituted)aminopurine analogs.[1,2] The unexpected biological activity of the thiopurine derivatives led to the preparation of α-(6-purinylthio)succinic acid[1] as an analog of *N*-(6-purinyl)aspartic acid.[3] Subsequently, the thiosuccinic acid derivative was found to promote growth of etiolated bean leaf disks either in the presence or absence of light.[4] In an effort to extend this latter study, additional purinylthiocarboxylic acid derivatives were prepared and their biological activity on bean leaf expansion will be reported elsewhere.

The desired compounds were synthesized by a condensation of the appropriate α or β-halocarboxylic acid with 6-mercaptopurine under alkaline conditions, using either an equivalent amount of dilute sodium hydroxide or an excess of triethylamine as indicated in Table I. Although the reactants did condense slowly at room temperature in most instances, several of the reactions were carried out in a glass-lined steel bomb heated to about 90°. The sodium hydroxide condensation mixtures, upon acidification, yielded a precipitate which was normally dissolved in alkali and reprecipitated with acid to yield a purified product. In the triethylamine condensation, the reaction mixture was reduced to dryness *in vacuo* in order to remove the excess amine, prior to crystallization.

As in the case of α-(6-purinylthio)succinic acid, the various purinylthiocarboxylic acids indicated in Table I showed little or no response in several biological systems which did respond to 6-alkylthio- and 6-alkylaminopurines. α-(6-Purinylthio)acetic acid at concentration levels as high as 1 mg./ml. did not inhibit hydra tentacle regeneration.[5,6] The purinylthiocarboxylic acids also did not possess either inhibitory or stimulatory effects on a pteridine-inhibited *Lactobacillus arabinosus* at concentration levels up to 40 γ/disk.[7] The presence of a carboxylic acid moiety in the alkyl group of 6-alkylthiopurines appears to cause a loss of biological activity of the compounds in many of these test systems. A decrease in biological activity was also

TABLE I

α- AND β-(6-PURINYLTHIO)CARBOXYLIC ACIDS



Halogen Acid Used	Reaction Conditions	Yield, %	M.p., °C.	Empirical Formula	Analysis N (Calcd.)	Analysis N (Found)
α-Bromoacetic	NaOH, 25°	93[a]	235–260(dec.)	$C_7H_6N_4O_2S$[c]	26.65	26.81
α-Bromopropionic	Triethylamine, 25°	59[a]	199–203	$C_8H_8N_4O_2S$	24.99	24.91
β-Bromopropionic	NaOH, 90°	55[a]	219–220	$C_8H_8N_4O_2S$	24.99	25.01
α-Bromobutyric	Triethylamine, 25°	32[a]	208–209	$C_9H_{10}N_4O_2S$	23.52	23.21
α-Bromovaleric	NaOH, 25°	45[b]	199–205	$C_{10}H_{12}N_4O_2S$	22.21	22.29
α-Bromocaproic	NaOH, 90°	64[b]	178–183	$C_{11}H_{14}N_4O_2S$	21.04	21.06
β-Bromocaproic	Triethylamine, 25°	46[b]	182–184	$C_{11}H_{14}N_4O_2S$[d]	—	—

[a] Recrystallized from water. [b] Recrystallized from ethanol-water. [c] *Anal.* Calcd.: C, 39.99; H, 2.88. Found: C, 40.15; H, 3.25. [d] *Anal.* Calcd.: C, 49.61; H, 5.30. Found: C, 49.33; H, 5.09.

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(3) C. E. Carter and L. H. Cohen, *J. Am. Chem. Soc.*, **77**, 499 (1955).
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observed in the hydra tentacle regeneration assay when a hydrophilic group was present in the alkyl side chain of certain 6-(substituted)aminopurines.[1]

A slight but definite stimulatory effect on the rate of germination was observed when lettuce seed (Early Curled Simpson) were presoaked in 10 γ/ml. solutions of α-(6-purinylthio)butyric acid and the corresponding valeric acid derivative. The butyric acid analog gave approximately a 250% increase in the number of seeds germinating after 72 hours in the dark at 30°, while the valeric acid derivative gave an 80% increase, as compared with seed presoaked in water alone. These values represent only moderate stimulations of seed germination in comparison with the more active 6-(substituted)purines.[2,8,9] It is interesting to note that the most active 6-alkylthiopurines with respect to stimulation of seed germination were those derivatives containing four to six carbon atoms in the substituent group, and correspondingly, the more active purinylthiocarboxylic acids are those which contain groups of similar size.

EXPERIMENTAL[10]

Biological assay techniques. The assay procedures used were the same as those previously reported in the study of similar 6-(substituted)purine compounds for stimulation of lettuce seed germination,[2] inhibition of hydra tentacle regeneration,[5] and microbiological assays.[7]

α- and β-(6-Purinylthio)carboxylic acids. These compounds were prepared by an alkaline-catalyzed condensation between the appropriate haloacid and 6-mercaptopurine, as indicated in Table I, following a procedure which has previously been reported.[1]

An alternate condensation procedure involved using an excess of triethylamine as the condensing agent and allowing the reaction to proceed at room temperature. The course of these reactions was followed by observing the decrease in ultraviolet absorption at 328 mμ and the appearance of an absorption band at 282–289 mμ. The former λ_{max} is associated with 6-mercaptopurine, and the latter absorption is indicative of a 6-(substituted)thiopurine.[11] The reaction mixtures were then taken to dryness *in vacuo* to remove the excess amine, and the residues were crystallized as indicated in Table I. Attempts to increase the rate and yield of the reactions by heating in the presence of triethylamine resulted in varying amounts of decomposition products.

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(8) C. G. Skinner, J. R. Claybrook, F. D. Talbert, and W. Shive, *Arch. Biochem. Biophys.*, **65**, 567 (1956).

(9) C. G. Skinner, P. D. Gardner, and W. Shive, *J. Am. Chem. Soc.*, **79**, 2843 (1957).

(10) All melting data were taken on a Fisher-Johns micro hot stage and the temperatures are uncorrected. The ultraviolet absorption spectra were determined on a Beckman model DK-2 recording spectrophotometer using a 10 γ/ml. solution of the appropriate compounds dissolved in 95% ethyl alcohol.

(11) C. G. Skinner, R. G. Ham, O. C. Fitzgerald, Jr., R. E. Eakin, and W. Shive, *J. Org. Chem.*, 21, 1330 (1956).

Reactions of Nitrate Esters. V.[1] Decomposition of Primary Nitrates in Perfluorinated Acids

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We wish to report the occurrence of an unusual decomposition reaction of simple primary aliphatic nitrates, which can be achieved by merely dissolving the esters in trifluoroacetic acid (TFA) and allowing the solutions to stand at room temperature for 24 hours or less. The main products obtained from the decomposition are nitric oxide and the carboxylic acid having the same number carbon atoms as the ester. The reaction is catalyzed by ultraviolet light, although it does proceed even in the dark. Atmospheric oxygen appears to have no effect. A similar reaction occurs in other perfluorinated acids but not in 100% acetic or 100% sulfuric acid.

In addition to the main decomposition products, which are produced in yields of the order of 50%, there are obtained traces of solid acidic materials, and significant amounts (*ca.* 50%) of the alkyl trifluoroacetates. The latter are presumably formed either by an ordinary metathesis, or by a complex ionization similar to that reported for solutions of alkyl nitrates in sulfuric acid.[2]

Most of the work thus far has been with *n*-butyl nitrate, and typical procedures are described in the Experimental portion. Ethyl and *n*-propyl nitrates react in the same way with TFA. The butyl nitrate decomposition proceeds in perfluorobutyric or perfluorohexanoic acid in the same manner as in TFA. The reactions of secondary mononitrates with TFA have not been investigated, but 2,3-dinitroxybutane has been found to react readily, giving oxides of nitrogen and diacetyl.

The rate of disappearance of butyl nitrate has been followed polarographically. Attempts to follow the reaction by observing changes in the ultraviolet spectrum led to ambiguous results, due to the fact that ultraviolet light catalyzes the reaction, and to the fact that reaction products absorb in the same spectral region (*ca.* 255 mμ) as does the nitrate ester. The absorbance in this region remains essentially constant for a period of several hours, after which it increases rapidly. The length of this apparent induction period varies with concentration and with the duration of exposure to ultraviolet light in the spectrophotometer. The existence of an apparent induction period seems to be due to a compensating effect of increasing absorbance by reaction products and decreasing absorbance (at the same wave length) by butyl nitrate, since no

(1) Previous paper: R. T. Merrow, *J. Am. Chem. Soc.*, **78**, 1297 (1956).

(2) L. P. Kuhn, *J. Am. Chem. Soc.*, **69**, 1974 (1947).

induction period was observed when the reaction was followed polarographically.

While the mild conditions and the nature of the solvent suggest an ionic mechanism for this decomposition, the nature of the products and catalysis by ultraviolet light are indicative of a radical process. Thermal[3] and photochemical[4] decompositions are known to proceed *via* an initial homolytic cleavage, *viz:*

$$RCH_2ONO_2 \longrightarrow RCH_2O\cdot + NO_2$$

This is followed by a number of possible reactions leading to the observed products, including nitric oxide, aldehydes, and nitrite esters. Such decompositions of simple mononitrates have never been reported under the mild conditions used in the present work.

Further investigation into the mechanism of this decomposition, and particularly into the role of the fluorinated acids, is in progress.

EXPERIMENTAL

All of the chemicals used were commercially available materials. Melting and boiling points are uncorrected.

Trifluoroacetolysis of n-butyl nitrate. One-tenth mole of *n*-butyl nitrate was dissolved in 40 ml. of ice cold trifluoroacetic acid in an Erlenmeyer flask fitted with a ground glass stopper. The solution was cooled for 6 hr. in an ice water bath, and then allowed to stand at room temperature for another 18 hr. The solution became quite yellow within the first hour, and then became green on standing. On admission of air the color rapidly changed to a yellow-brown, and brown fumes formed above the liquid. The mixture was distilled, yielding 7.0 g. (.04 mole) of *n*-butyl trifluoroacetate, b.p. (713 mm.) 102–103°, $n_D^{25.5}$ 1.3376 (lit.[5] b.p. 102.7–102.8°, n_D^{20} 1.3391) and 5.1 g. (0.058 mole) of butyric acid, b.p. (713 mm.) 158–160°. From the dark tarry residue, traces of a water-soluble white solid acid, m.p. (dec.) 125–130°, were obtained. There was not enough of this material to characterize.

Nitric oxide was determined in a separate experiment, by absorption in sulfuric acid and titration of the nitrosylsulfuric acid with permanganate.[6] This run was carried out under a stream of nitrogen, and proceeded in the same manner as the other experiment, except that no appreciable color developed in the solution. From 20.0 millimoles of butyl nitrate, there was obtained 9.27 millimoles (46%) of nitric oxide.

Ethyl and *n*-propyl nitrates in TFA decomposed to give, qualitatively, the same types of products. The solid material from ethyl nitrate was identified as oxalic acid, m.p. and mixed m.p. 101–102° (dihydrate, recrystallized from water).

Butyl nitrate was recovered quantitatively from solutions in 100% acetic acid after standing 24 hr. at room temperature. Solutions in sulfuric acid gave no oxides of nitrogen, although, as reported previously,[2] the nitrate ester cannot be recovered by drowning the solution in water.

Rate studies. A 0.025*M* solution of butyl nitrate in TFA was prepared. A portion of this was placed in a 1-cm quartz cell and scanned in the ultraviolet region periodically, using a Cary Model 11MS Recording Spectrophotometer. There was essentially no change in the absorbance at the maximum over the first 8 hr. After 24 hr., however, the absorbance was much greater than the range of the instrument. However, the bulk of the solution, which had remained in a glass flask, showed the same absorbance after 24 hr. as it did initially. The absorbance did not increase until sometime between 36 and 48 hr.

Samples of the same solution were polarographed periodically. One-ml. aliquots were added to 5 ml. of 95% ethanol containing 3 drops of methyl red (0.1%). The solutions were brought to the first permanent yellow color with 0.5*N* NaOH solution, and then made up to 10 ml. with 95% ethanol. These solutions were then polarographed from zero to −2.0 volts, using a Sargent Model 21 Recording Polarograph with a sensitivity setting of 0.100. It was found unnecessary to remove dissolved oxygen. A blank correction for oxygen, obtained by treating pure trifluoroacetic acid in the same manner as above, was subtracted from the total wave height obtained in the nitrate determinations. The butyl nitrate concentration was found to decrease steadily, with no "induction period." The half-life at this concentration was about 56 hr. The data for any given run fit a first-order rate law fairly well, but the values of k vary greatly with concentration.

The reaction was found to proceed even in the dark, but it was shown to be catalyzed by ultraviolet light. The apparent induction period (observed spectrophotometrically) was shortened, and the rate of butyl nitrate disappearance (measured polarographically) was increased by exposure of the solution to the unfiltered light of a mercury arc lamp (mostly 2537 A).

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(4) J. A. Gray and D. W. G. Style, *Trans. Faraday Soc.*, **49**, 52 (1953).

(5) K. N. Campbell, J. O. Knobloch, and B. K. Campbell, *J. Am. Chem. Soc.*, **72**, 4380 (1950).

(6) G. C. Whitnack, C. J. Holford, E. S. C. Gantz, and G. B. L. Smith, *Anal. Chem.*, **23**, 464 (1951).

Arenesulfonic Acids as Catalysts in the Alcoholysis of Nitriles to Esters

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Received March 3, 1958

Arenesulfonic acids have been found to be effective catalysts in the alcoholysis of nitriles to esters, and their use eliminates the objectionable features which have characterized this type of reaction when other catalysts were used. Earlier procedures called for the passing of anhydrous hydrogen chloride into a hot reaction mixture of nitrile, alcohol, and water[3] or refluxing a similar mixture with concentrated sulfuric acid.[4] The first of these involves difficulties in handling anhydrous hydrogen chloride at elevated temperatures. The second, in our experience, is often accompanied by more or less extensive charring. Presumably because of these disadvantages this reaction has not been used very extensively, although occasional

(1) Present address, E. I. du Pont de Nemours Co., Inc., Polychemicals Dept., Belle Works, Belle, W. Va.

(2) From the Master's thesis of W. H. B.

(3) W. Wislicenus, *Ber.*, **20**, 592 (1887).

(4) L. Spiegel, *Ber.*, **51**, 296 (1918).

TABLE I

YIELDS AND PROPERTIES OF CRUDE ESTERS

Ester	Acid Catalyst	Time of Reflux, Hr.	Yield, %	B.P., °C.	Sap. Equiv. Calcd.	Sap. Equiv. Found
Ethyl phenylacetate	*p*-Toluenesulfonic	2.5	66	119–121/27 mm.	164	177
n-Propyl phenylacetate	*p*-Toluenesulfonic	2.5	83	131–133/27 mm.	178	185
n-Butyl phenylacetate	Benzenesulfonic	6	72	143–145/28 mm.	192	205
n-Heptyl phenylacetate	*p*-Toluenesulfonic	6	70	174–183/27 mm.	234	259
n-Butyl propionate	*p*-Toluenesulfonic	6	49	124–126/400 mm.	130	130
Di-*n*-propyl adipate	*p*-Toluenesulfonic	6	16	154–163/28 mm.	115	122
Diisoamyl adipate	*p*-Toluenesulfonic	6	66	163–165/2.2 mm.	143	153
Di-*n*-propyl-β,β'-oxydipropionate	Benzenesulfonic	6	25	140–141/1.9 mm.	123	140

TABLE II

PROPERTIES OF PURIFIED ESTERS

Ester	B.P., °C.	Sap. Equiv. Calcd.	Sap. Equiv. Found	$n_D^{25°}$	$d_4^{25°}$	M_R Calcd. Vogel	M_R Observed
n-Heptyl phenylacetate	146–147/2.0 mm.	234.33	233.95	1.4812	0.95707	69.60	69.70
Di-*n*-propyl-β,β'-oxydipropionate	146–147/2.1 mm.	123.15	128.20	1.4309	1.01843	62.80	62.59

references to it appear in the literature.[5,6] It is used commercially, with concentrated sulfuric acid as the catalyst, under carefully controlled conditions, in the alcoholysis and esterification of cyanoacetic acid to diethyl malonate[7] and in the alcoholysis and dehydration of acetone cyanohydrin to methyl methacrylate.[8]

We have found that the difficulties described may be avoided by the use of *p*-toluenesulfonic acid or other arenesulfonic acid as the catalyst. The catalyst is needed in quantities equimolar with the nitrile, since the nitrogen of the nitrile is converted into the ammonium salt of the acid catalyst. An equimolar quantity of water must also be present.

$$R{-}CN + H_2O + HOR' + CH_3C_6H_4SO_2OH \longrightarrow R{-}COOR' + CH_3C_6H_4SO_2ONH_4$$

The necessary water was provided in our syntheses by the use of the monohydrate of *p*-toluenesulfonic acid or of benzenesulfonic acid as catalyst.

As a general procedure, we simply refluxed the reaction mixture for several hours. Mechanical stirring was used. Occasionally precipitation of the ammonium salt was so extensive that stirring became difficult. Addition of an inert solvent might help in such cases. After the period of reflux, water was added to dissolve the ammonium salt. The organic layer was separated, washed with aqueous sodium carbonate, and dried over anhydrous magnesium sulfate. Distillation from a Claisen flask gave crude esters of quality shown by the saponification equivalents in Table I.

Saponification equivalents were determined by the diethylene glycol method of Redeman and Lucas.[9] We found that unchanged nitrile, which may be assumed to be the principal impurity, does not interfere seriously with the determination of the saponification equivalent. Less than 1% of a sample of phenylacetonitrile was found to be saponified under the specified conditions. This is in agreement with the finding of Spiegel[4] that the presence of nitrile does not interfere with the determination of saponification equivalents by the more usual method of refluxing with alcoholic potassium hydroxide.

Table I is a summary of the results of the preparation of eight different esters by this method. In no case did charring occur. Yields ranged from 16% to 83%. Five of the eight preparations resulted in yields of 66% or higher. In two cases the catalyst was benzenesulfonic acid, with results about the same as with *p*-toluenesulfonic acid. Presumably other arenesulfonic acids would also be effective.

Two of the esters are not described in the literature. The crude ester in these two cases was fractionally distilled, and densities determined on the fractions of constant index of refraction. Results are given in Table II.

We made a brief study of the effect of time of refluxing upon the yield of *n*-butyl propionate.

(5) F. Bergel, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, 267 (1944).

(6) D. J. Dupré, J. Elks, B. A. Hems, K. N. Speyer, and R. M. Evans, *J. Chem. Soc.*, 507 (1949).

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

(8) H. T. Neher, *Ind. Eng. Chem.*, **28**, 267 (1936).

(9) C. E. Redeman and H. J. Lucas, *Anal. Chem.*, **9**, 521 (1937).

The yield improved steadily up to four hours, but further refluxing had little effect.

EXPERIMENTAL[10]

Experimental details are given only for the two previously undescribed esters. Similar procedures were used for the others.

n-Heptyl phenylacetate. Phenylacetonitrile (46.8 g., 0.40 mole), *n*-heptyl alcohol (46.5 g., 0.40 mole), and *p*-toluenesulfonic acid monohydrate (76.0 g., 0.40 mole, including 0.40 mole water) were refluxed with stirring for 6 hr. The addition of 100 ml. of water dissolved the ammonium salts, and caused separation into two layers. The ester layer was separated, washed with 20% sodium carbonate solution, dried over anhydrous magnesium sulfate, and distilled from a Claisen flask. Yield of crude ester, 66.0 g., 0.28 mole.

The crude ester was washed with 5% sodium carbonate solution, and 200 ml. of toluene was added. This was distilled off at atmospheric pressure for azeotropic removal of water. After removal of water, the ester was distilled through a 60-cm. tantalum wire spiral column, using a total reflux partial take-off head. The fraction of constant index of refraction boiled at 146–147° at 2.0 mm., and totaled 31.4 g. The neutralization number as determined with alcoholic potassium hydroxide was zero. Other properties are given in Table II.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 77.06; H, 9.79.

Di-n-propyl-β,β'-oxydipropionate. β,β'-Oxydipropionitrile (37.2 g., 0.30 mole), *n*-propyl alcohol (36.0 g., 0.60 mole), and benzenesulfonic acid monohydrate (105.6 g., 0.60 mole, including 0.60 mole of water) were refluxed with stirring for 6 hr., and the reaction mixture worked up as described above. The average yield of two runs was 18.6 g., 0.075 mole. Purification of the crude ester was performed as described above. Distillation of 21.7 g. of crude ester gave 9.1 g. of purified ester boiling at 146–147° at 2.0 mm. The neutralization number with alcoholic potassium hydroxide was almost zero. Other properties are given in Table II.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 56.75; H, 8.65.

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(10) Analyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Synthesis of a Steroidal Nitrogen Mustard[1]

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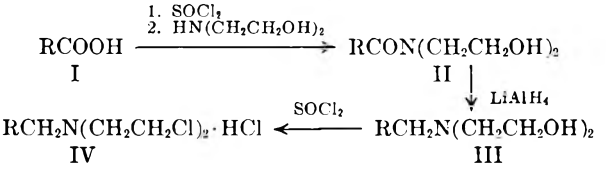
The nitrogen mustards are recognized as anticancer agents.[2] We wish to record the synthesis of a steroid-nitrogen mustard combination,[3] which was expected to have transport characteristics considerably different from those of the more familiar low-molecular weight nitrogen mustards. It was believed possible that such difference could reflect in enhanced activity.

The starting point in the synthesis was 5-cholestene-3β-carboxylic acid (I)[4] obtained from cholesteryl chloride by carbonation of the Grignard reagent.[5] Treatment with thionyl chloride followed by reaction of the acid chloride with diethanolamine gave the *N,N*-bis(hydroxyethyl) derivative



R = 3β-cholesteryl

II of 5-cholestene-3β-carboxamide. Lithium aluminum hydride, by reducing the amide grouping in II to amine, formed 3β-[bis(hydroxyethyl)aminomethyl]-5-cholestene(III).[6] To generate the nitrogen mustard, both hydroxyl groups were replaced with chlorine with help of thionyl chloride. The hydrochloride of the tertiary amine III as well as the hydrochloride IV of the nitrogen mustard were also prepared.

The nitrogen mustard was made available for assay to Drs. H. M. Lemon and H. H. Wotiz at Boston University Medical School who very kindly submitted the following report:

"The relative insolubility of the steroid-mustard in the conventionally used solvents for injection made the toxicity study extremely difficult. Nevertheless, preliminary studies were carried out by intraperitoneal administration of a suspension of the mustard in a starch solution.

The survival rates of mice, guinea pigs, or rats did not differ significantly from the controls following doses of 34, 250, 500, and 1000 mg./kg. Histopathological examination of the mouse livers showed evidence of plastic peritonitis, yellow atrophy, and multinucleated giant cells. The mouse kidneys showed evidence of interstitial hemorrhagic nephritis at the border of the cortex and medulla. Because of its extreme insolubility it is impossible to tell whether these effects were caused by the inherent toxicity of the mustard or by a local irritating effect due to its limited absorption from the peritoneum."

(1) These studies were aided by grants from the American Cancer Society and from the National Institutes of Health, and by an Institutional Research Grant from the American Cancer Society.

(2) *Cf.* A. Gellhorn, *Cancer Research*, **13**, 205 (1953); J. P. Greenstein, *Biochemistry of Cancer*, 2nd ed., Academic Press, Inc., New York, N. Y., 1954, p. 282.

(3) Compare (a) G. R. Vavasour, H. I. Bolker, and A. F. McKay, *Can. J. Chem.*, **30**, 933 (1952); (b) G. G. Hazen, Doctoral dissertation, University of Michigan, 1951, *Chem. Abstr.*, **47**, 8761 (1953). For the incorporation of a carcinogenic hydrocarbon in nitrogen mustard compounds see O. M. Friedman and A. M. Seligman, *J. Am. Chem. Soc.*, **70**, 3082 (1948).

(4) The orientation at the 3-position was shown by E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **75**, 6234 (1953); G. Roberts, C. W. Shoppee, and R. J. Stephenson, *J. Chem. Soc.*, 2705 (1954).

(5) *Cf.* R. H. Baker and E. N. Squire, *J. Am. Chem. Soc.*, **70**, 1487 (1948).

(6) A related sequence was reported starting with Δ⁵-3β-acetoxybisnorcholenic acid and giving the corresponding di-(hydroxyethyl)amine derivative. H. L. Herzog, C. C. Payne, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 5324 (1955).

EXPERIMENTAL[7]

5-Cholestene-3β-carboxylic acid (I). The necessary starting material was prepared by the reaction of cholesterol and thionyl chloride.[3a] The vacuum-dried cholesteryl chloride, after several crystallizations from absolute alcohol, showed m.p. 94.5–95° and $[\alpha]_D^{24.5}$ −33°. The yield was 61%. The constants recorded before for cholesteryl chloride are m.p. 95–96°[3a] and 96–97°[5], and $[\alpha]_D^{25}$ −26.4°[3a]. Grignardation and carbonation of cholesteryl chloride was performed by a modification of the method of Baker and Squire.[5]

A mixture of 3.39 g. (0.14 g.-atoms) of turnings of sublimed magnesium, 7.6 g. (0.070 mole) of dry ethyl bromide, and absolute ether was magnetically stirred in a three-necked flask that had been scrupulously dried and fitted with a condenser and dropping funnel. Dry nitrogen was used to blanket the reaction mixture throughout the experiment. The dropwise addition of a solution of 28.2 g. (0.069 mole) of cholesteryl chloride in 85 ml. of dry ether was begun at the onset of the vigorous reaction between the ethyl bromide and magnesium, and was completed over the course of 3 hr. During the addition and for 46 hr. thereafter, the reaction mixture was warmed to maintain a gentle reflux. At the end of this period the solution contained a gray-white precipitate; some unreacted magnesium was also apparent.

Dry carbon dioxide was bubbled into the vigorously stirred Grignard mixture for 12 hr. Dry ether was added at intervals to keep the volume close to 400 ml. The carbonation mixture was poured over 200 ml. of cold 10% sulfuric acid solution. The ether layer was filtered and the insoluble material was rinsed with several portions of ether. The combined ether solutions were dried with sodium sulfate, and then warmed on the steam bath to remove solvent. The viscous residue, after crystallization from benzene, gave 14.0 g. (49%) of white crystalline 5-cholestene-3β-carboxylic acid, m.p. 216–217°, $[\alpha]_D^{23.5}$ −13°. The values given before are, *inter alia*, m.p. 218–220°, 225–227°, and 226–227° (to opaque melt)[4,5], and $[\alpha]_D$ −10°[4] and $[\alpha]_D^{24}$ −14°.[8]

N,N-Bis(hydroxyethyl)-5-cholestene-3β-carboxamide (II). 5-Cholestene-3β-carbonyl chloride was prepared by boiling a solution of 8.41 g. (0.020 mole) of 5-cholestene-3β-carboxylic acid and 15 g. (0.13 mole) of thionyl chloride in 30 ml. of sodium-dried benzene for 5.5 hr. The reaction mixture was then allowed to stand overnight at room temperature. Exposure to reduced pressure at steam bath temperatures removed volatile materials and left the tan-colored acid chloride, which was washed with cold benzene and collected by filtration.

A homogeneous mixture of the acid chloride in 50 ml. of dry benzene containing 13.3 g. (0.13 mole) of dry diethanolamine was stirred and heated in an oil bath at 63° for 4 hr. The solid deposited on allowing the reaction mixture to stand overnight was collected, and was crystallized from methanol (*ca.* 40 ml.). The mother liquors were concentrated under reduced pressure on the steam bath, and water was added to the viscous residue. The resulting solid was collected by filtration and was crystallized from methanol. The two crops of crystals, combined and dried over potassium hydroxide pellets *in vacuo*, weighed 5.6 g. (56%) and showed an indefinite melting point with softening at 168° and complete liquefaction at approximately 190°. A sample of this product, after two crystallizations from methanol and vacuum drying, afforded *N,N*-bis(hydroxyethyl)-5-cholestene-3β-carboxamide, m.p. 182–189°, $[\alpha]_D^{24.6}$ −10°.

Anal. Calcd. for $C_{32}H_{55}O_3N$: N, 2.8. Found: N, 2.7.

The material as a mull with mineral oil showed an infrared absorption peak at 6.22 μ.

3β-[Bis(hydroxyethyl)aminomethyl]-5-cholestene (III). A mixture of amide II (5.61 g. or 0.11 mole), 5.0 g. (0.13 mole) of lithium aluminum hydride, and 100 ml. of ether was magnetically stirred at room temperature for 24 hr. Water was added dropwise, slowly and with stirring, followed by 700 ml. of a concentrated solution of sodium potassium tartrate and ammonium sulfate. The ether solution was removed, and the turbid aqueous layer was extracted with 3 portions of chloroform. The combined ether and chloroform solutions were dried with sodium sulfate, and all volatile material was removed by distillation on the steam bath at water pump pressure. The residual 3β-[bis(hydroxyethyl)aminomethyl]-5-cholestene, m.p. 119–124°, weighed 4.1 g. (76%). The analytical sample, prepared by three crystallizations from absolute alcohol, melted at 135–137.5° and showed $[\alpha]_D^{23.6}$ −24°.

Anal. Calcd. for $C_{32}H_{57}O_2N$: C, 78.8; H, 11.8; N, 2.9. Found: C, 79.3; H, 11.6; N, 3.1.

No absorption at 6.22 μ was evident.

The hydrochloride of amine III was prepared by saturating an acetone solution of the amine with dry gaseous hydrogen chloride. The white precipitate was collected, crystallized from acetone, and dried in high vacuum at 110°. The salt melted at 207.5° (dec.) with preliminary softening.

Anal. Calcd. for $C_{32}H_{58}O_2NCl$: Cl, 6.8. Found: Cl, 7.0.

3β-[Bis(chlorethyl)aminomethyl]-5-cholestene hydrochloride (IV). Thionyl chloride (8 g.; 0.07 mole) was added in 1 portion to a hot solution of 4.1 g. (0.085 mole) of amine III in 100 ml. of dry benzene. The mixture, in which a thick gelatinous precipitate had formed, was heated on the steam bath for 35 min. Volatile material was removed by vacuum distillation on the steam bath, and the brown residue was dried *in vacuo*. A hot chloroform solution of the crude product was treated with decolorizing carbon (Norit), the chloroform was removed by vacuum distillation, and the residue was crystallized from 150 ml. of absolute alcohol. The resulting tan crystals, after air-drying, weighed 3.4 g. (70%) and showed m.p. 203–210° (dec.) with preliminary softening. The melting point of salt IV, as well as of all the others, was not sharp, coloration and decomposition being evident. Three crystallizations of the product from absolute ethanol brought the melting point to 198.5–203°. In another experiment, crystallization once from methanol and twice from acetone followed by vacuum drying at 110° furnished hydrochloride IV with m.p. 196–201° (dec.) and $[\alpha]_D^{26.4}$ −17°.

Anal. Calcd. for $C_{32}H_{56}NCl_3$: Cl, 19.0. Found: Cl, 18.7.

In another preparation, the hydrochloride after recrystallization three times from alcohol and drying at 100° *in vacuo* had m.p. 192–194° (dec.), $[\alpha]_D^{26.6}$ −19°.

Anal. Calcd. for $C_{32}H_{56}NCl_3$: C, 68.5; H, 10.1; N, 2.5; Cl, 19.0. Found: C, 68.7; H, 10.1; N, 2.6; Cl, 18.8.

3β-[Bis(chloroethyl)aminomethyl]-5-cholestene. A sample of hydrochloride IV dissolved in chloroform was shaken with 10% potassium hydroxide solution. The chloroform solution was washed with water, dried with sodium sulfate, and all solvent was removed. The residual yellow oil was dissolved in acetone, and methanol was added until the solution was cloudy. Cooling resulted in the precipitation of white crystalline 3β-[bis(chloroethyl)aminomethyl]-5-cholestene (m.p. 67.5–70°), which after two crystallizations from absolute alcohol and drying *in vacuo* at 57°, showed m.p. 72–75°.

Anal. Calcd. for $C_{32}H_{55}NCl_2$: Cl, 13.5. Found: Cl, 13.3.

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(7) Melting points are uncorrected. Optical rotations were taken with 1% solutions in chloroform. The elementary analyses were performed by Carol K. Fitz, 115 Lexington Avenue, Needham Heights 94, Mass.

(8) R. H. Baker and E. N. Squire, *J. Am. Chem. Soc.*, 70, 4134 (1948).

Ion Exchange Paper Chromatography

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Separation or organic acids by paper chromatography usually requires the presence of an acid such as acetic or formic acid in the developing solvent to prevent streaking.[1] In a previous communication[2] the use of papers impregnated with alginic acid was described whereby the so-called swamping acids could be dispensed with and any desirable solvent utilized. This paper deals with the separation of organic acids using papers containing ion exchange resins[3] and *O*-(carboxymethyl)cellulose[4] in conjunction with non-acidic solvents.

The resin containing papers were prepared by adding the powdered ion exchange resin to the cellulose pulp before the sheets were made.[3] Four types of ion exchange resin papers were tested, two containing acid resins and two containing basic resins. Before use the papers containing the cation exchange resins were irrigated for 6 hr. with *N* hydrochloric acid, and those containing the anion exchange resins were treated with *N* sodium hydroxide. Thereafter all the papers were washed thoroughly with water to remove the excess of reagent and dried in the air.

The *O*-(carboxymethyl)cellulose papers were made by dipping Whatman No. 1 filter paper in a 1.5% aqueous solution of *O*-(carboxymethyl)cellulose (Type 130, medium)[4] and, after draining off the excess of the solution, the papers were dipped into 2*N* hydrochloric acid to precipitate the *O*-(carboxymethyl)cellulose onto the cellulose fibers. The papers were then washed with water to remove excess acid and dried in the air.[cf. 2]

Glyconic and glycuronic acids can be separated on the strongly acidic type resin paper using 1-butanol:ethanol:water (4:1:5) as the developing solvent. All the acids except D-glucosaccharo-6,3-lactone gave compact spots on the chromatograms as revealed by ammoniacal silver nitrate (Tollen's reagent). Malic and citric acids gave white spots on a light brown background whereas the rest (see Table I) appeared as dark spots.

Mono- and disaccharides showed about the same R_f values on paper impregnated with resins as on untreated cellulose papers. The resins do not interfere with the detection of the components.

The weakly acidic type of resin paper was most useful for separating amino acids[5] (see Table II) although it was noted that overloading had to be avoided or else streaking occurred. The weakly basic type of resin papers proved to be of no value for separating the amino acids; streaking was common and aspartic acid and glutamic acid displayed no movement.

TABLE I

SEPARATION OF ORGANIC ACIDS

Acid	Ion Exchange Paper[b]	*O*-(Carboxymethyl)-cellulose Paper
R_f values using 1-butanol:ethanol:water (4:1:5)[a]		
L-Ascorbic acid	0.48	0.39
L-Arabono-γ-lactone	0.43	0.39
Citric acid	0.62	0.47
D-Galactono-γ-lactone	0.34	0.30
D-Galacturonic acid	0.26	0.15
D-Glucoheptono-γ-lactone	0.22	0.16
D-Glucosaccharo-6,3-lactone	0.35	0.20
D-Glucurone	0.38	0.29
D-Glucuronic acid	0.31	0.17
L-Gulonic acid	0.25	0.20, 0.16[c]
5-Keto-D-gluconic acid	0.43	0.27
2-Keto-L-gulonic acid	0.33	0.17
Malic acid	0.63	0.52
D-Mannurone	0.44	0.33
D-Mannuronic acid	0.31	0.22
L-Tartaric acid	0.50	0.31

[a] Components detected with ammoniacal silver nitrate. [b] Impregnated with Amberlite IR-120 cation exchange resin (H^+ form). [c] The spot with the lower R_f value is due to acid and the other to the lactone.

TABLE II

SEPARATION OF AMINO ACIDS

Amino Acid	Ion Exchange Paper[b]	*O*-(Carboxymethyl)-cellulose Paper
R_f values using 1-butanol:ethanol:water (4:1:5)[a]		
Alanine	0.20	0.20
Aspartic acid	0.09[d]	0.13
Cysteine[c]	0.08[d]	0.22
Glycine	0.14	0.10
Glutamic acid	0.17	0.19
Histidine	0.06[d]	0.04
Leucine	0.38	0.57
Methionine	0.35	0.36
Phenylalanine	0.38	0.62
Proline	0.22	0.17
Threonine	0.18	0.16
Tryptophan	0.39	0.44
Valine	0.29	0.44

[a] Amino acids detected with ninhydrin. [b] Impregnated with Amberlite IRC-50 cation exchange resin (H^+ form). [c] Applied as hydrochloride. [d] Evaluated from leading edge of spot which extends back to origin.

Filter paper impregnated with *O*-(carboxymethyl)-cellulose[6] gave a good separation of the uronic acids

(1) J. W. H. Lugg and B. T. Overell, *Australian J. Sci. Research, Ser. A*, 1, 98 (1948).

(2) F. Smith and D. Spriesterbach, *Nature*, 174, 466 (1954).

(3) The authors thank The Rohm & Haas Co., Philadelphia, Pa., for a generous supply of these papers.

(4) The authors thank The Hercules Powder Co., Wilmington, Del., for the *O*-(carboxymethyl)cellulose.

(5) *Cf.* M. M. Tuckerman, *Anal. Chem.*, 30, 231 (1958).

(6) *Cf.* T. Willard and A. Berg, *Angew. Chem.*, 64, 418 (1952); E. Peterson and H. Sober, *J. Am. Chem. Soc.*, 78, 751 (1956).

and the lactones, D-glucurone and D-mannurone (see Table I). All the acids and lactones tested appeared as compact spots on the chromatograms.

The R_f values of the amino acids tested on the *O*-(carboxymethyl)cellulose paper were of the same order of magnitude as previously observed[7] and lower than those observed with phenol as the solvent.[8] In the case of histidine and proline the R_f values 0.04 and 0.17, respectively, were so much lower than those found on chromatograms developed with phenol:water[8] that the difference might be used to characterize these two amino acids.

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(7) J. A. Cifonelli and F. Smith, *Anal. Chem.*, **27**, 1501 (1955).

(8) R. Consden, A. H. Gordon and A. J. P. Martin, *Biochem. J.*, **38**, 224 (1944).

Synthesis and Reduction of Nitrosotrimethylhydrazine[1]

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As a logical extension to an investigation in this laboratory of the lower alkylhydrazines, an attempt was made to prepare an alkyl derivative of the unknown triazane, H_2NNHNH_2. A survey of the literature did not disclose any attempts to prepare compounds of this type, although a few aromatic triazanes have been prepared and characterized.[2] One route to the synthesis of such a compound appeared to lie in the reduction of nitrosotrimethylhydrazine: This compound was selected as a possible precursor to *N,N,N'*-trimethyltriazane because (*1*) nitrosamines can be reduced to hydrazines with little or no reductive cleavage of the N—N bond,[3] (*2*) *N*-nitroso-*N*-phenyl-*N'*-formylhydrazine has been successfully reduced to *N*-formyl-*N'*-phenyltriazane, which was characterized through its benzaldehyde derivative,[4] and (*3*) trimethyltriazane may be considerably more stable than a triazane containing fewer alkyl groups. This is suggested by the high order of stability of tetramethylmethylenediamine, $[(CH_3)_2N]_2CH_2$,[5] compared to that of the nonisolable parent compound, methylenediamine.

$$(CH_3)_2NNCH_3NO + 4\,[H] \longrightarrow (CH_3)_2NN(CH_3)NH_2 + 2H_2O$$

The unknown nitrosotrimethylhydrazine was synthesized from trimethylhydrazine and nitrous acid. It gives a positive Lieberman test for the nitroso group, and is miscible with water to give a neutral solution. The compound is stable for long periods of time at Dry Ice temperatures, but at room temperature it slowly decomposes. A sample stored at 23° became orange-yellow in about three days, and orange-brown in a week. An elemental analysis gave somewhat high values for nitrogen, but the results are considered satisfactory in view of the instability of the compound. The reduction of nitrosotrimethylhydrazine was characterized by cleavage of at least one of the N—N bonds in attempts to prepare the triazane by three different methods. In the direct hydrogenation of the nitroso compound under mild conditions with a catalyst of 10% palladium-on-charcoal, trimethylhydrazine was isolated in addition to unreacted nitroso compound. With lithium aluminum hydride in ether dimethylamine was obtained, while with sodium amalgam in ethanol, hydrazine and dimethylamine were obtained. The course of the reduction to produce hydrazine is not clear, although other nitroso compounds have also been found to yield hydrazine when reduced with sodium amalgam under similar conditions.[6]

EXPERIMENTAL[7]

Starting materials. Trimethylhydrazine was prepared by the method of Class.[8] A value of 100.5% was obtained for the purity of the product, b.p. 59–60° 749 mm., by titration with standard potassium iodate (four-electron change).[9] Lithium aluminum hydride was obtained from Metal Hydrides, Inc., Beverly, Mass. Sodium amalgam was prepared by the method given by Fieser.[10]

Preparation of nitrosotrimethylhydrazine. A solution of 25.9 g. (0.35 mole) of trimethylhydrazine in 100 ml. of water was neutralized to a *p*H of 7.00 with 1:1 hydrochloric acid, diluted to 280 ml. with water, and cooled to 0°. A solution of 72.5 g. (1.05 moles) of sodium nitrite in 200 ml. of water was then added dropwise to the well stirred trimethylhydrazine hydrochloride solution at such a rate that the temperature did not rise above 5°. After the addition, the *p*H was adjusted to 5.18 by the dropwise addition of 1:1 acetic acid. When the resulting solution, which degassed continuously, was stored overnight at 0°, the *p*H increased to 5.83 and the solution deepened in color (yellow). The *p*H was adjusted to 8.00 by the addition of solid potassium carbonate, and the solution was extracted continuously with 150 ml. of ether until nearly all of the yellow color had passed

(1) This investigation was carried out under a contract with the Office of Naval Research.

(2) T. C. Chaudhuri, *J. Chem. Soc.*, **117**, 1081 (1920).

(3) E. Fischer, *Ann.*, **199**, 283 (1879).

(4) A. Wohl, *Ber.*, **33**, 2759 (1900).

(5) F. Klages, G. Nober, F. Kircher, and M. Bock, *Ann.*, **547**, 24 (1941).

(6) L. F. Audrieth and B. A. Ogg, *The Chemistry of Hydrazine*, John Wiley & Sons, Inc., New York, N. Y., 1951, p. 16.

(7) The analysis of nitrosotrimethylhydrazine was performed by Elek Microanalytical Laboratories, Los Angeles.

(8) J. B. Class, J. G. Aston, and T. S. Oakwood, *J. Am. Chem. Soc.*, **75**, 2938 (1953).

(9) G. S. Jamieson, *Am. J. Sci.*, **33**, 352 (1912).

(10) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath & Co., New York, N. Y., 1941, p. 418.

into the ether layer (16 hr.). The ether extract was dried over anhydrous magnesium sulfate and fractionated. After removal of the ether, the product, 25.2 g. (70%) was collected in the range 41–42° at 10 mm. as a light yellow oil (f.p. −7°).

Anal. Calcd. for $C_3H_9N_3O$: C, 34.94, H, 8.80, N, 40.75. Found: C, 35.50, 35.41; H, 8.87, 8.83; N, 41.50, 41.45.

Nitrosotrimethylhydrazine gave a positive Lieberman test for the nitroso group when the reactions were carried out at about 0°. At higher temperatures oxidation of the test samples by concentrated sulfuric acid occurred.

Catalytic hydrogenation of nitrosotrimethylhydrazine. A solution of 7.35 g. (0.0713 mole) of nitrosotrimethylhydrazine in 133 ml. of water was reduced with hydrogen in the presence of 3.502 g. of a catalyst consisting of 10% palladium-on-charcoal at 25° and one atmosphere. The reduction was attended by a steadily decreasing rate of hydrogenation until a total of 1.2 moles of hydrogen per mole of nitroso compound had been adsorbed. The catalyst was removed by filtration, the filtrate was saturated at 30° with sodium hydroxide pellets, and the yellow oil which separated was dried over fresh sodium hydroxide and fractionated to give 1.5 g. of a colorless liquid, b_{749} 59–60°, and 0.5 g. of a yellow oil, b_{10} 42°. The latter fraction was considered to be nitrosotrimethylhydrazine on the basis of the boiling point and a positive Lieberman test. The former was shown to be trimethylhydrazine through the preparation of trimethylhydrazine picrate in ethereal picric acid. The recrystallized product (from absolute ethanol) melted at 113–114.5°. Mixed melting point determinations with an authentic sample of trimethylhydrazine picrate (m.p. 114–115°) at 2 compositions showed no depression. An analysis of the trimethylhydrazine fraction with standard potassium iodate indicated that trimethylhydrazine was present to the extent of 95.3% (four-electron change).

Reduction of nitrosotrimethylhydrazine with lithium aluminum hydride. Seven grams (0.068 mole) of nitrosotrimethylhydrazine in 100 ml. of ether was added over a period of 1 hr. at 25° to 5.0 g. (0.132 mole) of lithium aluminum hydride in 150 ml. of absolute ether. The reaction mixture was stirred for an additional hour, followed by the dropwise addition of water until the reaction mixture appeared white, and subsequently the addition of 75 ml. of 30% aqueous sodium hydroxide. The ether layer was removed, and the gelatinous solid was extracted with three 50-ml. portions of ether. The ether extracts were combined with the original ether layer, and the solution was dried over anhydrous magnesium sulfate. An appreciable liquid residue remained when the ether was distilled off. The distillate (200 ml.) was treated with ethereal picric acid (20 g. = 0.075 mole of acid), and the resulting precipitate was recrystallized three times from absolute ethanol to give 5.2 g. (28%) of dimethylamine picrate, m.p. 158–159°. Mixed melting point determinations at two compositions with authentic dimethylamine picrate (m.p. 158–159°) showed no depression.

Reduction of nitrosotrimethylhydrazine with sodium amalgam. Thirty grams of 3% sodium amalgam (0.9 g., 0.039 mole of sodium) was added in one portion to 2.0 g. (0.019 mole) of nitrosotrimethylhydrazine in 40 ml. of absolute ethanol at 0°, and the mixture was shaken for 6 hr. at 0°. The solution was filtered, and the filtrate was acidified with acetic acid. A twofold volume of water was added, followed by 2.1 g. (0.020 mole) of benzaldehyde. When the mixture was shaken, a yellow precipitate formed. The solution was filtered and the solid recrystallized from 95% ethanol to give 0.59 g. (15%) of benzalazine, m.p. 91–92°. Mixed melting point determinations at two compositions with authentic benzalazine (m.p. 92–93°) showed no depression. The alcohol and water were removed from the filtrate on the steam bath, and the residue was extracted with ether to remove benzaldehyde. The crude acetate residue was dissolved in 10 ml. of water, and half of the solution was saturated at 25° with solid sodium hydroxide and extracted 4 times with 5-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate, and the clear solution was treated with ethereal picric acid (2.3 g. = 0.010 mole of the acid). The precipitate which formed was recrystallized from absolute ethanol to give 0.39 g. (15%) of dimethylamine picrate, m.p. 157–158.5°. Mixed melting point determinations at two compositions with authentic dimethylamine picrate (m.p. 158–159°) showed no depression. The Hinsburg test, when applied to the other portion of the aqueous solution, confirmed the presence of dimethylamine, and indicated the absence of methylamine.

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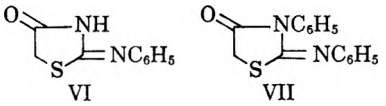
Formation of Isothiouronium Salts and Pseudothiohydantoins

A. J. SPEZIALE

Received March 10, 1958

Taniyama and Yusa[1] have recently shown that 2'-chloroacetanilide and 2'-chloro-4-nitroacetanilide with 1-phenyl and 1,3-diphenyl thiourea gave *N*-substituted pseudothiohydantoins (VI and VII) in alcohol at reflux. However, Knott and Morgan[2] have reported that thiourea and the chloroacetamides derived from ammonia, 2-aminothiazole, and 2-aminopyridine gave the corresponding isothiouranium salts



(III, R = amino, 2-thiazolylamino, and 2-pyridylamino) in refluxing ethanol.

Other investigators have reported that thiourea with chloroacetic acid,[3] methyl or ethyl chloroacetates[4] formed the corresponding isothiouranium salts (III, R = OH, OCH_3, OC_2H_5) in acetone at room temperature and that chloroacetic acid[5] in water at 80° formed pseudothiohydantoin (IV). A preparative method for IV and its hydrochloride from ethyl chloroacetate and thiourea in refluxing ethanol has been developed by Allan and Van Allan.[6]

In view of these results we wish to report an extension of our previous work.[7] Thiourea and 2-chloro-*N*,*N*-dipropylacetamide in dimethylformamide (DMF) at 30°, gave a 75% yield of the

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(2) E. B. Knott and J. Morgan, U. S. Patent **2,461,987**.
(3) P. C. Ray and F. V. Fernandes, *J. Chem. Soc.*, **105**, 2159 (1914).
(4) J. Taylor, *J. Chem. Soc.*, **117**, 4 (1920).
(5) R. Andreasch, *Monatsh.*, **8**, 407 (1887).
(6) C. F. H. Allan and J. A. Van Allan, *Org. Syntheses*, **27**, 71 (1947).
(7) A. J. Speziale and P. C. Hamm, *J. Am. Chem. Soc.*, **78**, 5580 (1956).

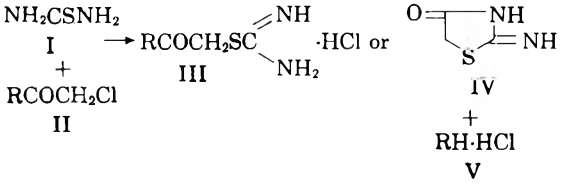
isothiouronium salt [III, R = $(C_3H_7)_2N$] and a 21% yield of pseudothiohydantoin (IV). In 95% ethanol at 25°, the dipropylamide and thiourea afforded a 57% yield of the isothiouronium salt and 17% yield of IV. In refluxing ethanol, none of III [R = $(C_3H_7)_2N$] was isolated but rather an 86% yield of IV and a 74% yield of dipropylamine hydrochloride. III [R = $(C_3H_7)_2N$] was converted to IV in refluxing ethanol.[4] 2-Chloro-*N*,*N*-diethylacetamide and thiourea in benzene at 80° for 2 hrs gave a 51.8% yield of IV.

Ethyl chloroacetate and thiourea gave a 57% yield of III(R = C_2H_5O) and 26% yield of IV (as the hydrochloride) at 25° in ethanol, and a 62% yield of III(R = C_2H_5O) and a 14% yield of IV·HCl in DMF at 25°. A slightly higher yield of the isothiouronium salt was obtained when the reaction was carried out for only 4 hr. rather than 24 hr. at 25° in ethanol.

The data, summarized in Table I, clearly indicate that solvents have no appreciable effect on the course of reaction of I and II, and that the amounts of III and IV formed are dependent on reaction temperature. Temperatures of about 25–30° favor the formation of the isothiouronium salts (III) while temperatures of about 80° favor the formation of IV.

TABLE I

REACTION OF THIOUREA WITH 2-HALOACETAMIDES AND 2-HALOACETATES



R	Solvent	Temp., °C.	Time, Hr.	% Yield III	% Yield IV
$(C_2H_5)_2N$	C_6H_6	80	2.0	—	51.8[a]
$(C_3H_7)_2N$	EtOH	80	1.5	—	86.0[b]
	DMF	30	18.0	75.0	20.7
	EtOH	25	23.0	57.0	17.3
	DMF	30	20.0	59.0	—[c]
C_2H_5O[d]	EtOH	25	24.0	56.8	25.6[f]
	DMF	25	24.0	61.8	14.1[f]
	DMF	25	4.0	70.4	—[c]
[e]	EtOH	80	3.0	—	79–82[f]

[a] 45.5% yield of diethylamine hydrochloride isolated. [b] 74% yield of dipropylamine hydrochloride isolated. [c] Attempt to isolate IV was unsuccessful. [d] With esters, IV is isolated as the hydrochloride (IV HCl) which on treatment with NaOAc gives IV. [e] Data from reference 6. [f] Yield of IV HCl.

EXPERIMENTAL

Thiourea and ethyl chloroacetate. The procedure used in the reactions of thiourea with 2-chloroacetates and 2-chloroacetamides[7] is illustrated by this typical example. A solution of 15.2 g. (0.2 mole) of thiourea and 24.5 g. (0.2 mole) of ethyl chloroacetate in 100 ml. of DMF was stirred at 25° for 24 hr. One liter of acetone was added to the clear solution and the precipitated solid was filtered; wt. 32.8 g. This was dissolved in 200 ml. of absolute ethanol and 4.3 g (14.1% yield) of pseudothiohydantoin hydrochloride was recovered by filtration of the alcohol insoluble material. The alcohol filtrate, diluted with 1.5 liters of ethyl acetate, afforded 24.5 g. (61.8% yield) of the isothiouronium hydrochloride [III, R = C_2H_5O], m.p. 110° (dec.).

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Prodigiosin Hydrochloride[1]

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Received March 10, 1958

Efimenko and co-workers[3] have claimed the isolation of prodigiosin hydrochloride from *Serratia marcescens* through a process involving chromatography of the bacterial pigment. Identification of the compound, which is described as red needles melting at 149°, rests solely upon analysis for carbon and hydrogen and apparently its absorption spectrum, λ_{max} 538–539 mμ[4] (presumably in ethanol). In a previous paper[5] we described the isolation of a magenta colored solid, m.p. 150.0–150.5° (dec.), from a powdered sugar chromatogram of the mixture resulting from the reaction of prodigiosin perchlorate with sodium hydroxide. At that time the similarity in the properties of the two products was noted. We have now established that the compound isolated by us is definitely prodigiosin hydrochloride. The substance gives a positive Beilstein test and elemental analyses are in good agreement with the calculated values for the hydrochloride, $C_{20}H_{26}ON_3Cl$. The ultraviolet-visible absorption spectrum is like that for prodigiosin perchlorate[5] with a main absorption maximum in isopropyl alcohol at 540 mμ ($\epsilon = 7.07 \times 10^4$) and a second very much weaker maximum at 294 mμ ($\epsilon = 1.08 \times 10^4$). The addition of aqueous sodium hydroxide to a solution of the magenta colored solid in isopropyl alcohol gave a mixture exhibiting absorption like that for prodigiosin with λ_{max} 468 mμ (ϵ 4.2×10^4). The observed[5] maximum

(1) This investigation was supported by a research grant, E-1335, from the National Institute of Allergy and Infectious Diseases, Public Health Service, to the University of Santa Clara.

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(3) O. M. Efimenko, G. A. Kutnesova, and P. A. Yakimov, *Biokhimiya*, 21, 416 (1956).

(4) Estimated by us from reported curve.

(5) A. J. Castro, A. H. Corwin, F. J. Waxham, and A. L. Beilby, submitted for publication in *J. Org. Chem.*

absorption for pure prodigiosin in isopropyl alcohol occurs at 466 mμ (ϵ 4.3 × 10^4). Moreover, a mixture of the magenta solid with prodigiosin hydrochloride, m.p. 148.5–150.0° (dec.), prepared from prodigiosin, showed no depression of the melting point and the infrared spectra for the two hydrochlorides are identical.

We attribute the presence of the hydrochloride in our chromatogram to an artifact arising from the introduction of traces of hydrogen chloride, or hydrochloric acid, during working up the mixture derived from the perchlorate. We were able to isolate 33.3 mg. of pure hydrochloride from the reaction of 2.00 g. of prodigiosin perchlorate with sodium hydroxide. Aside from operational losses, this corresponds to a yield of 2% and the combination of prodigiosin with 3.4 mg. of hydrogen chloride.

The compound described by the Russian workers is apparently identical with ours, as far as a comparison can be made. However, it should be pointed out that their product was derived by way of a process wherein the bacterial pigment was treated in one step with sodium hydroxide. We have observed an immediate change in color from that for the acid derivative (red) to that for the free base (orange) when sodium hydroxide is added to an isopropyl alcohol solution of the salt. Therefore, it cannot be unequivocally concluded from the earlier work that prodigiosin hydrochloride is a bacterial product. While it is possible that the conditions employed in the earlier study may have permitted incomplete reaction of any hydrochloride present, it would seem that another explanation, such as used to explain our results, should be considered.

EXPERIMENTAL

Magenta solid derived from prodigiosin perchlorate. The solid was isolated and purified as has already been described.[5]

Anal. Calcd. for $C_{20}H_{26}ON_3Cl$: C, 66.74; H, 7.28; N, 11.68; Cl, 9.86. Found: C, 66.90; H, 7.51; N, 11.56; Cl, 9.68.

The ultraviolet-visible absorption spectra were determined with a Beckman Model DU spectrophotometer. The spectrum for the magenta solid was measured using a solution containing 0.928 mg. of the compound per 100 ml. of isopropyl alcohol solution. The spectrum for the free base derived from the magenta solid was measured using the mixture obtained by adding 0.20 ml. of 0.507*N* aqueous sodium hydroxide to 9.80 ml. of a solution having 1.240 mg. of the magenta colored solid per 100 ml. of isopropyl alcohol solution.

Prodigiosin hydrochloride. One hundred milligrams of prodigiosin, m.p. 152.0–153.0° (dec.) was dissolved in about 15 ml. of petroleum ether and dry hydrogen chloride was added to the resulting solution until precipitation of the hydrochloride was complete. The mixture was stored in a refrigerator for an hour and the solid removed by filtration. After one recrystallization from a mixture of benzene and petroleum ether 65 mg. of magenta colored hydrochloride, m.p. 148.5-150.0° (dec.) was obtained.

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Preparation of 1-Methylsulfonyl-4-phenyl-1,3-butadiene

V. BALIAH AND SP. SHANMUGANATHAN

Received March 11, 1958

In connection with a study of conjugated sulfones, we required 1-methylsulfonyl-4-phenyl-1,3-butadiene. It was prepared by the following sequence:

$$CH_3SO_2CH_3 \xrightarrow{C_2H_5MgBr} CH_3SO_2CH_2MgBr$$

$$\xrightarrow[(2)\ HCl]{(1)\ C_6H_5CH=CHCHO} CH_3SO_2CH_2CHOHCH=CHC_6H_5$$

$$\longrightarrow CH_3SO_2CH=CHCH=CHC_6H_5$$

EXPERIMENTAL

3-Hydroxy-4-methylsulfonyl-1-phenyl-1-butene. A solution of ethylmagnesium bromide (prepared from 4.5 g. of magnesium, 20.8 g. of ethyl bromide and 100 ml. of ether) was added to 16.5 g. (0.18 mole) of dimethyl sulfone in 750 ml. dry anisole. A bulky white precipitate separated. The mixture was stirred by means of a liquid-sealed mechanical stirrer and heated on a water bath for 3 hr. and then stirred at room temperature for a further 2 hr. A solution of 16.5 g. (0.125 mole) of freshly distilled cinnamaldehyde in 50 ml. dry anisole was then added rapidly and stirring continued at room temperature for 16 hr. The reaction product was hydrolyzed with hydrochloric acid (2.5*N*, 100 ml.). The aqueous layer was separated and extracted with two 25-ml. portions of benzene. The benzene extract together with the anisole layer was washed thrice with 50-ml. portions of a saturated solution of sodium chloride and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure, the solid residue collected and washed with a few ml. of light petroleum (b.p. 70–80°). The yield of the crude product was 25.2 g. (90%). It crystallized as colorless plates from benzene and melted at 111–112°.

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 58.4; H, 6.2; S, 14.2. Found: C, 58.4; H, 5.9; S, 14.4.

The *acetate*, prepared with acetic anhydride and pyridine, crystallized from ethanol as needles, m.p. 85–86°.

Anal. Calcd. for $C_{13}H_{16}O_4S$: C, 58.2; H, 6.0. Found: C, 58.8; H, 6.2.

The *benzoate*, prepared in the usual manner, crystallized from ethanol as needles, m.p. 146–147°.

Anal. Calcd. for $C_{18}H_{18}O_4S$: C, 65.4; H, 5.5. Found: C, 65.7; H, 5.7.

1-Methylsulfonyl-4-phenyl-1,3-butadiene. A suspension of 2 g. of the foregoing hydroxy unsaturated sulfone in 4 ml. of 85% phosphoric acid was heated under reflux for 15 min., cooled, and diluted with water. A pasty mass was thrown out. It was dissolved in 50 ml. of hot benzene and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a yellow pasty mass which solidified after several days. The yield was 0.6 g. (32%). Recrystallization from ethanol gave colorless needles, m.p. 89–90.5°.

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.4; H, 5.8. Found: C, 63.1; H, 5.6.

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Some Properties of Fluorescein

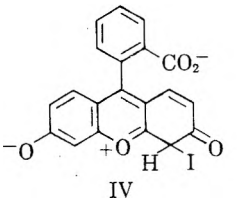
REUBEN B. SANDIN AND ROY L. ORVIS

Received March 14, 1958

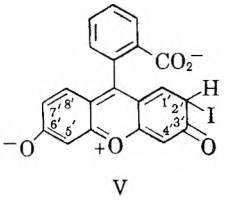
Previous investigators[1] have shown that electrophilic disubstitution, such as dinitration and dibromination, of fluorescein and sulfonefluorescein occurs in the hindered 4'- and 5'-positions. It has also been found that sulfonefluorescein, unlike fluorescein, does not undergo tetrabromination.[2] In order to account for the preference of 4',5'- over 2',7'-disubstitution it has been suggested[1b] that the xanthene dyes have a lactoid or quinoid structure in which there is fixation of double and single bonds. It was considered that a fixed structure for fluorescein and sulfonefluorescein was an extension of, and in accord with the theoretical prediction of Mills and Nixon.[3] However there has been much speculation regarding the reality of the Mills and Nixon effect. The structure of fluorescein nevertheless takes on an added interest, in view of the recent work of Davies and Jones[4] on the infrared absorptions of fluorescein and some alkali derivatives. Their results indicate that the classical lactoid structure is to be preferred. They also conclude that the dipolar ion structure is not the correct representation of fluorescein.

In the present work the iodination of fluorescein with excess iodine in ammonium hydroxide has been examined, and there is evidence that fluorescein is most susceptible to electrophilic attack by iodine at the hindered 4'- and 5'- positions. In ammonium hydroxide, fluorescein has shown a marked resistance to tetra substitution. The uptake of iodine at the end of 24 hr. was 95% of the amount calculated for diiodofluorescein, although the amount of iodine used was sufficient to form the tetraiodo compound.[5] At the end of 7 days the uptake of iodine was 103% of the amount calculated for diiodofluorescein. In a similar manner the compounds 4',5'-dibromo- (I), 2',7'-dibromo (II), and 2',7'-dichloro-fluorescein (III) have been treated with iodine. At the end of 7 days, I showed an uptake of iodine which was approximately 4%. The calculated amount for 4',5'-dibromo-2',7'-diiodofluorescein is 34.2%. On the other hand, II and III showed an iodine uptake which was almost the required amount for diiodination. From these results it is clear that there is definite resistance to 2',7'-disubstitution. However, it should be mentioned that the halogens already present at the 4'- and 5'-positions are deactivating.

A tentative explanation for the preferred 4',5'-substitution is the formation of an intermediate (IV) with naphthalene-like resonance stabilization, and which is therefore energetically favorable. Addition at a 2'- or 7'-position would give an intermediate (V) with a quinoid structure which would be less favorable.



IV



V

The present authors also suggest that the difference in properties between fluorescein and sulfonefluorescein, such as the nontetrabromination of sulfonefluorescein, may be due to the difference in nucleophilicity of the carboxylate and sulfonate ion.

EXPERIMENTAL

Materials. Fluorescein was prepared and purified by the procedure of Orndorff and Hemmer.[6] The dibromination of fluorescein was carried out according to Phillips[7] and afforded 4',5'-dibromofluorescein (I) which was purified through the diacetate. The tetrabromination of fluorescein was carried out according to Orndorff and Hemmer.[6] The procedure of Kolthoff, Lauer, and Sunde[8] for the preparation of 2',7'-dichlorofluorescein (II) gave excellent results. The dichloro compound was purified through the diacetate. However, it was found best to hydrolyze the diacetate by heating it on a water bath for several hours with 85% sulfuric acid. 2',7'-Dibromofluorescein[1b] (III) was made by heating tetrabromofluorescein with stannous chloride and hydrochloric acid in a glacial acetic acid–dioxane medium.

Iodination of fluorescein. To a solution of 4.0 g. (.012 mole) fluorescein in concentrated ammonium hydroxide (250 ml.) was added 12.2 g. (0.048 mole) of iodine dissolved in a solution of potassium iodide (25 g.) in water (50 ml.). The reaction mixture was allowed to stand at room temperature for 7 days. During this period the mixture was stirred occasionally and *care was taken to prevent the accumulation of explosive nitrogen triiodide on the inside walls of the container.* At the end of 24 hr., any solid material had usually dissolved. After 7 days the clear solution was poured with stirring into a mixture of concentrated hydrochloric acid (400 ml.) and ice (1 kg.). After warming gently, the precipitate was filtered off and washed thoroughly with hot water. The solid was dissolved in dilute sodium hydroxide and the precipitation, filtration, and washing procedure repeated. The material was

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(2) W. R. Orndorff and R. S. Vose, *J. Am. Chem. Soc.*, **46**, 1896 (1924).

(3) W. E. Mills and I. G. Nixon, *J. Chem. Soc.*, 2510 (1930).

(4) M. Davies and R. L. Jones, *J. Chem. Soc.*, 120 (1954).

(5) In the present work there is no rigid proof for the structure of diiodofluorescein. However, on the basis of a similarity between iodination and other electrophilic substitution reactions such as bromination and nitration, the structure is assumed to be 4',5'-diiodofluorescein. Also the fact that substituents in the 2',7'-positions do not hinder iodination is in favor of a 4',5'-diiodo structure.

(6) W. R. Orndorff and A. J. Hemmer, *J. Am. Chem. Soc.*, **49**, 1272 (1927).

(7) M. A. Phillips, *J. Chem. Soc.*, 724 (1932).

(8) I. M. Kolthoff, W. M. Lauer, and C. J. Sunde, *J. Am. Chem. Soc.*, 51, 3273 (1929).

dried and no attempt was made to purify it, since the purpose of this work was to determine only the extent of iodination.

Anal. Calcd. for $C_{20}H_{10}O_5I_2$: I, 43.5. Found: I, 44.8, 44.9.

In a similar manner, after 24 hr., the reaction mixture afforded a crude diiodofluorescein which was analyzed.

Anal. Calcd. for $C_{20}H_{10}O_5I_2$: I, 43.5. Found: I, 41.4, 41.3.

Iodination of I, II, *and* III. Compounds I, II, and III were allowed to react for 7 days with excess iodine in ammonium hydroxide, in the manner described for fluorescein, and the crude products were analyzed. In the case of I, some iodination took place.

Anal. Found for 0.2086 g. of $C_{20}H_8O_5Br_2I_2$: Ag halide, 0.1688.

The combined AgI and AgBr was converted into AgCl.[9] Found: AgCl, 0.1264 g. On this basis the extent of iodination is 4.1%.

Calcd. for $C_{20}H_8O_5Br_2I_2$: I, 34.2.

Compounds II and III showed an uptake of iodine which was close to the required amount.

Anal. Found for 0.3548 g. of $C_{20}H_8O_5Cl_2I_2$: Ag halide, 0.3914 g. Found: AgCl, 0.3014 g. The extent of iodination was 35.2%. Calcd. for $C_{20}H_8O_5Cl_2I_2$: I, 38.8.

Anal. Found for 0.4034 g. of $C_{20}H_8O_5Br_2I_2$: Ag halide, 0.4570 g. Found: AgCl, 0.3126 g. The extent of iodination was 32.3%. Calcd. for $C_{20}H_8O_5Br_2I_2$: I, 34.2.

Acknowledgment. We are very grateful to Dr. F. Marshall Beringer of the Department of Chemistry of the Polytechnic Institute of Brooklyn for many helpful suggestions.

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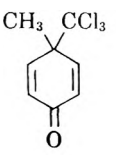
(9) E. P. Treadwell and W. T. Hall, *Analytical Chemistry*, Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1935, p. 310.

Communications TO THE EDITOR

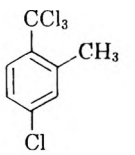
A New Rearrangement Involving a Trichloromethyl Group

Sir:

The rearrangement of 4-methyl-4-trichloromethyl-2,5-cyclohexadienone (I) to 3-methyl-4-trichloromethylchlorobenzene (II) on treatment with phosphorus pentachloride has been reported.[1] In an attempt to make 3,5-dimethyl-4-trichloromethyl chlorobenzene by a similar rearrangement, we prepared 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (III).[2] When treated with phosphorus pentachloride, III underwent a new rearrangement to yield 3-(β,β,β-trichloroethyl)-4-methylchlorobenzene (IV) in 88% yield. No trace of a benzotrichloride product was detectable.



I



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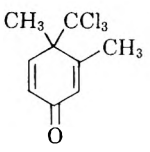
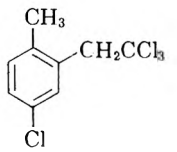


III



IV

The structure of IV was established by the following facts. Oxidation with alkaline permanganate yielded 4-chlorophthalic acid. Oxidation with a theoretical amount of chromic acid yielded 2-(β,β,β-trichloroethyl)-4-chlorobenzoic acid. Treatment of IV with sodium ethoxide readily afforded 3-(β,β-dichlorovinyl)-4-methyl chlorobenzene (V) which in turn yielded 2-methyl-5-chlorobenzoic acid on oxidation.

3,4-Dimethyl-4-trichloromethyl-2,5-cyclohexadienone (III) was prepared by the reaction of 61.1 g. of 3,4-dimethylphenol, 400 ml. of carbon tetrachloride, and 166 g. of anhydrous aluminum chloride at 5–20° for 2.5 hr. The yield was 92.1 g. (76.6%) of III, m.p. 60.0–61.0°. (*Anal.* Calcd. for $C_9H_9OCl_3$: C, 45.0; H, 3.8; Cl, 44.5. Found: C, 45.1; H, 3.6; Cl, 44.5.) The spontaneous exothermic reaction of 24 g. of III with 21 g. of phosphorus pentachloride yielded 22.8 g. (88.5%) of 3-(β,β,β-trichloroethyl)-4-methylchlorobenzene (IV), b.p. 121.0–128.0° at 4 mm., m.p. 35.0–36.1°. (*Anal.* Calcd. for $C_9H_8Cl_4$: C, 41.9; H, 3.1; Cl, 55.0. Found: C, 41.5; H, 3.2; Cl, 55.0.) The oxidation of 1.3 g. of IV with 1.3 g. of sodium dichromate dihydrate in a mixture of 60 ml. of glacial acetic acid and 2 ml. of concentrated sulfuric acid for 12 hr. on a steam bath yielded 1.34 g. (93.0%) of 2-(β,β,β-trichloroethyl)-4-chlorobenzoic acid, m.p. 168.0–169.5°. (*Anal.* Calcd. for $C_9H_6Cl_4O_2$: C, 37.8; H, 2.1; Cl, 49.0. Found: C, 37.7; H, 2.2; Cl, 49.0.)

The slow addition of an ethanolic solution of 10 g. of sodium ethoxide to an ethanolic solution of 38.5 g. of IV yielded 13.5 g. (40.8%) of 3-(β,β-dichlorovinyl)-4-methylchlorobenzene (V) as the major product, b.p. 114.5–115.5° at 16 mm. (*Anal.* Calcd. for $C_9H_7Cl_3$: C, 48.9; H, 3.2; Cl, 48.1. Found: C, 49.0; H, 3.3; Cl, 47.8.) The oxidation of 2.2 g. of V with 3.2 g. of potassium permanganate in a 4 to 1 pyridine-water mixture was completed in 10 min. at 25° to yield 1.05 g. (62.0%) of 5-chloro-2-methylbenzoic acid, m.p. 169.5–171.0°. A mixed m.p. with authentic 5-chloro-2-methylbenzoic acid[1] was unchanged.

Details of this and related work will be reported later.

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(1) K. Von Auwers and W. Julicher, *Ber.*, **55**, 2180 (1922).

(2) Compare Th. Zincke and R. Suhl, *Ber.*, **39**, 4152 (1906).

Favorable Effect of Imidazole on Peptide Synthesis by the Tetraethylpyrophosphite Method

Sir:

It has been proposed that the imidazole group of histidine is an active site on enzyme molecules, and imidazole has been shown to be a catalyst for the hydrolysis of esters.[1,2] Acyl imidazoles are known to be highly reactive, and in fact peptide derivatives have been synthesized *via* *N*-acylation of the imidazole ring of methyl *N*-benzoyl-L-histidinate.[3] It was, therefore, of interest to study the effect of added imidazole on the synthesis of peptides by several of the commonly used procedures.

No improvement of yields was found in preliminary experiments using the isobutyl chlorocarbonate

(1) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652 (1957).

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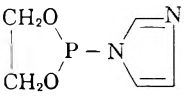
(3) T. Wieland and G. Schneider, *Ann.*, **580**, 159 (1953).

and azide procedures. In contrast, yields were consistently improved when imidazole was used in peptide syntheses by the tetraethylpyrophosphite procedure. For example, the reaction of carbobenzoxyglycine with ethyl L-tyrosinate gave crude yields of 60–70% of ethyl carbobenzoxyglycyl-L-tyrosinate[4,5] by the standard tetraethylpyrophosphite procedure,[5] and 85–90% when an equivalent of imidazole was present; recrystallized yields were in proportion. Several experiments showed that the rate of peptide formation was approximately doubled. For example, the reaction of carbobenzoxyglycine with ethyl DL-phenylalaninate hydrobromide in diethyl phosphite with trimethyl phosphite as HBr acceptor and tetraethyl pyrophosphite as reagent by the standard procedure[5] was timed so that the reaction was incomplete: heating for 180 seconds on a steam bath gave a 41% yield of ethyl carbobenzoxyglycyl-DL-phenylalaninate when no imidazole was present, and 75% when an equivalent of imidazole was present.

Maximum yields are obtained when imidazole is used in molar equivalence to the amino acid or peptide reactants. Also, best results are obtained when the imidazole is mixed with tetraethylpyrophosphite before addition of the latter to the peptide-forming reactants.

An attempt to isolate a possible intermediate, diethyl 1-imidazolephosphite, from reaction of tetraethyl pyrophosphite with imidazole was unsuccessful. However, the reaction of ethylene chlorophosphite with imidazole in benzene in the presence of triethylamine gave cyclic ethylene 1-imidazolephosphite [2-(1-imidazolyl)-1,3,2-dioxaphospholane] (I) as a very hygroscopic, crystalline solid, m.p. about 35°.



(I)

Anal: Calcd.: C, 37.98%; H, 4.46%. Found: C, 38.59; 37.94%; H, 4.85, 4.72%. A sample quickly weighed out was used in place of tetraethylpyrophosphite to prepare ethyl carbobenzoxyglycyl-L-tyrosinate by the standard procedure, giving a 91% crude yield, m.p. 122–125°. Recrystallization from ethanol-water gave an over-all yield of 77% with m.p. 125.5–127°. Thus cyclic ethylene 1-imidazolephosphite is an excellent peptide-forming reagent, but its hygroscopicity might limit its utility.

The effects of substituted imidazoles and related heterocycles are under investigation and will be reported at a later date.

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Received June 26, 1958

(4) J. R. Vaughan, Jr. and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(5) G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5309 (1952).