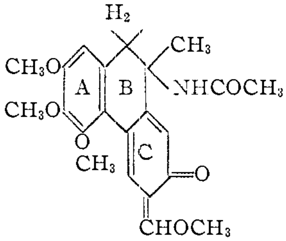
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Studies on the Structure of Colchicine

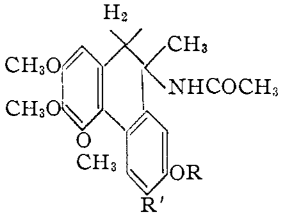
BY D. STANLEY TARBELL, H. RICHARD FRANK[1] AND PAUL E. FANTA[2]

Interest in the compound colchicine, obtained from the seeds of the autumn crocus, has been markedly increased in recent years by the discovery that it arrests the process of cell division (mitosis) in plant or animal cells,[3] but its structure is still not definitely known in all details. The present paper reports some observations in this field, in which we have been interested for some time.

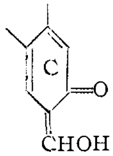
Fundamental work on the structure of colchicine was done by Windaus,[4] who proposed formula I.[4d,5]



I



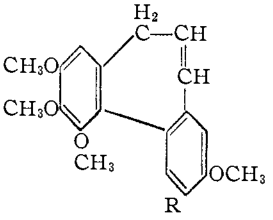
III, R = H, R' = I
IV, R = CH_3, R' = I
V, R = CH_3, R' = H



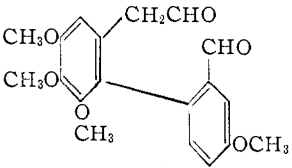
II

One of the key degradation products obtained by Windaus was deaminocolchinol methyl ether, obtained by the following series of reactions. Hydrolysis of colchicine with very dilute acid yielded colchiceine (II), with loss of the methyl group, the rest of the molecule being unchanged. Treatment of II with alkaline hypoiodite replaced the hydroxymethylene group with iodine, yielding N-acetyliodocolchinol (III), which, in contrast to II, behaved like a phenol and could be methylated by the ordinary methods, yielding IV. Removal of the iodine from IV gave N-acetylcolchinol methyl ether (V), and this on acid hydrolysis lost the N-acetyl group to form the corresponding amino compound, colchinol methyl ether. Hofmann exhaustive methylation of this amine led to the nitrogen-free compound, deaminocolchinol methyl ether, which Windaus regarded as a 9-methyltetramethoxyphenanthrene, because on cleavage of the methoxyl groups with hydriodic acid followed by zinc dust distillation, 9-methylphenanthrene was obtained. Windaus' conclusion that in colchicine itself ring B was 6-membered was questioned by Cohen, Cook and Roe,[6] who suggested that ring B might be seven-membered.[7]

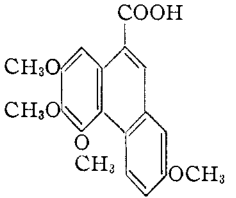
The structure of deaminocolchinol methyl ether was not established by Windaus, but on his formulation it should be 2,3,4,6(or 7)-tetramethoxy-9-methylphenanthrene. In recent studies[8] J. W. Cook has shown that it is not a phenanthrene derivative, since it forms no picrate and is reduced catalytically by palladium to a dihydride, in contrast to the synthetic 2,3,4,6- and 2,3,4,7-tetramethoxy-9-methylphenanthrenes. The seven-membered ring structure VI postulated for deaminocolchinol methyl ether was supported by oxidation to a glycol with osmium tetroxide, which, on cleavage with lead tetraacetate, yielded a gummy product believed to be the dialdehyde VIII. The gum gradually formed a crystalline monoaldehyde by an aldol condensation. This was shown to be 2,3,4,7-tetramethoxy-10-phenanthraldehyde by oxidation to the corresponding acid IX which was synthesized; this result incidentally establishes the position of the methoxyl group in ring C of the colchicine derivatives IV and V.



VI, R = H
VII, R = I



VIII



IX

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[1] Abbott Laboratories Fellow, 1944–1946.

[2] Abbott Laboratories Fellow, 1943–1944.

[3] For references to the effect of colchicine as a mitotic poison, which has had important applications in botany and in the study of cancer, see (a) Lettré and Fernholz, *Z. physiol. Chem.*, **278**, 175 (1943); (b) Henry, "The Plant Alkaloids," 3rd ed., Blakiston, Philadelphia, 1939, pp. 577–578.

[4] (a) Windaus, *Sitzber. Heidelberg. Akad. Wiss., Math. naturw. Klasse*, 2. abh (1911); (b) *ibid.*, 18. abh (1914); (c) *ibid.*, 16. abh (1919); (d) *Ann.*, **439**, 59 (1924); this paper summarizes his earlier work.

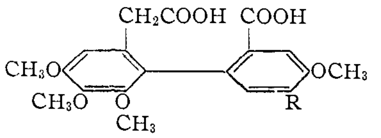
[5] Grewe, *Ber.*, **71**, 907 (1939).

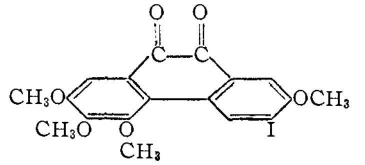
[6] Cohen, Cook and Roe, *J. Chem. Soc.*, 194 (1940).

[7] The interesting suggestion [Dewar, *Nature*, **155**, 141 (1945)] that ring C of colchicine and colchiceine is 7-membered, and is isomerized to an aromatic ring on treatment with hypoiodite, may account for the peculiar properties of these compounds. In this connection, attention may be called to the fact that colchicine is an indicator and is colored in dilute alkali [*cf.* Davies and Grier, *Pharm. J.*, **109**, 210 (1922)]. Absorption curves for colchicine in neutral and basic solution are given in Fig. 1. The curve in dilute acid (*p*H 2) is almost identical with the one in neutral solution.

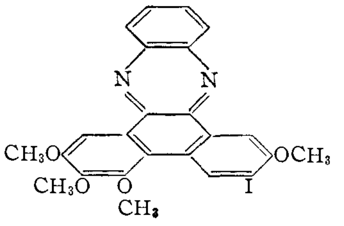
[8] (a) Buchanan, Cook and Loudon, *J. Chem. Soc.*, 325 (1944); (b) Barton, Cook and Loudon, *ibid.*, 176 (1945).

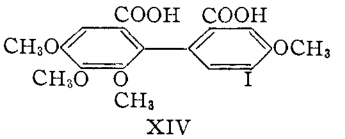
We have been able to provide independent evidence for the presence of a seven-membered ring[9] in deaminoiodocolchinol methyl ether (VII); the iodine-containing compound was studied since the members of this series crystallize better than the iodine-free analogs. Oxidation of VII with permanganate in acetone at room temperature gave a dibasic acid in yields up to 25%, whose


X, R = I
XI, R = H


XII

composition and neutral equivalent agreed with structure X. The iodine atom was removed by reduction with hydrogen and nickel, yielding XI. Accompanying the dibasic acid was a very small amount (one or two mg. per run) of a red compound, which must be the phenanthrenequinone XII analogous to an iodine-free quinone obtained by Cook. It was converted into the quinoxaline XIII.


XIII


XIV

These acids X and XI are significant since they possess the methylene group; this means that they were derived from a seven-membered ring. The percentage composition of the acid X is appreciably different from that of the diphenic acid XIV, and no compound corresponding to the composition of this acid was obtained from the oxidation.

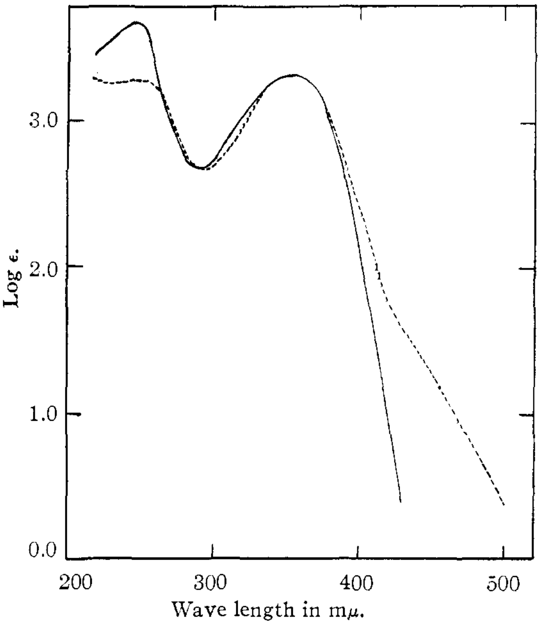
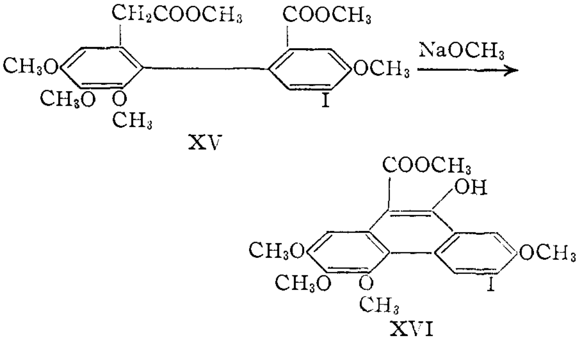


Fig. 1.—Molar extinction curves in aqueous solution: colchicine —— in water, *p*H 7; - - - - in 0.01 *N* sodium hydroxide, *p*H 12.

To demonstrate conclusively the presence of the methylene group in X, it was esterified with diazomethane to the diester XV, and this was treated with sodium methoxide, yielding a crystalline product formed by loss of methanol. This product can only be the phenanthrol XVI; it is insoluble in aqueous alkali, but can be dissolved in methanolic alkali.


XV
XVI

The absorption curves for XV and XVI, given in Fig. 2, show some resemblance, but the maxima are shifted to longer wave length in the phenanthrol XVI, which is in agreement with the higher degree of conjugation in this compound. Curves for the quinone XII and for deaminoiodocolchinol methyl ether (VII) are also given. The latter has a maximum at about the same point as N-acetylcolchinol methyl ether,[6] although the shape of the curve is not very similar.

When this work was started, the most important contribution to the problem seemed to be the synthesis of the tetramethoxymethylphenanthrenes previously mentioned. A promising approach seemed to be the elegant phenanthrene synthesis of Bradsher,[10] and the following scheme was

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[9] It is of course recognized that the position of the double bond in VII is not proved, and the uncertainty carries over to the dibasic acids X and XI.

[10] Bradsher and Schneider, THIS JOURNAL, **60**, 2960 (1938), and later papers.

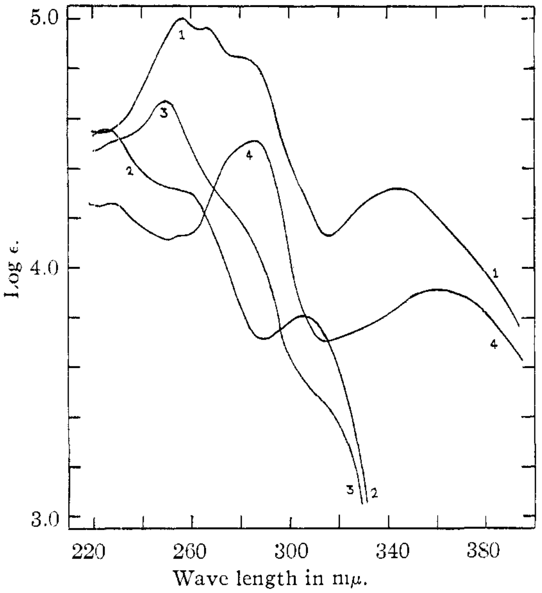
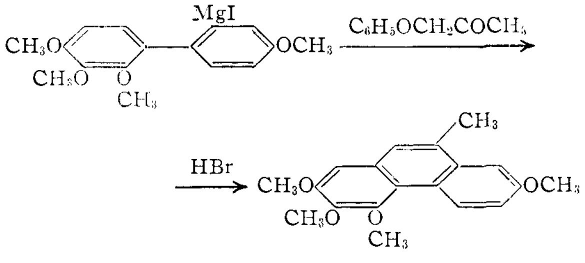


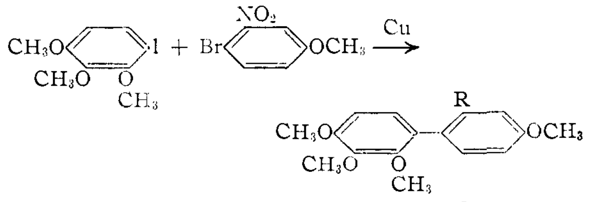
Fig. 2.—Molar extinction curves in ethanol; (1) phenanthrol XVI, (2) ester XV, (3) cycloheptatriene VII, (4) phenanthraquinone XII.

planned for the synthesis of 2,3,4,7-tetramethoxy-9-methylphenanthrene. At the time of Cook's

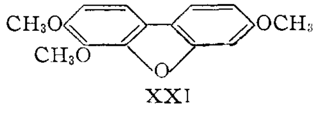


publication of the syntheses of the phenanthrene compounds, we had prepared the required iodobiphenyl derivative by the method described below; this substance offers an attractive starting point for other syntheses in this series, which are being investigated.

2,3,4,4′-Tetramethoxy-2′-nitrobiphenyl (XVII) was prepared by a crossed Ullmann reaction in 36% yield; neither of the symmetrical biphenyls was isolated.[11] The nitrobiphenyl XVII was catalytically reduced to the amine, and this was converted in rather low yield to the iodine compound. In spite of a large number of trials under different conditions the yield could not be raised above 35%.



XVII, R = NO_2
XVIII, R = NH_2
XIX, R = $NHCOCH_3$
XX, R = I



XXI

The diazotized amine XVIII when warmed in acid solution yielded a neutral compound, which is believed to be 3,4,7-trimethoxydibenzofuran (XXI), formed by demethylation and loss of nitrogen. The structure is supported by the analysis and by comparison of the absorption spectrum of the material with that of dibenzofuran itself, shown in Fig. 3; the curves are of the same general character, although the curve of XXI is shifted toward longer wave length and has less fine structure.[12]

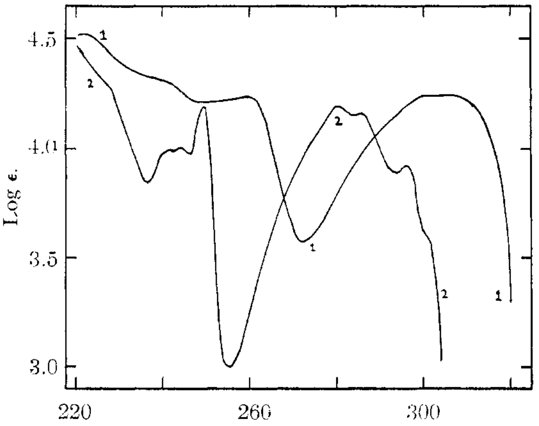


Fig. 3.—Molar extinction curves of (1) trimethoxydibenzofuran XXI, (2) dibenzofuran in ethanol.

The formation of dibenzofuran[13] itself from 2-amino-2′-methoxybiphenyl has been observed under similar conditions. Pschorr and Knöffler[14] reported the formation of an interesting compound containing a seven-membered ring in an analogous type of ring closure involving demethylation and loss of nitrogen.

Experimental[15]

N-Acetyl iodocolchinol methyl ether (IV)[4b] was prepared more advantageously by the inverse methylation procedure, adding concentrated sodium hydroxide dropwise to a solution of dimethyl sulfate and III in methanol.

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[11] For a comprehensive summary of the Ullmann reaction, see Fanta, *Chem. Rev.*, **38**, February (1946).

[12] The absorption curve for dibenzofuran has been reported by Hillmer and Schorning, *Z. physik. Chem.*, **A168**, 81 (1934), and Ley and Specker, *Z. wiss. Phot.*, **38**, 12 (1939), in hexane solution, and is very similar to our curve taken in alcohol.

[13] Mascarelli and Pirona, *Gazz. chim. ital.*, **68**, 117 (1938); *C. A.*, **32**, 6235 (1938).

[14] Pschorr and Knöffler, *Ann.*, **382**, 50 (1911).

[15] All melting points are corrected and were taken on the heated stage; microanalyses by Dr. Carl Tiedcke and Mr. Carl Claus. Absorption curves were taken with a Beckmann Spectrophotometer, using ethanol as solvent which had been purified by the method of Leighton, Crary and Schipp, THIS JOURNAL, **53**, 3017 (1931). We are indebted to Drs. E. H. Volwiler and M. T. Leffler of the Abbott Laboratories for assistance in obtaining the colchicine used.

Deaminoiodocolchinol Methyl Ether (VII).—This compound was prepared much more conveniently by a modification of the procedure of Cook and Graham[16] than by exhaustive methylation. In a 200-cc. three-necked flask, fitted with condenser, stirrer and addition tube, one gram of N-acetyliodocolchinol methyl ether was suspended in 100 cc. of purified dried xylene. To the reaction mixture, heated in an oil-bath, was added three grams of phosphorus pentoxide in one portion as soon as the bath temperature reached 120° with vigorous stirring throughout. The bath temperature was raised rapidly to 150–160° and held there for five minutes, until the violet color of iodine was visible in the refluxing xylene. After rapid cooling, the solution was decanted and evaporated to dryness at reduced pressure. The phosphorus pentoxide residue was extracted with benzene and the extract added to the solution to be evaporated. The residue, recrystallized from a mixture of methanol–acetone or glacial acetic acid, melted at 175–176°. The product was very soluble in benzene, moderately soluble in acetone and ethanol, slightly soluble in methanol. Yields from 50–70% were obtained in some runs.

Anal. Calcd. for $C_{19}H_{19}O_4I$: C, 52.07; H, 4.37. Found: C, 52.09; H, 4.45.

Oxidation of Deaminoiodocolchinol Methyl Ether; Formation of X.—A solution of 100 mg. of deaminoiodocolchinol methyl ether (VII) in 50 cc. of purified acetone containing 100 mg. of potassium permanganate was left standing at room temperature until the violet color had been discharged (about four hours are necessary).

The brown precipitate was filtered and decomposed with 1 *N* oxalic acid solution to which a few drops of concentrated hydrochloric acid had been added. The residue on the filter was dissolved in bicarbonate, and precipitated by adding dilute hydrochloric acid dropwise. Evaporation of the acetone filtrate left a residue of starting material and bicarbonate-soluble product, which was combined with the above acid. The flocculent precipitate was dissolved in acetone after drying, and after evaporation of the acetone allowed to crystallize from benzene, m. p. 255–257°, raised after three recrystallizations to 264–265°. In one case 40 mg. of product was obtained (25% yield), but, in general, yields were about 15%. Potentiometric titration gave a curve with two breaks, corresponding to molecular weights of 566, 595. $C_{19}H_{19}O_8I + C_6H_6$ requires 580. The benzene of crystallization was incompletely removed by vacuum drying at 65°, but a sample of the acid, dried in a vacuum at 100°, analyzed correctly.

Anal. Calcd. for $C_{19}H_{19}O_8I$: C, 45.43; H, 3.81. Found: C, 45.08, 45.30; H, 3.71, 3.54. Calcd. for $C_{18}H_{17}O_8I$ (one less CH_2 group): C, 44.28; H, 3.51.

A solution of 400 mg. of deaminoiodocolchinol methyl ether in 50 cc. of acetone, refluxed with 2.0 g. of potassium permanganate for four hours, yielded by the above method of purification 10 mg. of an acid; it crystallized in light yellow prisms, m. p. 214–216° after previous sintering, slightly soluble in ether and benzene, moderately soluble in methanol. Microanalysis gave C, 41.67, 41.55; H, 4.22, 4.19. The quantity obtained was insufficient for further investigation. The methyl ester, prepared with ethereal diazomethane, formed white plates from methanol, m. p. 138–141°.

The Quinone XII.—The bicarbonate-insoluble organic residue in the manganese dioxide precipitate from the above oxidation was dissolved in a few drops of methanol and turned dark red when evaporated in a stream of air. A small amount, about 3 mg., of dark red needles, of m. p. 213° when recrystallized from ethanol, was obtained which was identical with a product isolated from the oxidation of VII with chromic anhydride and acetic acid.

Anal. Calcd. for $C_{18}H_{15}O_6I$: C, 47.60; H, 3.33. Found: C, 47.60; H, 3.54.

The Quinoxaline XIII was prepared by adding 2 mg. of *o*-phenylenediamine in methanol to a solution of 4.5 mg. of the quinone in benzene. On warming, the red solution turned bright yellow. After evaporating the solvent, the product was recrystallized from ethanol, forming orange-yellow needles of m. p. 270–271°.

Anal. Calcd. for $C_{24}H_{19}O_4N_2I$: C, 54.77; H, 3.64. Found: C, 54.74; H, 3.75.

Preparation of the Iodine-free Acid XI.—The pure acid X (50 mg.) was reduced in ethanol solution containing a little bicarbonate with Raney nickel, shaking for two hours with hydrogen at three atm. and room temperature. After filtering from Raney nickel, the solution was evaporated to dryness at reduced pressure. On acidification with dilute mineral acid, the product precipitated as white flakes, and recrystallized as colorless plates from benzene, m. p. 243–245° (yield, 90%).

Anal. Calcd. for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36. Found: C, 60.40, 60.66; H, 5.17, 5.27. Calcd. for $C_{18}H_{18}O_8$ (one less CH_2 group): C, 59.72; H, 5.01.

The Dimethyl Ester XV.—A solution of the pure acid X in ether was treated with excess ethereal diazomethane solution, the ether evaporated, and the ester obtained in almost quantitative yield; recrystallized from ethanol, it melted at 146–148°. When less highly purified acid was methylated, three recrystallizations of the methyl ester were necessary.

Anal. Calcd. for $C_{21}H_{23}O_8I$: C, 47.56; H, 4.37. Found: C, 47.23, 47.35; H, 4.30, 4.24. Calcd. for $C_{20}H_{21}O_8I$ (one less CH_2 group): C, 46.52; H, 4.10.

Condensation of the Dimethyl Ester XV.—To a solution of 44 mg. of the dimethyl ester in 3 cc. of benzene a threefold excess of sodium methoxide was added. After refluxing an hour, the solid, consisting of the sodium salt of the product and sodium methoxide, was collected by filtration, the starting material staying in solution. The solid was taken up in methanol, acidified with hydrochloric acid, and the methanol evaporated in an air-stream. The residue was washed with bicarbonate and water, and the product (6 mg.) recrystallized from methanol, in which it is only slightly soluble, forming fine yellowish needles of m. p. 194–195.5°. The product was insoluble in aqueous alkali but soluble in alcoholic alkali.

Anal. Calcd. for $C_{20}H_{19}O_7I$: C, 48.21; H, 3.84. Found: C, 48.07; H, 4.13.

2-Nitro-4-methoxybromobenzene was prepared in 69% yield by the Sandmeyer reaction from 2-nitro-4-methoxyaniline.[17] The product was isolated by ether extraction and vacuum distillation, b. p. 135–137 (4 mm.); this material was dark orange in color and did not solidify completely on cooling to room temperature.[18]

2,3,4,4′-Tetramethoxy-2′-nitrobiphenyl (XVII).—Eighty-eight grams (0.30 mole) of 4-iodopyrogallol trimethyl ether[19] and 46 g. (0.20 mole) of 2-nitro-4-methoxybromobenzene were heated to 200° in a Wood's metal bath and 92 g. of copper powder (Baker copper powder, precip.) was added in small portions during one and one-half hours with intermittent stirring while the temperature was gradually raised to 250°. The temperature must not be allowed to rise above 250° and the reaction must be watched carefully, as it may become vigorously exothermic. Heating and intermittent stirring were continued for one and one-half hours after all of the copper had been added. At the end of this time the molten material was poured while hot into a 2-liter Erlenmeyer flask and stirred while cooling to produce small, more readily extractable lumps. The product was extracted with three 300-cc. portions of hot alcohol, the extracts decolorized with charcoal and cooled to 0°. Two recrystallizations from 750-cc. portions of alcohol, using 5 g. of charcoal each time, gave 23.1 g. (36% based on the amount of 2-

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[16] Cook and Graham, *J. Chem. Soc.*, 322 (1944).

[17] Fanta and Tarbell, "Organic Syntheses," **25**, 78 (1945).

[18] The reported melting point [Hodgson and Dyson, *J. Chem. Soc.*, 947 (1935)] is 32° after recrystallization from alcohol. Recrystallization is unnecessary when the product is to be used in the Ullmann reaction.

[19] Erdtman, *Proc. Roy. Soc. (London)*, **A143**, 191 (1934).

nitro-4-methoxybromobenzene used) of slightly brownish-yellow plates, m. p. 110–112°. A further recrystallization from alcohol after long boiling with charcoal gave pale yellow plates, m. p. 112–113°.

Anal. Calcd. for $C_{16}H_{17}O_6N$: C, 60.16; H, 5.37. Found: C, 59.73; H, 5.41.

2,3,4,4′-Tetramethoxy-2′-aminobiphenyl (XVIII).—The nitro compound (8.15 g.) was reduced with hydrogen and Raney nickel at 115° and 800 lb.; the product (6.6 g., 90%) after crystallization from alcohol, formed slightly tan plates, m. p. 107.5–109°. Recrystallization from alcohol gave white plates, m. p. 109.5–110°.

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.40; H, 6.62. Found: C, 66.13; H, 6.64.

An **acetyl derivative, XIX,** after crystallization from dilute methyl alcohol and petroleum ether–benzene, gave fine, white needles, m. p. 98–99°.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.22: H, 6.39. Found: C, 65.02; H, 6.30.

2,3,4,4′-Tetramethoxy-2′-iodobiphenyl (XX).—A solution of 2.89 g. of 2,3,4,4′-tetramethoxy-2′-aminobiphenyl in 25 cc. of 3.6 *N* sulfuric acid, diluted after the amine had dissolved to 45 cc., was diazotized at 0° by adding slowly a solution of 0.7 g. of sodium nitrite in 5 cc. of water. The diazonium solution was then poured with stirring into an ice-cold suspension of 15 g. of copper powder in 25 cc. of 50% potassium iodide solution. Slow evolution of nitrogen took place, and the decomposition of the diazonium iodide was completed by leaving the mixture in the ice-box overnight, then slowly heating up to 100°. The copper powder, on which the organic material was adsorbed, was collected by filtration, washed with water and dried, and extracted with several portions of hot benzene. The extracts were evaporated to dryness with a stream of air. The residue, after it had been taken up in hot methanol and boiled with charcoal, filtered and cooled, deposited 1.40 g. (a 35% yield) of white granular crystals of the iodobiphenyl, m. p. 102–103° after a second crystallization from methanol. A 25% yield was obtained when no copper was used to disperse the diazonium complex, which then formed a viscous dark red oil, from which the product was purified only with difficulty.

Anal. Calcd. for $C_{16}H_{17}O_4I$: C, 48.00; H, 4.28; I, 31.7. Found: C, 48.06; H, 4.61; I, 31.9 (Parr bomb).

3,4,7-Trimethoxydibenzofuran (XXI).—On diazotizing the above amine under the same conditions, and allowing the diazonium solution to warm up slowly to room temperature, a reddish oil was deposited on the sides of the flask. After boiling with charcoal in methanol solution, a neutral compound crystallized on diluting with water, m. p. 75–76°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.73; H, 5.54.

Summary

1. Deaminoiodocolchinol methyl ether has been shown to contain a seven-membered ring by oxidation to a dibasic acid. The dimethyl ester of the acid undergoes an ester condensation with sodium methoxide to form a phenanthrol, proving the presence of α-hydrogens in the ester.

2. 2,3,4,4′-Tetramethoxy-2′-nitrobiphenyl has been prepared by a crossed Ullmann reaction between 4-iodopyrogallol trimethyl ether, and 2-nitro-4-methoxybromobenzene, and has been converted into the corresponding amino and iodo compounds. 3,4,7-Trimethoxydibenzofuran is formed from diazotized 2,3,4,4′-tetramethoxy-2′-aminobiphenyl in acid solution.

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

The Thermal Decomposition of Tetrahydrofuran

BY CHARLES H. KLUTE[1] AND W. D. WALTERS

It has been observed that the homogeneous thermal decomposition of the cyclic ether, dioxane, proceeds mainly by a chain reaction.[2] However, other studies[3] have indicated that saturated cyclic compounds such as cyclopentane, methyl cyclopentane, cyclohexane and succinic anhydride, thermally decompose chiefly by non-chain processes. In certain instances, in addition to decomposition into compounds with fewer carbon atoms, dehydrogenation of the ring appears to occur as a homogeneous reaction. The earlier work on the thermal behavior of the cyclic ether, tetrahydrofuran, was concerned with the production of butadiene by catalytic dehydration, particularly over phosphate catalysts having an acid reaction.[4] The present investigation of the products as well as the kinetics of the decomposition was undertaken in order to obtain more information concerning the homogeneous thermal decomposition of cyclic compounds.

Experimental

Materials.—Tetrahydrofuran was prepared by the hydrogenation of furan over a Raney nickel catalyst at room temperature under a gage pressure of 60 psi. Prior to hydrogenation the absolute alcohol under which the Raney nickel had been stored was completely removed from the catalyst by evacuation with a diffusion pump and then dry furan was distilled under vacuum into the flask containing the catalyst. The furan was obtained either from the Eastman Kodak Company or from the Quaker Oats Company. After hydrogenation the tetrahydrofuran was dried with fused sodium hydroxide pellets and separated into three fractions by distillation in a stream of nitrogen through a vacuum-jacketed fractionating column. The middle fraction was dried over freshly cut metallic sodium and then tested for peroxides by means of the ferric ion–thiocyanate test.[5] If peroxides

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