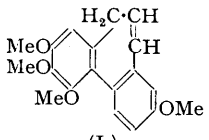
# 230. *Colchicine and Related Compounds. Part VIII. Preliminary Synthetic Experiments.*

By N. Barton, J. W. Cook, J. D. Loudon, and (in part) J. MacMillan.

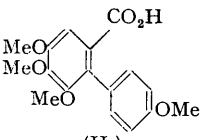
In connection with a project to synthesise colchinol methyl ether, the acid (III) has been prepared through the intermediary (II), obtained satisfactorily by a Gomberg–Hey type of reaction. Cyclisation of the bromo-acid (IV), obtained from (III), did not lead to seven-membered ring formation but was attended by displacement and migration of bromine. The resulting bromo-ketone (probably X) was reduced to 5 : 6 : 7-trimethoxy-4-*p*-methoxyphenyl-1-indanone (IX), identical with specimens obtained by direct cyclisation of (III).

2 : 3 : 4 : 7-Tetramethoxyfluorenone (VII), obtained by cyclisation of (II) and also from 4 : 5 : 6 : 4′-*tetramethoxydiphenic acid* (XII), was transformed by diazomethane into a mixture from which was isolated 2 : 3 : 4 : 7 : 9 (or 10)-*pentamethoxyphenanthrene* (XIII).

The chemical behaviour of deaminocolchinol methyl ether, described in Part V (Barton, Cook, and Loudon, *J.*, 1945, 176), led to the conclusion that this important degradation product of colchicine is 9 : 12 : 13 : 14-tetramethoxy-3 : 4 : 5 : 6-dibenz*cyclo*hepta-1 : 3 : 5-triene (I). The synthesis of dibenz*cyclo*heptatrienes and related compounds raises a general problem to which we are devoting attention, but the particular substitution pattern of (I) appeared to invite a more individual treatment on the lines described below; moreover, its successful issue would provide necessary information on the structure proposed (Part V) for colchinol methyl ether. The work described was substantially complete by June, 1946 (cf. Barton, Ph.D. Thesis, Glasgow, 1946), when it was already evident that this particular synthetic route did not lead to the desired objective, although at the time the point of deviation remained unsettled. Recently Frank, Fanta, and Tarbell (*J. Amer. Chem. Soc.*, 1948, **70**, 2314) have published an account of some equally inconclusive experiments along similar lines. Since our results differ from and supplement theirs in several notable respects and since we have now ascertained the point at which the projected synthesis miscarries, we record here the relevant features of our work together with a related synthesis of 4 : 5 : 6 : 4′-*tetramethoxydiphenic acid* (XII), itself a degradation product of colchicine.



(I.)



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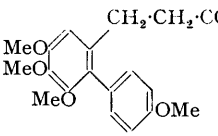

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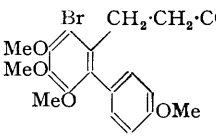
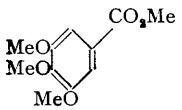


(IV.)

Like ourselves, the aforementioned authors have prepared the acids (II), (III), and (IV) and have attempted to cyclise the acid (IV) to the ketone (VIII), but, whereas in the preparative stages they achieved the union of the two aryl nuclei by appropriate crossed-Ullmann reactions and discarded as here impracticable the Gomberg–Hey type of reaction, the latter process in the form described by Elks and Hey (*J.*, 1943, 441) has given satisfactory results in our hands. Methyl 3 : 4 : 5-trimethoxybenzoate (V), condensed with 1-p-*methoxyphenyl*-3 : 3-*dimethyltriazen*, yielded the methyl ester of (II) together with a small quantity of a second *methyl* ester, $C_{16}H_{16}O_5$, which apparently results from displacement of one methoxyl group of (V) by the *p*-methoxyphenyl residue. The precise structure of this interesting by-product was not investigated, but the formation of analogous products by the interaction of (V) with other triazens has been observed in these laboratories, and, in view of the known mobility of the 4-methoxyl group in compounds related to (V) (cf. Asahina, *Ber.*, 1936, **69**, 1643; Richtzenhain, *ibid.*, 1944, **77**, 1; Haller and Schaffer, *J. Amer. Chem. Soc.*, 1939, **61**, 2175; Hurd and Winsberg, *ibid.*, 1942, **64**, 2085), the by-product is in all probability *methyl* 3 : 5-*dimethoxy*-4-p-*methoxyphenylbenzoate* (VI). In harmony with this view it was found that whereas the carboxylic *acid* obtained by saponifying the ester by-product yielded in normal fashion an acid chloride and *amide*, the acid (II) was rapidly converted by treatment with thionyl chloride into the fluorenone (VII)—a compound also described by Frank, Fanta, and Tarbell. In contrast to the findings of these authors, however, we found no difficulty in preparing the *hydrazide* of (II) and hence, by the method of McFadyen and Stevens (*J.*, 1936, 584), readily obtained the aldehyde (II; CHO for $CO_2H$), *viz.*, 3 : 4 : 5-*trimethoxy*-2-p-*methoxyphenylbenzaldehyde*. This aldehyde was condensed with malonic acid to yield the corresponding *cinnamic acid* from which by successive reduction and bromination the acids (III) and (IV) respectively were prepared.

Frank, Fanta, and Tarbell have sufficiently emphasised the difficulties—which we also experienced—in cyclising the acid (IV). As product of a Friedel–Crafts reaction they describe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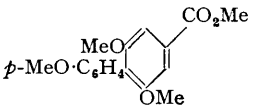
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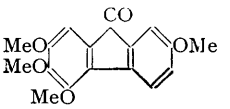
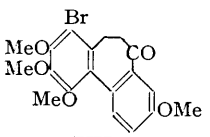
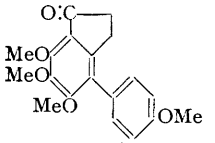
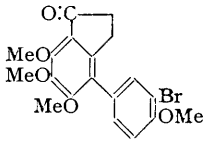

(VII.)

a bromo-ketone, m. p. 145° (corr.), which is probably identical with a bromo-ketone, m. p. 143° (uncorr.), obtained by us, although in our experience the latter compound was accompanied by a mono-demethylated *analogue* separable only with difficulty and of cryptophenolic nature. Our bromo-ketone was debrominated by hydrogen in presence of palladised strontium carbonate, and the resulting ketone was converted *via* its oxime into the corresponding primary amine which was characterised as the *picrate* and *acetyl* derivative. Deamination of the amine by the method of Cook and Graham (Part III, *J.*, 1944, 322; cf. Cook, Dickson, Ellis, and Loudon, Part VII, preceding paper) gave a product which, although insufficient in quantity for analysis, was definitely shown to be distinct from deaminocolchinol methyl ether (I). Moreover, model experiments having shown that dibenz*cyclo*heptadienones analogous to (VIII) are smoothly oxidisable to phenanthraquinones (Cook, Dickson, and Loudon, Part VI, *J.*, 1947, 746), the completely negative results obtained by applying this sensitive test to our bromo-ketone and its debromination product conclusively showed at this stage that neither of these ketones had the required 7-membered ring-structure of (VIII). Positive identification of our cyclisation products was retarded by a mistaken m. p. for the indanone (IX) which we had prepared by cyclisation of the acid (III) with anhydrous hydrofluoric acid. Frank, Fanta, and Tarbell, who report (*loc. cit.*, p. 2319) that (III) is not cyclised by this means, effected the ring-closure by an internal Friedel–Crafts reaction. The discrepancies of technique and melting point which thus became apparent caused us to re-examine both methods of cyclising (III) with the result that, whilst we confirmed the efficacy of hydrofluoric acid, we obtained by both methods the same product of m. p. approximating to the value recorded by the above authors. Furthermore, this product and the derived oxime were identical with the ketone and oxime respectively, obtained as described from (IV) by successive cyclisation and debromination.


(VIII.)


(IX.)

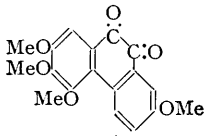

(X.)

Taken in conjunction with the proof of structure advanced by Frank, Fanta, and Tarbell for the acid (IV), these results make it clear that cyclisation of this acid by the Friedel–Crafts reaction involves displacement and migration of the bromine substituent. The bromo-ketone so produced is formulated as (X) since on oxidation (see Experimental) it affords an acid which still retains the bromine, thereby excluding the alternative formula in which bromine has entered the methylene group adjacent to carbonyl.* Oxidation of the debrominated ketone, *viz.* (IX), yields an analogous *acid*, $C_{19}H_{20}O_7$. Frank, Fanta, and Tarbell do not record debromination of their bromo-ketone although they suggest that debromination was incidental in one attempt to cyclise (IV); the significance of the observation that the ill-defined product in this case was distinct from (IX) cannot be assessed at present.

In Part V (*loc. cit.*), 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone (XI) was produced by oxidising deaminocolchinol methyl ether with sodium dichromate in acetic acid, and its synthesis was achieved by similar oxidation of the rather inaccessible 2 : 3 : 4 : 7-tetramethoxyphenanthrene-9- and -10-carboxylic acids. It has now been shown that the phenanthraquinone is itself readily oxidised by hydrogen peroxide in presence of alkali to the corresponding *diphenic acid* (XII), and that this acid on distillation affords the fluorenone (VII). The reverse process, *viz.*, conversion of (VII) into (XI) and (XII), acquires considerable value from the accessibility

* *Note added in proof.* Since this paper was submitted, Huang, Tarbell, and Arnstein (*J. Amer. Chem. Soc.*, 1948, **70**, 4181) have likewise concluded that the bromo-ketone is (X).

of the fluorenone, through cyclisation of (II) as described above, and from the potentialities for further synthesis contained in the diphenic acid (XII). Accordingly expansion of the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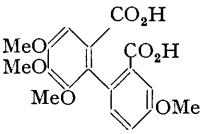
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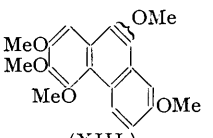
(XIII.)

5-membered ring of (VII) to the 6-membered phenanthrene type was effected by reaction with diazomethane (cf. Schultz, Schultz, and Cochran, *J. Amer. Chem. Soc.*, 1940, **62**, 2902), and from the mixture so produced 2 : 3 : 4 : 7 : 9(or 10)-*pentamethoxyphenanthrene* (XIII) was isolated; this yielded (XI) on oxidation. More conveniently, the crude reaction products were oxidised directly and afforded an easily separable mixture of (XI) with regenerated fluorenone (VII).

## Experimental.

1-p-*Methoxyphenyl*-3 : 3-*dimethyltriazen*.—*p*-Anisidine (100 g.) in concentrated hydrochloric acid (290 c.c.) and water (200 c.c.) was diazotised with a concentrated solution of sodium nitrite (56 g.) in water. The diazo-solution, kept at 0°, was added dropwise to a cooled and stirred mixture of dimethylamine (280 g.; 25%) and 30% aqueous sodium carbonate (800 c.c.). The resulting oil, stirred for 30 minutes following the addition, was extracted with benzene, dried (KOH), and recovered from the solvent. It distilled as a pale yellow liquid (110 g.), b. p. 150—152°/10 mm. (Found: N, 23·2. $C_9H_{13}ON_3$ requires N, 23·5%).

*Methyl* 3 : 4 : 5-*Trimethoxy*-2-p-*methoxyphenylbenzoate*.—The above triazen (56 g.) and methyl 3 : 4 : 5-trimethoxybenzoate (V) (280 g.) were slowly treated with acetic acid (72 c.c.) at 100°, and the whole was heated on the water-bath for 16 hours. The resulting dark liquid was dissolved in chloroform, and the solution was washed thoroughly with dilute hydrochloric acid, water, dilute sodium hydroxide, and water. After drying and recovery, distillation gave a few drops of anisole followed by the unchanged, solid ester (230 g.), b. p. 175—190°/10 mm. which was used directly for renewed reaction with triazen, and a residue. The latter, combined with corresponding residues from several runs, gave on fractionation (1) a small quantity of unchanged ester, b. p. 158—172°/1 mm.; (2) a slight intermediate oily fraction, b. p. 172—195°/0·8 mm.; (3) the main oily fraction, b. p. 195—206°/0·8 mm.; and (4) a small oily fraction, b. p. >206/1 mm. (some decomp.). Fractions (2) and (3), when rubbed with a little methanol and allowed to stand, deposited solids which crystallised together from methanol as a mixture of stout prisms (main constituent) and fine needles. Most of the needles were removed by swirling and decanting with the mother-liquor which was then used, with slight warming, to extract the remainder of the needles from the prisms, the process being repeated on further crops obtained by concentrating the methanol mother-liquors. These crystalline products were slightly augmented by redistilling the combined gums recovered from the various methanol solutions, and repeating the above treatment. In this way from 270 g. of the triazen there were obtained 75 g. of the prisms consisting of methyl 3 : 4 : 5-trimethoxy-2-(*p*-methoxyphenyl)benzoate, m. p. 74° (Frank, Fanta, and Tarbell, *loc. cit.*, give m. p. 63°) (Found: C, 64·9; H, 5·85. Calc. for $C_{18}H_{20}O_6$: C, 65·1; H, 6·0%), and 5·5 g. of the needles, provisionally regarded as *methyl* 3 : 5-*dimethoxy*-4-p-*methoxyphenylbenzoate* (VI), m. p. 133—134° from methanol (Found: C, 67·2; H, 5·7; OMe, 40·65. $C_{17}H_{18}O_5$ requires C, 67·5; H, 5·95; OMe, 41·1%).

The final methanol mother-liquors, when combined and heated with 50% sodium hydroxide, gave a non-saponifiable oil, which was extracted with ether and discarded, and a mixture of two acids which were separated by fractional crystallisation from methanol. The first crop formed prisms or flakes from methanol, m. p. 166—168° with previous softening, consisting of 3 : 4 : 5-trimethoxy-2-(*p*-methoxyphenyl)benzoic acid (II) (Found after drying at 100° in a vacuum: C, 64·45; H, 5·7. Calc. for $C_{17}H_{18}O_6$: C, 64·15; H, 5·7%), and converted by diazomethane in ether into the above methyl ester, m. p. and mixed m. p. 74°. The second, less abundant and less soluble, fraction formed long needles of 3 : 5-*dimethoxy*-4-p-*methoxyphenylbenzoic acid*, m. p. 227—228° from methanol (Found after drying at 100° in a vacuum: C, 66·6; H, 5·5; OMe, 32·55. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6; OMe, 32·3%) converted (*a*) by diazomethane in ether into the above methyl ester, m. p. and mixed m. p. 133°, (*b*) by warming with an excess of thionyl chloride into an acid chloride which was obtained crude by distilling off the excess of reagent and yielded an *amide*, m. p. 232° from ethanol, on addition of concentrated ammonia (Found: C, 66·6; H, 5·65. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9%).

3 : 4 : 5-*Trimethoxy*-2-p-*methoxyphenylbenzaldehyde*.—A solution of methyl 3 : 4 : 5-trimethoxy-2-(*p*-methoxyphenyl)benzoate (14·6 g.) in methanol (30 c.c.) and 99% hydrazine hydrate (30 c.c.) was heated under reflux for 7½ hours. The *hydrazide* (13 g.) collected from the cooled solution after boiling with charcoal and augmented by concentration of the mother-liquor formed colourless rods, m. p. 154—155° from ethanol (Found: C, 61·5; H, 6·0. $C_{17}H_{20}O_5N_2$ requires C, 61·45; H, 6·0%). After being dried at 100° it (14 g.) was dissolved in dry pyridine (82 c.c.), benzenesulphonyl chloride (8·2 c.c.) was added at 0°, and the whole was kept—finally at room temperature—for 3 hours. The *benzenesulphonylhydrazide* (17·5 g.), obtained when the mixture was stirred into dilute hydrochloric acid, had m. p. 177·5—178·5° from methanol (Found: C, 58·25; H, 5·3. $C_{23}H_{24}O_7N_2S$ requires C, 58·5; H, 5·1%). It (14 g.) was dissolved in ethylene glycol (140 c.c.) at 160°, sodium carbonate (8·4 g.) was added in one lot, and the whole was vigorously stirred for 130 seconds before terminating the reaction by adding hot water (140 c.c.). The *aldehyde*, recovered from a chloroform extract of the cooled

mixture, crystallised as colourless prisms, m. p. 62—63° (6—7 g.) from methanol (Found : C, 67·4; H, 6·0. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%).

3 : 4 : 5-*Trimethoxy*-2-p-*methoxyphenylcinnamic Acid.*—A solution of the above aldehyde (3 g.) in pyridine (6 c.c.) to which a few drops of piperidine had been added was heated with malonic acid (2·0 g., first on the water-bath (moisture guard) for 1 hour and then under reflux for 15 minutes. The product (2·9 g.), obtained by pouring the mixture on crushed ice and hydrochloric acid, formed colourless prisms, m. p. 187—188° from methanol (Found : C, 66·5; H, 6·2. $C_{19}H_{20}O_6$ requiresC, 66·3; H, 5·8%).

β-(3 : 4 : 5 : 4′-*Tetramethoxydiphenylyl*)*propionic Acid.*—A solution of the above acid (2·8 g.) in acetic acid (50 c.c.) was hydrogenated at 20° in presence of palladium black (0·17 g.). The product, recovered from the filtered solution, crystallised from methanol as colourless prisms, m. p. 103° (2·67 g.) (Found : C, 65·75; H, 6·3. Calc. for $C_{19}H_{22}O_6$ : C, 65·9; H, 6·4%).

β-(6-*Bromo*-3 : 4 : 5 : 4′-*tetramethoxydiphenylylpropionic Acid* (IV).—Solution of bromine (0·4 c.c.) in chloroform (10 c.c.) and of the above phenylpropionic acid (2·47 g.) also in chloroform (50 c.c.) were mixed and left at room temperature for 2 hours. The solution was washed with water until free from hydrobromic acid, and the recovered product was crystallised first from benzene–ligroin and then (2·9 g.) from methanol. It had m. p. 169—170° (Found : C, 53·3; H, 5·0. Calc. for $C_{19}H_{21}O_6Br$ : C, 53·6; H, 4·9%). When heated with methanol in presence of a little concentrated sulphuric acid it formed a methyl ester which was isolated by distillation, b. p. 180—210° (air bath)/0·2 mm., and was crystallised from methanol; needle clusters, m. p. 90—91° (Found : C, 54·6; H, 5·25. Calc. for $C_{20}H_{23}O_6Br$ : C, 54·7; H, 5·2%).

*Cyclisation of Acid* (IV).—A suspension of the bromo-acid (1 g.) in pure dry benzene (10 c.c.) was shaken with phosphorus pentachloride at room temperature under moisture guard until it had completely dissolved (about 1 hour). Volatile material was removed by warming (*ca.* 60°) under reduced pressure and finally by evacuation at room temperature (1 hour). The residual, usually crystalline, acid chloride [micro-m. p. 91—93° (from ligroin)] was dissolved in carbon disulphide (2 c.c.), finely ground fresh aluminium chloride (0·8 g.) was added, and the whole, protected from moisture, was left with occasional shaking at 0° for 2 days. After addition of some dilute hydrochloric acid and removal of the solvent in steam the crude product was worked up in one of two ways :

(*a*) A chloroform extract was washed with dilute sodium carbonate (from which original bromo-acid, *ca.* 0·25 g., of very variable quality was recovered and purified through its methyl ester) and then with sodium hydroxide solution (which removed some phenolic, but not cryptophenolic material, see below). The product (0·75 g.), recovered from the dried chloroform solution, distilled at 180—200° (air bath)/0·4 mm., yielding half its weight of a distillate (charring and resinification) in which the presence of cryptophenolic material was shown by a violet colour with ferric chloride in aqueous methanol. This constituent was best separated by passing a solution of the distillate in benzene through a column of alumina which retained the cryptophenol, while the benzene eluate afforded on evaporation pale yellow rods of the required *product*, m. p. 143—143·5° (softening 140°) (from benzene–ligroin), giving a negative ferric chloride test (Found : C, 56·2; H, 4·8. $C_{19}H_{19}O_5Br$ reqires C, 56·0; H, 4·7%).

(*b*) The crude product was extracted with ether in which it partly dissolved. The ethereal solution was washed as above with sodium carbonate and sodium hydroxide solutions, dried, and evaporated. The residual gum (0·225 g.), which gave no ferric chloride reaction, was dissolved in benzene and recovered as a pink glass (0·20 g.) after pasing through a column of alumina. It was directly employed for debromination (cf. below) with good results. The ether-insoluble fraction, which remained as a white solid suspended in the aqueous layer, was extracted with chloroform, washed with the same alkali washings as used for the ether solution, dried, recovered (0·50 g.), and purified by dissolving it in benzene and passing the solution through a column of alumina. The benzene eluate contained some of the above fully methylated material, m. p. 143°, while demethylated product was retained on the column and was washed out by means of benzene to which some methanol had been added. This *compound* formed pale yellow prisms, m. p. 149—150° from methanol, depressed to micro-m. p. *ca.* 135° by admixture with the product of m. p. 143°. It was quite insoluble in aqueous sodium hydroxide and only sparingly soluble in aqueous alcoholic sodium hydroxide, and gave a violet colour with ferric chloride in aqueous methanol (Found : C, 54·9; H, 4·5. $C_{18}H_{17}O_5Br$ requires C, 55·0; H, 4·3%). When methylated by heating (7 hours) with methyl sulphate and potassium carbonate in dry benzene, followed by purification (alumina), it gave the above ketone, m. p. and mixed m. p. 141—143°, in small yield.

Although the yields varied, the above processes, with minor modifications, gave a 10—15% yield of fully methylated product and a similar quantity of mono-demethylated product. Modifications—employing nitrobenzene as solvent, extended reaction time, higher reaction temperature, aluminium bromide as condensing agent—all failed to give better results, and a sparingly soluble, neutral product of m. p. 348—350° from benzene–nitrobenzene was often encountered and possibly resulted from polymerisation (Found : C, 55·3; H, 4·9%). Attempted ring-closure by means of concentrated sulphuric acid was impracticable owing to sulphonation, and the use of phosphoric oxide in boiling xylene gave a crystalline product of micro-m. p. 110—111° (Found : C, 62·9; H, 3·9%) which did not yield a dinitrophenylhydrazone and was not further examined.

*Oxidation of the Bromo-ketone,* $C_{19}H_{19}O_5Br$.—The bromo-ketone (0·15 g.) and sodium dichromate (1 g.) in aqueous acetic acid were heated under reflux for 1 hour. After cooling, dilution with water, and extraction with ether, the product was separated by dilute sodium hydroxide into neutral and acidic fractions. The former, recovered from the ether solution, consisted of unchanged bromo-ketone (0·05 g.), m. p. and mixed m. p. 143°, there being no trace of a (coloured) phenanthraquinone. The acidic fraction, recovered in ether from the acidified aqueous solution, had m. p. 216° from dilute acetic acid. Although it was not obtained analytically pure (Found : C, 52·7; H, 4·6. Calc. for $C_{19}H_{19}O_7Br$ : C, 51·9; H, 4·3%) it was probably the bromo-derivative of the acid similarly obtained from the debrominated ketone (below).

5 : 6 : 7-*Trimethoxy*-4-p-*methoxyphenyl*-1-*indanone* (IX).—*Cyclisation of* (III). A solution of (III) (0·20 g.) in anhydrous hydrogen fluoride (4 c.c.) was allowed to evaporate in absence of moisture. The

resulting gum was dissolved in ether and, after being washed with dilute sodium hydroxide and recovered, formed colourless prisms, m. p. 86°, from methanol, identical with a sample, m. p. and mixed m. p. 85—86° (oxime, m. p. and mixed m. p. 219°), obtained by Friedel–Crafts cyclisation as described by Frank, Fanta, and Tarbell (*loc. cit.*) who give corrected m. p. 89° (oxime, m. p. 217° decomp.).

*Debromination of* (X). A solution of the bromo-ketone (0·10 g.) in methanol (30 c.c.) was shaken with 2% palladised strontium carbonate in an atmosphere of hydrogen for 3—4 hours. The debrominated ketone, recovered from the filtered solution, distilled between 160° and 175° (air bath)/0·2 mm. and had m. p. and mixed m. p. 84—85° (Found : C, 69·4; H, 6·0. Calc. for $C_{19}H_{20}O_5$ : C, 69·5; H, 6·1%). It formed an oxime, m. p. and mixed m. p. 218—219° (Found : C, 66·6; H, 6·2. Calc. for $C_{19}H_{21}O_5N$ : C, 66·5; H, 6·1%). In an earlier experiment with a specimen of the bromo-ketone contaminated with cryptophenolic material, the product from the above treatment yielded long colourless prisms which gave a deep violet colouration with ferric chloride in aqueous methanol and had m. p. 122—123° from methanol : it was probably the monodemethylated *product* of the above ketone (Found : C, 68·4; H, 5·8. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%).

*Oxidation.* A sample of (IX) (obtained by debromination), when oxidised as described for the bromo-ketone, was partly recovered unchanged and partly converted into a carboxylic *acid*, (micro-) m. p. 166—168° (from chloroform then benzene–petroleum) (Found : C, 63·4; H, 5·5. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·55%).

1-*Amino*-5 : 6 : 7-*trimethoxy*-4-p-*methoxyphenylindane.*—The oxime of (IX) (0·2 g.) dissolved in ethanol (70—80 c.c.) was hydrogenated (4 hours) at 80—90°/60—65 atmospheres in presence of Raney nickel (0·2 g.). After filtration and recovery from the solvent, the product was dissolved in ether from which by addition of picric acid in ether the *picrate* was precipitated, m. p. 216—220° (with darkening) from methanol (Found : C, 53·7; H, 4·6. $C_{19}H_{23}O_4N,C_6H_3O_7N_3$ requires C, 53·8; H, 4·6%). When the gummy base, regenerated from the picrate, was rubbed with concentrated hydrochloric acid, it gave the *hydrochloride* as clusters of fine white rods, m. p. 211—212°, from moderately strong hydrochloric acid (Found : C, 62·3; H, 6·4. $C_{19}H_{23}O_4N,HCl$ requires C, 62·4; H, 6·6%). The base, regenerated from its hydrochloride, was acetylated by allowing it to stand with acetic anhydride (½ hour) and then shaking the mixture with 2N-sodium hydroxide. The *acetyl* derivative formed colourless prisms, m. p. 180—181° (Found : C, 68·0; H, 6·8; OMe, 33·8. $C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·75; OMe, 33·4%).

*Deamination.* The acetyl derivative (20 mg.) was heated for 20 minutes with phosphoric oxide (40 mg.) in dry xylene (1 c.c.). The gum, recovered from the decanted solution, was partly purified by passing its solution in benzene through alumina. Recovery from the eluate and subsequent distillation gave a non-basic product, b. p. 140—145° (air bath)/0·2 mm., which had (micro-) m. p. 70—72° from methanol. There was insufficient material for analysis, but the compound was probably 4 : 5 : 6-trimethoxy-7-*p*-methoxyphenylindene.

[With J. MacMillan] 4 : 5 : 6 : 4′-*Tetramethoxydiphenic Acid* (XII).—2N-Sodium hydroxide (0·18 c.c.) was added (10 minutes) with shaking to a suspension of 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone (XI) (56 mg.) in methanol (1 c.c.) containing 30% hydrogen peroxide (0·12 c.c.). Since the solid did not completely dissolve on warming, more hydrogen peroxide (0·12 c.c.) was added until dissolution was complete (about 1 hour). The methanol was distilled off, the resulting precipitate was dissolved by addition of water, and the solution was clarified by filtration through kieselguhr and made acid to Congo-red. The *acid*, recovered from chloroform, formed colourless prisms from aqueous alcohol, m. p. 240—241° after sublimation (210—220°/0·3 mm.) (Found : C, 59·7; H, 4·95. $C_{18}H_{18}O_8$ requires C, 59·7; H, 5·0%).

2 : 3 : 4 : 7-*Tetramethoxyfluorenone* (VII).—(*a*) A solution of 3 : 4 : 5-trimethoxy-2-*p*-methoxyphenylbenzoic acid (0·5 g.) in thionyl chloride (1·5 c.c.) was gently warmed (10 minutes) on the water-bath; excess of thionyl chloride was distilled off, and the solid residue was obtained as matted brick-red needles from methanol, m. p. 115° (Found : C, 67·8; H, 5·3. Calc. for $C_{17}H_{16}O_5$ : C, 68·0; H, 5·3%). (*b*) The same compound, m. p. 108—110° from methanol and mixed m. p. 110—111°, was obtained when the above tetramethoxydiphenic acid was heated for 10 minutes in a " Pyrex " tube at 350—360°. The product formed a red distillate, collected by cutting the tube and recovery from benzene solution after washing with dilute sodium carbonate.

*Ring-enlargement* of 2 : 3 : 4 : 7-*Tetramethoxyfluorenone* (VII).—A cooled solution of the fluorenone (0·5 g.) in ether (20 c.c.) and methanol (40 c.c.) was slowly treated with a large excess of diazomethane in ether, and the mixture was kept first for 2 hours at 0° and then for 12 hours at room temperature. The dark red gum (0·56 g.), recovered from the solution, was treated as follows in separate experiments :

(*a*) By means of aqueous sodium hydrogen carbonate it was separated into an acidic (0·05 g.) and a non-acidic (0·49 g.) gum. A solution of the latter in benzene–petroleum (1 : 1), when passed through a column of alumina, produced a chromatogram of two colourless fluorescent bands separated by a broad pink band. These were eluted in turn and afforded after recovery (i) 2 : 3 : 4 : 7 : 9(or 10)-*pentamethoxyphenanthrene* (XIII) (0·24 g.) as colourless needles, m. p. 115—117° from methanol (Found : C, 69·6; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%); (ii) unchanged tetramethoxyfluorenone (0·045 g.), m. p. and mixed m. p. 112—113°; (iii) a colourless gum (0·2 g.). On separate oxidation (compare *b*) fraction (i) gave the phenanthraquinone (XI); fraction (iii) gave the fluorenone (VII); while the acidic gum gave a mixture of (XI) and (VII) which was separated by chromatography.

(*b*) The red gum (1 g.) in acetic acid (14·5 c.c.) was slowly treated with a solution of sodium dichromate (2·9 g.) in acetic acid (2·9 c.c.) and water (1·5 c.c.), and the mixture was heated under reflux for 45 minutes, cooled, and diluted with water. The product was extracted with benzene, the extract being washed with dilute sodium hydroxide, dried, and evaporated. A solution of the resulting gum in benzene–petroleum (3 : 2) was passed through a column of alumina from which, by elution with benzene, a broad orange band afforded the fluorenone (VII; 0·385 g.), while the subsequent eluate of a violet-red band gave the phenanthraquinone (XI; 0·285 g.), m. p. and mixed m. p. 192—194° (diazine from *o*-phenylenediamine, m. p. and mixed m. p. 176—177°).

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