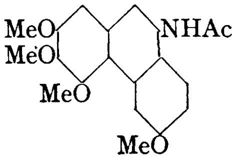
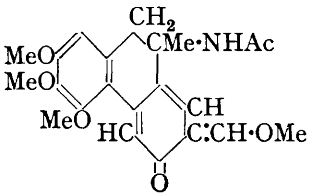
262. 9-*Acetamido*-2 : 3 : 4 : 6-*tetramethoxyphenanthrene*.

By Thomas M. Sharp.

In connexion with chemotherapeutic work being carried out by a colleague, it was desirable to prepare 9-*acetamido*-2 : 3 : 4 : 6-*tetramethoxyphenanthrene* (I). The synthesis was effected by the following stages. 3 : 4 : 5-Trimethoxybenzaldehyde was nitrated, yielding the 2-*nitro*-derivative; this was condensed with sodium *p*-methoxyphenylacetate to give 2-*nitro*-3 : 4 : 5-*trimethoxy*-α-p-*methoxyphenylcinnamic acid*, and reduction furnished the corresponding *amino*-derivative. Pschorr's original method for the synthesis of phenanthrenes from *o*-amino-α-phenylcinnamic acids by diazotisation and treatment with copper powder (*Ber.*, 1896, **29**, 496) gave a poor yield of phenanthrene derivative, but a later modification by Pschorr and Zeidler (*Annalen*, 1910, **373**, 78) applied to the above amino-compound led to the formation of 2 : 3 : 4 : 6-*tetramethoxyphenanthrene*-9-*carboxylic acid*. This was converted into 9-*amino*-2 : 3 : 4 : 6-*tetramethoxyphenanthrene* by the Curtius method, and on acetylation this yielded the desired substance (I).

(I.)





(II.)

Colchicine, to which Windaus (*Annalen*, 1924, **439**, 59) ascribes formula (II), on hydrolysis readily loses the methyl group in the side chain at position 7, with the formation of colchiceine. The latter has many of the properties of an aromatic hydroxyaldehyde, and it was therefore thought of interest to attempt to introduce an aldehyde group into position 7 of (I), in order to compare the properties of such a substance with those of colchicine. The methods used by Smith (J., 1916, **109**, 569) for the introduction of an aldehyde group into 3-phenanthrol, and by Hinkel, Ayling, and Beynon (this vol., p. **344**) for the preparation of phenanthrene-9-aldehyde were tried with (I), but the products in each case were dark-coloured resinous substances from which crystalline aldehyde could not be obtained; unfortunately, sufficient material was not available to permit of extended trial under varying conditions.

The nitration of 3 : 4 : 5-trimethoxybenzaldehyde presented considerable difficulties; the best yield of nitro-compound obtained was about 20%, and 4 : 5-dinitrotrimethylpyrogallol and 2 : 6-dimethoxy-*p*-benzoquinone were identified as by-products. The loss of the aldehyde group in the nitration of ethers of other aromatic hydroxyaldehydes has been noticed previously. Salway (J., 1909, **95**, 1155) concluded that the aldehyde group in such compounds was replaced directly by the nitro-group: analogous replacements have been obtained with ethers of polyhydroxybenzoic acids (Harding, J., **1911**, **99**, 1585, who reviews earlier results). 4 : 5-Dinitrotrimethylpyrogallol has been observed as a nitration product of trimethylgallic acid (Thomas and Siebeling, *Ber.*, 1911, **44**, 2115; Harding, *loc. cit.*), and 2 : 6-dimethoxy-*p*-benzoquinone as one of the products of the action of nitric acid on trimethylpyrogallol (Will, *Ber.*, 1888, **21**, 613).

EXPERIMENTAL.

Trimethylgallaldehyde was prepared by Rosenmund's method (*Ber.*, 1918, **51**, 585, 594) by the catalytic reduction of trimethylgalloyl chloride (Slotta and Szyska, *J. pr. Chem.*, 1933, **137**, 343) with hydrogen in boiling xylene solution in the presence of palladised barium sulphate. This process has previously been used by other investigators, who record yields of from about 50% (Baker and Robinson, J., 1929, 156) to 80% (Nierenstein, *J. pr. Chem.*, 1931, **132**, 200), and reaction times of 6—80 hours. The present author used Nierenstein's process, and found that pure sulphur-free xylene gave mainly trimethylgallic anhydride, while the " commercial-purified " grade of xylene with the addition of a trace of sulphurised quinoline (Rosenmund, *Ber.*, 1921, **54**, 425) gave yields of pure aldehyde of 70—80%. The reaction time was about 20 hours with fresh catalyst, but less with catalyst which had been used for previous batches. The non-aldehydic product of the reaction contained trimethylgallic anhydride, m. p. 160—161° (Fischer and Freudenberg, *Ber.*, 1913, **46**, 1116) (Found : C, 59·1; H, 5·47. Calc. for $C_{20}H_{22}O_9$: C, 59·1; H, 5·46%).

2-*Nitro*-3 : 4 : 5-*trimethoxybenzaldehyde*.—Finely powdered sodium persulphate (5 g.) was dissolved in concentrated sulphuric acid (450 c.c.), and trimethylgallaldehyde (25 g.) added in small portions to the stirred solution. When complete solution was obtained, the mixture was cooled to − 8° (if nuclei are undissolved the sulphuric acid usually crystallises and prevents mixing), and nitric acid (*d* 1·42, 8·25 c.c.) in concentrated sulphuric acid (75 c.c.) added during 20 minutes; stirring was continued for a further 5 minutes, and the dark brown mixture poured on about 2 kg. of ice. The sticky brown precipitate formed soon became granular; it was filtered off, dissolved in ether, the solution washed with sodium bicarbonate, and shaken with sodium bisulphite solution. The bisulphite compound after decomposition with sodium hydroxide furnished crude aldehyde (7—8·8 g.). This on crystallisation from alcohol gave pale yellow needles or platelets, m. p. 76—77° (corr.) (4—6 g.) (Found : C, 50·2; H, 4·7; N, 6·15. $C_{10}H_{11}O_6N$ requires C, 49·8; H, 4·6; N, 5·8%). The ethereal residue afforded 4 : 5-dinitro-1 : 2 : 3-trimethoxybenzene, m. p. 121—122° (Found : C, 42·3; H, 4·06; N, 10·5. Calc. for $C_9H_{10}O_7N_2$: C, 41·8; H, 3·9; N, 10·86%). Unchanged trimethylgallaldehyde (about 2 g.) was recovered from the aqueous acid mother-liquors by extraction with ether; subsequent extraction with chloroform furnished 2 : 6-dimethoxy-*p*-benzoquinone, golden-yellow needles from ethyl acetate, m. p. 253—255° (corr.) (Found : C, 57·55; H, 4·8. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%).

2-*Nitro*-3 : 4 : 5-*trimethoxy*-α-p-*methoxyphenylcinnamic Acid*.—Sodium *p*-methoxyphenylacetate (Dakin, *J. Biol. Chem.*, 1910, **8**, 22) (16·3 g.), dried at 130°, was mixed with 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde (21 g.) and acetic anhydride (156 c.c.), heated under reflux for 8 hours (oil-bath) at 135°, and set aside over-night; water (150 c.c.) was added, and the mixture warmed to decompose the acetic anhydride. The condensation product precipitated by water was extracted with ether, the extract washed with water, re-extracted with sodium carbonate solution, and the *acid* recovered; it crystallised from alcohol in pale yellow, stout prisms, m. p. 170—171° (corr.) (Found : C, 58·7; H, 4·6; N, 3·7. $C_{19}H_{19}O_8N$ requires C, 58·6; H, 4·9; N, 3·6%); yield 15·85 g.

2-*Amino*-3 : 4 : 5-*trimethoxy*-α-p-*methoxyphenylcinnamic Acid*.—A solution of ferrous sulphate (120 g., $7H_2O$) in water (370 c.c.) was mixed with ammonia (*d* 0·880, 315 c.c.), warmed on a water-bath to 70°, and treated with the foregoing nitro-acid (17·7 g.) in ammonia (*d* 0·880, 60 c.c.). The mixture was heated for an hour on the water-bath, filtered, the filtrate cooled to 0°, made slightly acid to Congo-red, and extracted with ether. On evaporation this left the *amine* (14·46 g.) as a yellow solid which crystallised from alcohol in stout prisms, m. p. 167—168° (corr.) (yield, pure, 13·8 g.) (Found : C, 63·3; H, 5·7; N, 3·95. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·9; N, 3·9%). A second form was occasionally obtained which crystallised from alcohol in thin yellow plates, m. p. 159°. The two forms are interconvertible by crystallisation from alcohol, a seed of the desired form being used.

2 : 3 : 4 : 6-*Tetramethoxyphenanthrene*-9-*carboxylic Acid*.—The above amino-acid (12·36 g.) was dissolved in sulphuric acid (5%, 300 c.c.) with the aid of heat, cooled to 50°, and sodium nitrite (4 g.) in water (20 c.c.) added slowly with stirring. The mixture darkened and a tarry substance separated. Heating was continued for 20 minutes, after which the products of reaction were extracted with ether. They were separated into acid and non-acid fractions by extraction with sodium carbonate solution. The former gave 2 : 3 : 4 : 6-*tetramethoxyphenanthrene*-9-*carboxylic acid*, small light-brown sandy crystals from alcohol, m. p. 172—173° (corr.) (5·7 g.) (Found : C, 67·1; H, 5·5. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%), and the latter

(3 g.) yielded a nitrogenous substance, which has not been identified, separating from benzene or alcohol in pale yellow rectangular plates, m. p. 162—163°.

9-Amino-2 : 3 : 4 : 6-tetramethoxyphenanthrene.—2 : 3 : 4 : 6-Tetramethoxyphenanthrene-9-carboxylic acid (5·14 g.) was esterified with dry alcohol and hydrogen chloride, and the crude ester (4·85 g., m. p. 122°) without further purification converted into the hydrazide by boiling with hydrazine hydrate (15 c.c.) for 4 hours under reflux. Alcohol (25 c.c.) was added, and boiling continued for an hour to complete the reaction. Alcohol and excess of hydrazine were removed by evaporation under reduced pressure on the water-bath. The residue was dissolved in absolute alcohol, from which the crude hydrazide separated as an almost white solid (3·5 g., m. p. 191—196°); it was suspended in alcohol (70 c.c.) and converted into the azide by the addition of alcoholic hydrogen chloride (3·8*N*, 9·5 c.c.) and amyl nitrite (7 c.c.). The colour became similar to that of red phosphorus. After an hour in the ice-chest, the azide was filtered off, washed with alcohol, and dried in a desiccator (2·81 g., m. p. 97°, decomp.). It was boiled under reflux with dry alcohol (28 c.c.) for an hour and concentrated to about 2/3 volume. The urethane then crystallised out (2·44 g., m. p. 119—120°). Without further purification, it was boiled under reflux with 10% methyl-alcoholic potassium hydroxide (60 c.c.) for 3½ hours, water added, the methyl alcohol distilled off, and the amine isolated by extraction with ether, in which it is rather sparingly soluble. There were thus obtained 1·8 g. of 9-*amino*-2 : 3 : 4 : 6-*tetramethoxyphenanthrene* as a dark-coloured solid which, after crystallisation from alcohol (charcoal), formed colourless needles, m. p. 157—159° (corr.) (Found : C, 69·3; H, 5·95; N, 4·5. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1; N, 4·5%). This base was stirred for 5 minutes with an equal weight of acetic anhydride; water was then added, the *acetyl* derivative (I) collected, and recrystallised from methyl alcohol; it formed colourless needles, m. p. 152—153° (corr.) (Found : C, 67·2; H, 5·6; N, 4·05. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 5·96; N, 3·9%).

The author thanks Dr. T. A. Henry for his interest and advice, Mr. A. G. Turner for assistance in the preparative work, and Messrs. A. Bennett and H. C. Clarke for the micro-analyses.

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[*Received, June 22nd,* 1936.]