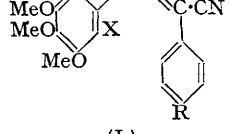
86. *Colchicine and Related Compounds. Part III.*

By J. W. Cook, Walter Graham, and (in part) A. Cohen, R. W. Lapsley, and (the late) C. A. Lawrence.

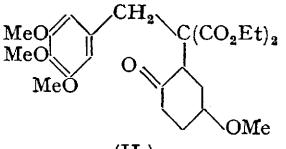
With the dual object of synthesising a colchicine degradation product and thus establishing its structure, and of obtaining analogous compounds for biological study, possible synthetic routes to methoxylated phenanthrenes have been explored. The above-mentioned degradation product, prepared by Windaus by Hofmann degradation of colchinol methyl ether and regarded by him as 2 : 3 : 4 : (6 or 7)-tetramethoxy-9-methylphenanthrene, has been obtained more simply by the action of phosphoric oxide on *N*-acetylcolchinol methyl ether.

In Part I (Cohen, Cook, and Roe, J., 1940, 194) attention was drawn to the desirability of synthesising 2 : 3 : 4 : 6- and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene for comparison with a product obtained by Windaus (*Annalen*, 1924, **439**, 59) by degradation of colchicine. An obvious intermediate to use is 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde, which Sharp (J., 1936, 1234) obtained by direct nitration in yields never exceeding 20%. In our hands this nitration always gave even smaller yields (compare Cook and Engel, J., 1940, 198), and nitration of the *diacetate* formed by the action of acetic anhydride on 3 : 4 : 5-trimethoxybenzaldehyde gave no crystalline product. We were therefore led to examine synthetic routes which did not require the use of the nitro-aldehyde. In the selection of such methods we had in mind also their application to the synthesis of compounds more closely related in structure to the alkaloid itself and also to the production of compounds which might show its biological activity.

Bromination of α-cyano-α-*p*-anisyl-β-(3 : 4 : 5-trimethoxyphenyl)ethylene led to the 2-*bromo*-compound (I; X = Br, R = OMe). Hydrolysis of this gave α-p-*anisyl*-β-(2-*bromo*-3 : 4 : 5-*trimethoxyphenyl*)*acrylamide*, together with a neutral gum which was oxidised by alkaline permanganate to 2-bromo-3 : 4 : 5-trimethoxybenzoic acid. Unsuccessful attempts were made to cyclise the bromo-compound (I; X = Br, R = OMe) to a phenanthrene derivative by fused potassium hydroxide at 240°, by this alkali in boiling quinoline, and by potassium acetate in naphthalene at 190°. 2-Nitro-3 : 4 : 5-trimethoxybenzaldehyde readily condensed with *p*-methoxybenzyl cyanide to give α-*cyano*-α-p-*anisyl*-β-(2-*nitro*-3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; X = NO_2, R = OMe), and 3 : 4 : 5-trimethoxybenzaldehyde condensed with *p*-hydroxybenzyl cyanide to give α-*cyano*-α-p-*hydroxyphenyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; X = H, R = OH).



(I.)



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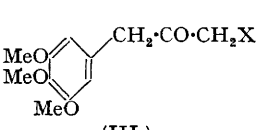

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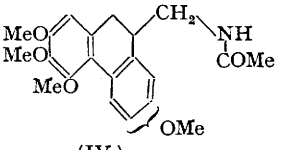

(IV.)

Grewe (*Ber.*, 1939, **72**, 426) has described a synthesis of hydrophenanthrene derivatives which seemed to lend itself to the production of compounds related to colchicine. In an attempt to adapt this, 3 : 4 : 5-*trimethoxybenzyl chloride* was condensed with ethyl malonate, and the *product* was condensed further with 2-bromo-4-methoxy*cyclo*hexanone. The required intermediate (II) could not be isolated from the products of this reaction.

3 : 4 : 5-Trimethoxyphenylacetamide failed to react with methylmagnesium iodide to give the ketone (III; X = H), which was required for condensation with *m*- and *p*-methoxyphenylmagnesium bromide. Dehydration of the amide with thionyl chloride in boiling benzene gave a crystalline product, presumably 3 : 4 : 5-trimethoxyphenylacetonitrile, in too poor yield to be of synthetic value. The action of ethereal hydrogen chloride on the diazo-ketone prepared from 3 : 4 : 5-trimethoxyphenylacetyl chloride and diazomethane led to a chloro-ketone (III; X = Cl) which was resistant to reduction. Trimethoxyphenylacetyl chloride failed to undergo a normal Friedel–Crafts reaction with anisole.

If the acetamido-group of colchicine is not attached to the nucleus, as postulated by Windaus, but is in the side chain (compare Cohen, Cook, and Roe, *loc. cit.*), then *N*-acetylcolchinol methyl ether should have the structure (IV) and would be expected to undergo cyclo-dehydration to a tetracyclic compound, by a reaction analogous to a Pictet–Decker *iso*quinoline synthesis. Treatment of this tetramethoxy-compound with phosphoric oxide in boiling xylene led to elimination of acetamide, and the formation of the compound obtained by Windaus (*Annalen*, 1924, **439**, 59) by Hofmann degradation of colchinol methyl ether and formulated by him as 2 : 3 : 4 : (6 or 7)-tetramethoxy-9-methylphenanthrene. This result, which is reminiscent of the thermal elimination of benzamide from another colchicine degradation product, *N*-benzoylcolchide (Windaus, *Sitzungs-*

ber. Heidelberg. Akad. Wiss., Math.-Nat. Kl., A, 1911, 2 Abh.), is in better accord with Windaus's structure for *N*-acetylcolchinol methyl ether. This structure, however, is difficult to reconcile with the results described in the following paper.

The methoxymethylene ketone grouping of colchicine [compare formula (I), p. 325] or the hydroxymethylene ketone grouping of its hydrolysis product, colchiceine, should enable a new ring to be formed with suitable reagents. Neither colchicine nor colchiceine could be condensed with acetamidine, under conditions used for pyrimidine ring synthesis. Colchicamide (Zeisel, *Monatsh.*, 1888, **9**, 1), the corresponding aminomethylene compound, likewise failed to condense with ethyl cyanoacetate in presence of alcoholic sodium ethoxide or piperidine, but interaction took place between colchicine and cyanoacetamide in presence of alcoholic sodium ethoxide at room temperature. The amorphous product probably consisted mainly of the expected quinoline or *iso*quinoline derivative, but neither the base nor its hydrochloride could be obtained crystalline.

Experimental.

3 : 4 : 5-*Trimethoxybenzaldehyde* (A. Cohen).—Reduction of 3 : 4 : 5-trimethoxybenzoyl chloride by Rosenmund's method gives uncertain yields, and it was found that the method of Sonn and Müller may be used as an alternative. **3 : 4 : 5-*Trimethoxybenzanilide*** was prepared by treatment of 3 : 4 : 5-trimethoxybenzoyl chloride with aniline (2 mols.) in chloroform solution at room temperature. It formed elongated plates (from aqueous methyl alcohol), m. p. 136—137° (Found : C, 66·6; H, 5·9. $C_{16}H_{17}O_4N$ requires C, 66·85; H, 6·0%). A solution of this anilide (80 g.) in tetrachloroethane (300 c.c.) was treated with phosphorus pentachloride (60 g.) and heated at 150° for ½ hour. The phosphorus oxychloride and some of the solvent were removed under reduced pressure, and the residual solution of chloro-imine was added to an ice-cold suspension of stannous chloride (224 g.) in dry ether (1200 c.c.) which had been saturated at 0° with dry hydrogen chloride. The mixture was kept overnight in the refrigerator (0—3°), and the orange solid in suspension was collected, washed with ether, and hydrolysed by 1 hour's boiling with acetic acid (200 c.c.), concentrated hydrochloric acid (175 c.c.), and water (325 c.c.). The product was extracted with ether, after dilution with water, and the ethereal extract washed, dried, and distilled, giving 3 : 4 : 5-trimethoxybenzaldehyde (36 g.), b. p. 143—146°/0·4 mm. The *diacetate* was obtained (R. W. Lapsley) when a solution of this aldehyde (2 g.) in cold acetic anhydride (12 c.c.) was treated with a trace of concentrated sulphuric acid. The solution was kept for 1½ hours, poured into ice-water, and the precipitate crystallised from alcohol. It formed colourless needles (2·15 g.), m. p. 112—113° (Found : C, 56·6; H, 6·1. $C_{14}H_{18}O_7$ requires C, 56·5; H, 6·1%).

α-*Cyano*-α-p-*anisyl*-β-(2-*bromo*-3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; X = Br, R = OMe).—A solution of bromine (0·5 g.) in dry chloroform (5 c.c.) was added to a cold solution of α-cyano-α-*p*-anisyl-β-(3 : 4 : 5-trimethoxyphenyl)ethylene (Cook and Engel, *loc. cit.*) (1 g.) in dry chloroform (20 c.c.). After 1½ hours the solvent was removed and the residual *bromo*-compound was crystallised from alcohol, forming fine pale yellow needles, m. p. 141—142·5° (1·25 g.) (Found : C, 56·75; H, 4·6. $C_{19}H_{18}O_4NBr$ requires C, 56·4; H, 4·45%). This bromo-compound (1 g.) was hydrolysed by 16 hours' boiling with 6N-sodium hydroxide solution containing a little alcohol. An acid product was not formed. The neutral products were separated by means of benzene into the sparingly soluble **α-p-*anisyl*-β-(2-*bromo*-3 : 4 : 5-*trimethoxyphenyl*)-*acrylamide*** (0·17 g.), colourless microscopic rhombs, m. p. 179—181° (from benzene) (Found : C, 54·3; H, 4·7; OMe, 29·2. $C_{19}H_{20}O_5NBr$ requires C, 54·0; H, 4·7; OMe, 29·4%), and an easily soluble red gum (0·6 g.) which was oxidised by boiling alkaline potassium permanganate (1·2 g.) to 2-bromo-3 : 4 : 5-trimethoxybenzoic acid (0·35 g.), m. p. 151—152° (Found : C, 41·3; H, 3·9. Calc. for $C_{10}H_{11}O_5Br$: C, 41·2; H, 3·8%) (Hamburg, *Monatsh.*, 1898, **19**, 598, gives m. p. 151°).

α-*Cyano*-α-p-*anisyl*-β-(2-*nitro*-3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; X = NO_2, R = OMe) (C. A. Lawrence).—A cold solution of 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde (0·55 g.; from 12·5 g. of trimethoxybenzaldehyde) and *p*-methoxybenzyl cyanide (0·35 g.) in alcohol (8 c.c.) was treated with 2N-sodium hydroxide (1·2 c.c.). After 2 hours at 0° the solid was collected, washed, and recrystallised from alcohol. The *product* (I; X = NO_2, R = OMe) (yield, almost quantitative) formed long, primrose-yellow, felted needles, m. p. 164·5—165·5° (Found : C, 61·6; H, 5·0. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9%).

α-*Cyano*-α-p-*hydroxyphenyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; X = H, R = OH) (Graham, Lapsley, and Lawrence).—A solution of 3 : 4 : 5-trimethoxybenzaldehyde (4 g.) and *p*-hydroxybenzyl cyanide (2·5 g.) in alcoholic sodium ethoxide (from 1 g. of sodium and 25 c.c. of alcohol) was kept at room temperature for 48 hours, and then treated with dilute hydrochloric acid. The precipitate crystallised from aqueous alcohol in fine, pale yellow needles (3·2 g.), m. p. 169·5—170·5° (Found : C, 69·6; H, 5·7. $C_{18}H_{17}O_4N$ requires C, 69·4; H, 5·5%). Its acetate had m. p. 162°, and its benzoate m. p. 159—160°. Several attempts were made to hydrogenate the hydroxy-compound and its acetate over Adams's platinum oxide catalyst, but the amount of crystalline reduction products was very small. Most of the material resisted hydrogenation. An attempt to reduce the hydroxy-compound with sodium and alcohol gave, as the only crystalline product, **α-p-*hydroxyphenyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*acrylamide***, m. p. 211° (benzene–acetone) (Found : C, 65·4; H, 5·9. $C_{18}H_{19}O_5N$ requires C, 65·7; H, 5·8%).

3 : 4 : 5-*Trimethoxybenzyl Alcohol.*—(a) (A. Cohen.) A solution of 3 : 4 : 5-trimethoxybenzaldehyde (10·5 g.) in warm alcohol (100 c.c.) was shaken with hydrogen and platinum black (0·45 g.). Absorption was complete in 15 hours. The filtered solution was distilled, giving 3 : 4 : 5-trimethoxybenzyl alcohol (10·1 g.) as a colourless viscous oil, b. p. 145—150°/0·4 mm. Its **3 : 5-*dinitrobenzoate*** formed yellow leaflets (from alcohol), m. p. 147—148° (Found : C, 52·2; H, 4·2. $C_{17}H_{16}O_9N_2$ requires C, 52·0; H, 4·1%).

For conversion into the chloride, a mixture of the alcohol (10 g.) and dimethylaniline (8 g.) was treated at 0° with thionyl chloride (6·6 g.). After being kept at 0° for ½ hour and then at 100° for 15 minutes the resulting mixture was treated with very dilute hydrochloric acid and extracted with ether. The ethereal extract was washed, dried, and distilled. 3 : 4 : 5-Trimethoxybenzyl chloride (7·4 g.), b. p. 135°/0·5 mm., crystallised from light petroleum in colourless flat needles, m. p. 60—61° (Found : C, 55·9; H, 6·1. Calc. for $C_{10}H_{13}O_3Cl$: C, 55·4; H, 6·05%) (compare I.G., D.R.-P. 526,172). This chloride failed to react with magnesium to give the Grignard compound which was required for condensation with *p*-methoxyacetophenone. Such inertness to magnesium seems characteristic of highly methoxylated halogen compounds.

(b) 1 : 3-Dimethylpyrogallol (Hahn and Wassmuth, *Ber.*, 1934, **67**, 701) (7 g.) was treated with formalin and sodium hydroxide solution by a procedure which was essentially that of D.R.-P. 453,277. The resulting syringic alcohol (5 g.) had m. p. 131—132° (Found : C, 58·6; H, 6·6; OMe, 33·6. Calc. for $C_9H_{12}O_4$: C, 58·6; H, 6·5; OMe, 33·7%). Methylation with methyl iodide and sodium ethoxide (D.R.-P. 526,172) gave 3 : 4 : 5-trimethoxybenzyl alcohol which formed a 3 : 5-dinitrobenzoate identical with that described under (a). When this methylation was effected with methyl *p*-toluenesulphonate and aqueous potassium hydroxide at 100° the result was less satisfactory. The crude methylation product was a viscous liquid which slowly resinified. Trituration of the resin with ether gave a white solid, probably

1 : 2 : 3 : 5 : 6 : 7-*hexamethoxy*-9 : 10-*dihydroanthracene*, which crystallised from alcohol in colourless prisms, m. p. 201° (Found : C, 67·1; H, 6·7; OMe, 52·0. $C_{20}H_{24}O_6$ requires C, 66·7; H, 6·7; OMe, 51·7%).

4-Methoxy*cyclo*hexanol was prepared in excellent yield by hydrogenation of quinol monomethyl ether over Raney nickel at 120° and 130 atm. (compare Ruggli, Leupin, and Businger, *Helv. Chim. Acta*, 1941, **24**, 339). A solution of chromic acid (5·7 g.) in 80% acetic acid (25 c.c.) was added during ¾ hour to a stirred and cooled solution of 4-methoxy-*cyclo*hexanol (10 g.) in acetic acid (100 c.c.), the temperature being kept below 10—12°. Stirring was continued for an hour, the solution kept overnight, and most of the acetic acid distilled under reduced pressure. The residue was neutralised with sodium carbonate solution, and extracted with ether. Distillation of the dried extract gave 4-methoxy-*cyclo*hexanone (7·5 g.), b. p. 81—83°/11 mm. This oxidation procedure gave better yields than that of Helfer (*ibid.*, 1924, **7**, 952).

A solution of bromine (7·3 g.) in dry chloroform (70 c.c.) was added to a cooled, stirred solution of 4-methoxy*cyclo*hexanone (5·9 g.) in chloroform (60 c.c.) at such a rate that the colour remained faintly yellow. After an hour the chloroform was removed under reduced pressure, and the residue was dissolved in ether, washed with sodium hydrogen carbonate solution, dried, and distilled. The fraction, b. p. 127—135°/12 mm. (3·85 g.), was assumed to be 2-bromo-4-methoxy*cyclo*hexanone. For characterisation this colourless liquid (1·1 g.) was mixed with thiourea (0·4 g.); an exothermic reaction set in and the syrup which was formed gradually solidified. For completion of the reaction, the mixture was heated on the water-bath for a short time. Dilute sodium hydroxide was added, and the insoluble material collected, washed with ether, and recrystallised from benzene–*cyclo*hexane and finally benzene. 2-*Amino*-6-*methoxy*-4 : 5 : 6 : 7-*tetrahydrobenzthiazole* formed colourless prisms, m. p. 141·5—144° (Found : C, 52·4; H, 6·5. $C_8H_{12}ON_2S$ requires C, 52·2; H, 6·4%).

Ethyl 3 : 4 : 5-*Trimethoxybenzylmalonate*.—3 : 4 : 5-Trimethoxybenzyl chloride (4·4 g.) was added to a solution of ethyl sodiomalonate (from 0·5 g. of sodium, 9 c.c. of alcohol, and 3·25 g. of ethyl malonate). After being kept at room temperature for an hour, the mixture was heated on the water-bath for 15 minutes, and the alcohol distilled off under reduced pressure. The residue was treated with water and extracted with ether. From the ethereal extract was obtained *ethyl* 3 : 4 : 5-*trimethoxybenzylmalonate*, which crystallised from light petroleum in colourless prisms, m. p. 67—71° (Found : C, 59·7; H, 7·0. $C_{17}H_{24}O_7$ requires C, 60·0; H, 7·1%). Alkaline hydrolysis, followed by thermal decarboxylation of the acid, gave β-3 : 4 : 5-*trimethoxyphenylpropionic acid*, which formed colourless needles (from benzene–light petroleum), m. p. 100—102° (Found : C, 60·2; H, 6·4. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

A solution of 2-bromo-4-methoxy*cyclo*hexanone (2·55 g.) in dry benzene (15 c.c.) was added to the ice-cooled sodio-compound prepared by heating ethyl 3 : 4 : 5-trimethoxybenzylmalonate (4·2 g.) and sodium (0·28 g.) in dry benzene (30 c.c.). The mixture was heated on the water-bath for 4 hours, cooled, and then treated with water. The benzene solution gave an oil (5·5 g.) which did not crystallise. Hydrolysis with boiling alcoholic sodium hydroxide gave (*a*) a sparingly soluble sodium salt (1 g.), (*b*) a filtrate which gave resinous material (1·8 g.) when diluted with water and acidified, and (*c*) a red gum (1·4 g.) which was isolated by evaporating the acid filtrate and extracting the dry residue with acetone. The sparingly soluble sodium salt (*a*) was dissolved in water, and the solution acidified and evaporated to dryness under reduced pressure. From the dry residue acetone extracted 3 : 4 : 5-*trimethoxybenzylmalonic acid*, which crystallised from benzene–alcohol in colourless prisms, m. p. 115—116° (Found : C, 55·2; H, 5·4. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·6%), and was decarboxylated at 135° to 3 : 4 : 5-trimethoxyphenylpropionic acid, m. p. 100°. More of this acid was obtained from fraction (*c*). Fraction (*b*) was decarboxylated and then heated for ½ hour with syrupy phosphoric acid at 105°. Chromatographic purification of the benzene-insoluble fraction of the product gave a very small amount of colourless crystals, m. p. 230° (Found : C, 54·1; H, 6·4%). The amount was insufficient for further examination.

Partial Reduction of 2 : 4-*Dinitrophenylacetic Acid*.—This acid was readily obtained by nitration of phenylacetic acid (Borsche, *Ber.*, 1909, **42**, 1313). Gabriel and Meyer (*Ber.*, 1881, **14**, 824) claim to have reduced the 4-nitro-group with ammonium sulphide, but give few details (compare Parkes and Aldis, J., 1938, 1841). Attempts to effect this reduction with sodium polysulphide or with hydrazine hydrate (compare Curtius, *J. pr. Chem.*, 1907, **76**, 291) led to decarboxylation, 2-nitro-4-aminotoluene being formed by the former method and 2 : 4-dinitrotoluene by the latter (Lapsley).

Methyl 2 : 4-dinitrophenylacetate (Borsche, *loc. cit.*) (2 g.) was heated for an hour in boiling methyl alcohol (20 c.c.) with 50% hydrazine hydrate (3·5 c.c.), and gave pale yellow needles of 2 : 4-*dinitrophenylacethydrazide*, m. p. 135·5—137° (Found : N, 23·4. $C_8H_8O_5N_4$ requires N, 23·3%).

A series of experiments was carried out on the catalytic hydrogenation of methyl 2 : 4-dinitrophenylacetate. Under the most favourable conditions (ether as solvent; palladium black as catalyst; interruption before the calculated amount of hydrogen had been absorbed) yields up to 15% of methyl 2-nitro-4-aminophenylacetate, m. p. 90°, were obtained. Unchanged dinitro-ester was also isolated, together with a white solid, m. p. 100°, apparently methyl 2 : 4-diamino-phenylacetate.

When condensation was attempted between sodium 2 : 4-dinitrophenylacetate and 3 : 4 : 5-trimethoxybenzaldehyde in presence of acetic anhydride at 100°, the product was 2 : 4-dinitrotoluene. Methyl 2 : 4-dinitrophenylacetate failed to condense with 3 : 4 : 5-trimethoxybenzaldehyde in presence of pyridine, piperidine, or piperidine acetate.

3 : 4 : 5-*Trimethoxyphenylacetamide* (Lapsley and Graham).—3 : 4 : 5-Trimethoxybenzoyl chloride was converted by means of diazomethane into ω-diazo-3 : 4 : 5-trimethoxyacetophenone, m. p. 101° (Baker, Morgans, and Robinson, J., 1933, 374; Slotta and Müller, *Z. physiol. Chem.*, 1936, **238**, 14), and this (2 g.) was added slowly at 50—60° to a stirred solution of 20% ammonia (25 c.c.) to which had been added 10% silver nitrate solution (2·5 c.c.). The temperature was then gradually raised to 80°. When the effervescence had subsided the solution was diluted with water, boiled for an hour, and filtered hot. The trimethoxyphenylacetamide (1·5 g.) which crystallised from the cooled solution had m. p. 122—123° (compare Slotta and Müller, *loc. cit.*). A solution of this amide (0·5 g.) in benzene (5 c.c.) and thionyl chloride (1·5 g.) was boiled for 20 minutes, and the product was distilled under reduced pressure. The solid distillate crystallised from benzene–light petroleum and then had m. p. 72—74°. The yield of this compound, probably trimethoxyphenylacetonitrile, was poor, and other conditions gave no better result (Hahn and Wassmuth, *Ber.*, 1934, **67**, 707, give m. p. 81°).

3 : 4 : 5-Trimethoxyphenylacetic acid was obtained in almost quantitative yield by hydrolysis of the amide with 10N-sodium hydroxide solution (10 parts; 6 hours' boiling). The chloride of this acid was unstable, and could not be distilled without extensive decomposition, even under reduced pressure. A solution of the acid (1 g.) in thionyl chloride (2·5 g.) was heated at 40° for 30 minutes, and then boiled for 5 minutes. A little dry benzene was added, and the solvents evaporated under reduced pressure, this process being repeated twice. The residue, freed in this way from thionyl chloride, was dissolved in a little ether and added to ethereal diazomethane prepared from 6 c.c. of nitrosomethylurethane. Ethereal hydrogen chloride was then added until effervescence ceased (compare Haworth and Atkinson, J., 1938, 805). After an hour, the solution was washed with water and dilute sodium carbonate solution, dried over sodium sulphate, and the ether removed. The dark residual solid was purified by passing its solution in benzene through a column of alumina, and was crystallised from ether, forming colourless needles, m. p. 75°. This substance, which contained chlorine and gave a 2 : 4-dinitrophenylhydrazone, m. p. 118°, was evidently γ-chloro-α-3 : 4 : 5-trimethoxyphenylacetone (III; X = Cl).

Action of Phosphoric Oxide on N-*Acetylcolchinol Methyl Ether.*—Phosphoric oxide (0·8 g.) was added to a solution of *N*-acetylcolchinol methyl ether (Windaus, *Sitzungsber Heidelberg. Akad. Wiss.*, Math.-Nat. Kl., *A*, 1919, 16 Abh.) (0·4 g.) in dry purified xylene (20 c.c.), and the mixture boiled for 15 minutes (oil-bath heating). After cooling, the xylene solution was decanted from the residue, which gave no basic material with alkali, and was evaporated under reduced pressure. The residual gum crystallised from methyl alcohol in colourless plates which mostly melted at 100°; the melt resolidified and melted again at 109—110° (Found: C, 73·1; H, 6·1. Calc. for $C_{19}H_{20}O_4$: C, 73·05; H, 6·4). This compound, which did not contain nitrogen, was shown by direct comparison with an authentic specimen prepared by Dr. Loudon to be identical with the compound prepared by Windaus (*Annalen*, 1924, **439**, 59) by Hofmann degradation of colchinol methyl ether.

Condensation of Colchicine with Cyanoacetamide.—A solution of colchicine (0·2 g.) and cyanoacetamide (0·05 g.) in alcoholic sodium ethoxide (from 0·012 g. of sodium and 8 c.c. of alcohol) was kept at room temperature for 4 days, during which the colour changed to orange and then dark red. The alcohol was removed under reduced pressure, and the residue was taken up in water and acidified with dilute hydrochloric acid. The precipitate was collected, more being obtained by extraction of the filtrate with chloroform. It could not be crystallised, but was purified for analysis by addition of benzene to its hot solution in alcohol. The orange-yellow amorphous powder thus precipitated began to sinter at 175° and decomposed at 205° (Found, after allowance for ash: C, 61·1; H, 5·7; N, 8·7. $C_{24}H_{24}O_5N_3Cl$ requires C, 61·3; H, 5·1; N, 8·9%). This *product* is probably the hydrochloride of a complex quinoline derivative (compare the condensation of hydroxymethylene*cyclo*hexanone with cyanoacetamide, Sen-Gupta, J., 1915, **107**, 1354).

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