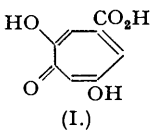
522. *A Synthesis of Stipitatic Acid.*

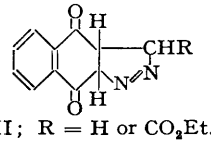
By J. R. Bartels-Keith, A. W. Johnson, and W. I. Taylor.

A method of synthesis of the tropolone ring has been developed which involves a ring expansion of veratroles with diazoacetic ester and subsequent oxidative hydrolysis of the products. Syntheses of tropolone-β-carboxylic acid, and therefore of tropolone itself, and of stipitatic acid are described, as well as several derivatives of the acids.

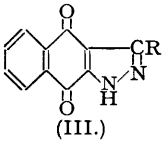
In an earlier paper (Corbett, Johnson, and Todd, *J.*, 1950, 147), the correctness of the tropolone formulation (I) for stipitatic acid (Birkinshaw, Chambers, and Raistrick, *Biochem. J.*, 1942, **36**, 242), as originally advanced by Dewar (*Nature*, 1945, **155**, 50), was established unequivocally on degradative evidence. At that time no tropolone syntheses had been described, and after a number of unsuccessful approaches the reaction between diazoacetic ester and methoxybenzoquinone was investigated, which, if a ring enlargement occurred, should have given a methyl ether of stipitatic acid directly. The reaction between 1 : 4-quinones and diazoacetic ester has been investigated previously only in the case of 1 : 4-naphthaquinone (Fieser and Peters, *J. Amer. Chem. Soc.*, 1931, **53**, 4080), although there are several examples of the reaction of quinones with diazomethane (*inter alia* : Fieser and Peters, *loc. cit.*; Wallenfels, *Ber.*, 1942, **75**, 787; Spruit, *Rec. Trav. chim.*, 1947, **66**, 655; 1949, **68**, 304). The course of these earlier reactions was not encouraging from the point of view of synthesis of tropolone; the first-formed pyrazoline-quinones [*e.g.*, (II) from 1 : 4-naphthaquinone] rearranged to the pyrazole-quinols, which were oxidised to the corresponding quinones (*e.g.*, III). The final products did not evolve nitrogen when heated.



(I.)



(II; R = H or CO_2Et.)



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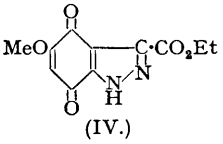
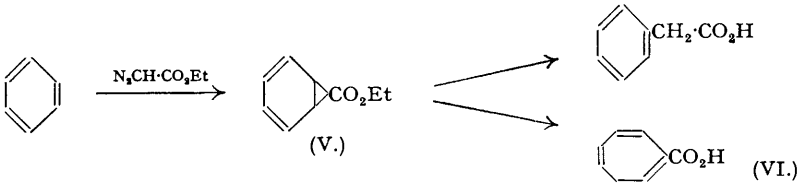


(IV.)

The reaction between methoxybenzoquinone and diazoacetic ester exactly paralleled that with 1 : 4-naphthaquinone, the product (IV), 5 (or 6)-methoxyindazole-4 : 7-quinone-3-carboxylic ester, being pale yellow and not evolving nitrogen even at 200°. It is well known that the presence of substituents on the nuclear carbon atoms of the quinone diminish the ease of addition reactions to the double bonds, and there can be little doubt that the addition of diazoacetic ester occurs at the unsubstituted double bond of methoxybenzoquinone as indicated.

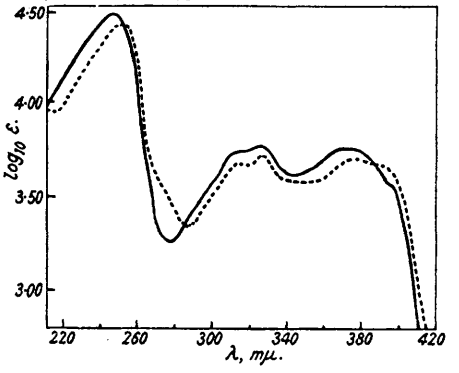
Attention was therefore turned to the reaction of diazoacetic ester with methoxyquinol in the form of its dimethyl ether, 1 : 2 : 4-trimethoxybenzene, and as a preliminary the corresponding reaction with 1 : 2-dimethoxybenzene, veratrole, was investigated in order to assess the feasibility of preparing tropolones in this manner. The ring expansion of benzenoid compounds with diazomethane and its derivatives is well known, the reaction having been studied in detail by Buchner and his co-workers (*Ber.*, 1920, **53**, 865, and numerous earlier papers). They showed that the first-formed norcaradienecarboxylic esters (V) can be rearranged, especially by alkalis or at high temperatures, to derivatives of phenylacetic acid or the *cyclo*-

heptatrienecarboxylic acids (*e.g.*, VI). Other workers (*e.g.*, Smith *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 2167; 1938, **60**, 648; Drake and Sweeney, *J. Org. Chem.*, 1946, **11**, 67) have extended Buchner's observations, and in particular, Plattner and his school have used the method for



the synthesis of the azulene ring system from indanes (review : Pommer, *Angew. Chem.*, 1950, **62**, 281). In the case of veratrole, the dimethoxy*cyclo*heptatrienecarboxylic ester formed as one of the products from the diazoacetic ester condensation is an enol ether of a dihydrotropolonecarboxylic ester, and thus in order to obtain the tropolonecarboxylic ester itself it was necessary to effect an oxidative acid hydrolysis. Of the various reagents tried for this step, bromine (1 mol.) in chloroform solution proved to be the most effective, and a tropolonecarboxylic ester was thereby obtained in approximately 7% overall yield from veratrole. Smaller yields were also obtained by the use of *N*-bromosuccinimide in carbon tetrachloride solution, a reagent which we had already used in a preparation of benzotropolone from 3 : 4-benzo*cyclo*heptane-1 : 2-dione (cf. Cook and Somerville, *Nature*, 1949, **163**, 410). Tropolonecarboxylic ester was extracted from the crude reaction product by virtue of its solubility in sodium hydrogen carbonate solution, and was readily purified by crystallisation or by sublimation under reduced pressure. It formed beautiful yellow needles, which gave green colours with both ferric chloride and cupric sulphate, and like the other tropolones it gave no typical carbonyl reactions. The most convincing evidence for the presence of the tropolone ring system in the ester came from the infra-red spectrum, which showed bands at 1736 (carbethoxy-group) and at 1620, 1560, 1478, 1440, and 1250 cm.$^{-1}$, which are characteristic of the tropolone nucleus (Scott and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 240). Since this work was first reported in preliminary form (Bartels-Keith and Johnson, *Chem. and Ind.*, 1950, 677), there has been much further study of the infra-red spectra of tropolones (*e.g.*, Koch, *J.*, 1951, 512; Haworth and Hobson, *ibid.*, p. 561; Aulin-Erdtman, *Acta Chem. Scand.*, 1950, **4**, 1490; Johnson, Sheppard, and Todd, *J.*, 1951, 1139), so this ring system may now be detected readily by the characteristic infra-red spectrum. The ultra-violet absorption spectrum of the tropolonecarboxylic ester is shown in the figure.

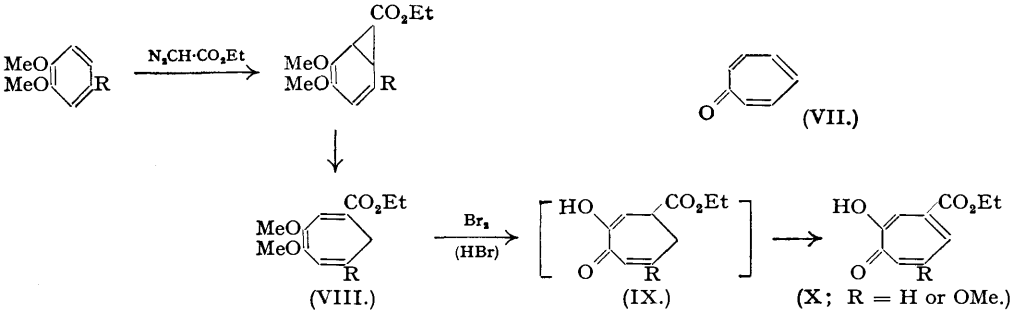
Ultra-violet absorption spectra of tropolone-β-carboxylic acid (———) and its ethyl ester (- - - - -) in 95% ethanol solution.



Since the initiation of the above synthesis, several other routes to the tropolones have been described, in particular the dehydrogenation of *cyclo*heptane-1 : 2-dione (Cook, Gibb, Raphael, and Somerville, *Chem. and Ind.*, 1950, 427; *J.*, 1951, 503) and the degradation of purpurogallin to β-methyltropolone and thence to tropolone itself (Haworth and Hobson, *loc. cit.*; *Chem. and Ind.*, 1950, 441). In another approach, Doering and Knox (*J. Amer. Chem. Soc.*, 1950, **72**, 2305; 1951, **73**, 828) have prepared tropolone by the permanganate oxidation of *cyclo*heptatriene (tropilidene), itself obtained either from *cyclo*heptene by dehydrogenation or from benzene and diazomethane by irradiation. It is obvious that Doering and Knox's method bears a close relation to the present method, but the presence of the oxygen atoms as protected hydroxy-groups in the nucleus before ring expansion avoids the permanganate oxidation which gives rise to many by-products. This has been recognised by the American workers, for in a recent note describing the preparation of the parent ketone, tropone (VII), they use the ring expansion of anisole with diazomethane in ultra-violet light. For studies of the mechanism of these ring-expansion reactions and the determination of the exact structure of the intermediates, the use of diazoacetic ester has the obvious advantage over diazomethane

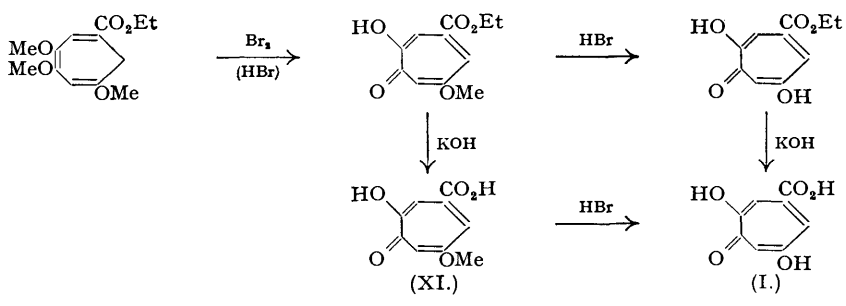
in that the carbon atom introduced by the reagent is marked by the carbethoxy-group. These studies, which should lead to improvements in the low yields of tropolones obtained at present, will be discussed in forthcoming papers.

Hydrolysis of the tropolonecarboxylic ester gave the corresponding acid, m. p. 217—219°, and by direct comparison it was shown to be identical with tropolone-β-carboxylic acid, an authentic specimen of which was kindly provided by Professor R. D. Haworth. As the decarboxylation of this acid to tropolone itself has already been described (Haworth and Hobson, *loc. cit.*), the present method represents a further synthesis of tropolone itself. The course of the veratrole–diazoacetic ester reaction to produce tropolone-β-carboxylic ester (X; R = H) may therefore be represented as follows (R = H), although the exact positions of the double bonds in (VIII) and (IX) have still to be determined.



Besides tropolone-β-carboxylic ester there was also obtained, in approximately equal quantities from the reaction of veratrole with diazoacetic ester, a colourless acid $C_8H_6O_4$, m. p. 149°, the structure of which is under consideration, but which is not a tropolone, on the basis of its infra-red spectrum.

The extension of this synthesis to the preparation of other naturally occurring tropolones, including stipitatic acid, is of course obvious. Thus the use of 1 : 2 : 3 : 4-tetramethoxybenzene and diazoacetic ester should give puberulic acid, and likewise the various alkyltropolones should be obtained from the alkylveratroles, or from veratrole itself with the diazoalkanes or diazoalkanecarboxylic esters. From the reaction of 1 : 2 : 4-trimethoxybenzene with diazoacetic ester, the crude trimethoxy*cyclo*heptatrienecarboxylic ester was isolated in 44% yield. Considerable insight into the nature of the impurities in this product has been gained from a study of the acids obtained by alkaline hydrolysis, but this aspect of the subject will be discussed in detail in a later paper. Bromine (1 mol.) in acetic acid proved to be the most satisfactory reagent for the oxidative hydrolysis and from the crude reaction mixture there were obtained three products, ethyl *O*-methylstipitatate (X; R = OMe), ethyl stipitatate, and an unidentified bright yellow compound, m. p. 182—184°, which is still under investigation. Synthetic stipitatic ester was identical with the ethyl ester prepared from authentic stipitatic acid. Alkaline hydrolysis of the two esters gave the corresponding acids, stipitatic acid and its *O*-methyl ether, the latter being identical with the product obtained by direct methylation of stipitatic acid with methyl sulphate (Birkinshaw, Chambers, and Raistrick, *loc. cit.*). The



formulation of *O*-methylstipitatic acid as (XI) rather than as the isomeric methyl ether is preferred because the compound is not easily hydrolysed (*e.g.*, it was recovered unchanged from a solution in 48% hydrobromic acid after 20 minutes at 50°), whereas tropolone methyl

ethers are known to be readily hydrolysed in acids and alkalis. This is in agreement with Dewar's suggestion (*loc. cit.*) concerning the nature of this compound. A second synthesis of stipitatic acid was achieved by the demethylation of this *O*-methyl ether with hydrogen bromide, and the ethyl stipitatate isolated from the products of the original bromination was no doubt formed by a similar mechanism. Synthetic stipitatic acid was identical with the natural product in all respects, including the infra-red spectrum (Johnson, Sheppard, and Todd, *loc. cit.*; Aulin-Erdtman, *loc. cit.*).

Experimental.

Reaction of Methoxybenzoquinone and Ethyl Diazoacetate.—Methoxybenzoquinone (3 g.; Erdtman, *Proc. Roy. Soc.*, 1933, *A*, **143**, 177) was dissolved in boiling light petroleum (400 c.c.; b. p. 80—100°), and ethyl diazoacetate (2·4 g.) added slowly during 1 hour. The reaction mixture was heated under reflux for a further hour, during which some darkening took place. On cooling, a brown solid was precipitated which was separated and washed with acetone (3 c.c.), leaving a greenish-brown crystalline solid (940 mg.), m. p. 127—132°. Unchanged methoxybenzoquinone was removed from the product by sublimation at 100°/1 mm., and the brownish residue (150 mg.) was crystallised from ethanol to give pale yellow needles of *ethyl* 5(6)-*methoxyindazole*-4 : 7-*quinone*-3-*carboxylate*, m. p. 245—247° (decomp.) (Found : C, 53·1; H, 3·8; N, 11·3. $C_{11}H_{10}O_5N_2$ requires C, 52·8; H, 4·0; N, 11·2%).

Reaction of Veratrole and Ethyl Diazoacetate.—Redistilled veratrole (200 g.) was heated to 150°, and ethyl diazoacetate (40 g.) added dropwise with stirring during 2 hours. After 15—30 minutes a steady stream of nitrogen was evolved, and the temperature was kept at 150—155° throughout the addition. The mixture was kept at the same temperature for a further 3½ hours, after which the volume of nitrogen evolved (collected over water) was 92% of theory (calc. on diazoacetic ester). The dark red product was distilled under reduced pressure to remove the excess of veratrole (187 g.; b. p. 50—60°/0·2 mm.), and the residue distilled in high vacuum, yielding a yellow oil (17·8 g.; b. p. 80—95°/2 × 10^{-4} mm.). The distillate was redistilled, and a middle cut (b. p. 84—87°/1·3 × 10^{-4} mm., n_D^{16} 1·5175) taken for analysis (Found : C, 63·7; H, 7·1. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%). The *ethyl dimethoxycyclo-heptatrienecarboxylate* slowly darkened on exposure to air, and formed deep yellow solutions in concentrated sulphuric acid or hydrochloric acid. Permanganate in acid or alkaline solution was instantly reduced and bromine was immediately decolorised. The ultra-violet absorption spectrum of a solution in 95% ethanol showed a maximum at 2740—2750 A. (log $\varepsilon_{max.}$ 3·51), with inflexions at 3120—3130, 3060—3100, 2950—2970 A.; log $\varepsilon_{max.}$ 3·30, 3·30, and 3·33, respectively.

Ethyl Tropolone-β-carboxylate.—The foregoing crude ester (1·84 g.) was dissolved in chloroform (30 c.c.), and a solution of bromine (1·35 g., 1 mol.) in chloroform added. Hydrogen bromide was evolved, and the mixture was then heated for 5 hours under reflux. The chloroform was removed, the residue dissolved in ether, and the solution repeatedly extracted with saturated sodium hydrogen carbonate solution (8 × 20 c.c.). The combined yellow aqueous extracts were acidified and the solution was extracted with ether (6 × 20 c.c.). The solvent was removed from the ethereal extracts, and the residue sublimed under reduced pressure (80—100°/20 mm.) to give *ethyl tropolone-β-carboxylate* as yellow needles (110 mg., 6·9%) which after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 90—91° (Found : C, 61·2; H, 5·1. $C_{10}H_{10}O_4$ requires C, 61·3; H, 5·2%). The ultra-violet absorption spectrum of a solution in 95% ethanol showed maxima at 2505, 3130, 3250, 3745, and 3885 A.; log $\varepsilon_{max.}$ 4·43, 3·69, 3·73, 3·72, and 3·68, respectively.

When the crude product before sublimation was extracted with light petroleum (b. p. 40—60°) so as to remove most of the tropolone-β-carboxylic ester, a further extraction with light petroleum (b. p. 80—100°) yielded a second product (187 mg. from 15·2 g. of crude dimethoxy*cyclo*heptatrienecarboxylic ester); purified by sublimation at 100°/0·05 mm. and crystallisation from *n*-hexane, this *substance* formed colourless needles, m. p. 149° (decomp.) (Found : C, 57·8; H, 3·5. $C_8H_6O_4$ requires C, 57·8; H, 3·6%). The ultra-violet absorption spectrum (95% ethanol as solvent) showed maxima at 2100—2110, 2530, and 3170 A.; log $\varepsilon_{max.}$ 4·15, 4·44, and 3·48, respectively. Alkaline solutions were colourless and the acid gave no marked ferric test.

Tropolone-β-carboxylic Acid.—Tropolone-β-carboxylic ester (64 mg.) was dissolved in aqueous sodium carbonate (41 mg. in 5 c.c.), and the solution heated under reflux for 2½ hours. No change in colour was observed. The solution was cooled, acidified with 3N-hydrochloric acid, and set aside at 0°; a yellow solid (33 mg.) separated, and a further quantity (19 mg.) was obtained by extraction of the filtrate with ether (6 × 3 c.c.) and evaporation of the combined ethereal extracts. The crude product, m. p. 213—218°, was obtained as buff-coloured needles, m. p. 217—219°, not depressed on admixture with an authentic specimen, m. p. 217—218° (Haworth and Hobson, *J.*, 1950, 561) (Found : C, 57·8; H, 3·7. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·6%). The ultra-violet absorption spectrum in 95% ethanol showed maxima at 2440—2460, 3240—3250, and 3670—3690 A.; log $\varepsilon_{max.}$ 4·49, 3·79, and 3·77, respectively. The infra-red spectrum of the acid, as a mull in Nujol, showed absorption maxima at 1770, 1605, 1530, 1468, 1427, 1400, 1272, 1245, 1220, 950, 790, and 707 cm.$^{-1}$. The acid gave a green colour with ferric chloride and formed yellow solutions in alkalis. Like the corresponding ester, the solution in concentrated hydrochloric acid was colourless.

1 : 2 : 4-*Trimethoxybenzene.*—Methoxyquinol (Dakin, *J. Amer. Chem. Soc.*, 1909, **42**, 496) was methylated with methyl sulphate to yield 1 : 2 : 4-trimethoxybenzene (60%; b. p. 96°/0·4 mm.).

Reaction of 1 : 2 : 4-*Trimethoxybenzene with Ethyl Diazoacetate: Ethyl* O-*Methylstipitatate.*—Ethyl diazoacetate (60 c.c.) was added dropwise during 2½ hours to 1 : 2 : 4-trimethoxybenzene (300 g.) at 150° with stirring, and the mixture kept at this temperature for a further 3½ hours; the unchanged trimethoxybenzene (250 g.) was then removed by distillation at 0·1 mm. The residues from two such

preparations were combined and distilled, and the following fractions were taken: (i) b. p. 55—70°/10^{-4} mm. (8·8 g.), giving a red colour with sulphuric acid; (ii) b. p. 80—100°/10^{-4} mm. (36·8 g.), red colour with sulphuric acid; (iii) b. p. 109—120°/10^{-4} mm. (29·0 g.), orange colour with sulphuric acid.

Fraction (ii) (35·8 g.) was oxidised in small portions (1·5 g.) each in acetic acid (20 c.c.) and water (4 c.c.). Bromine (0·3 c.c., 1 mol.) in acetic acid (10 c.c.) was added dropwise with shaking during 15 minutes, and the mixture set aside at room temperature for a further 15 minutes and then heated for 40 minutes on the steam-bath. The acetic acid was removed *in vacuo* and the residue extracted with N-sodium carbonate solution (3 × 15 c.c.). The extract was washed with ether (2 × 30 c.c.), acidified with 3N-hydrochloric acid, and extracted with ether (3 × 35 c.c.). The combined ethereal extracts were washed well with water and dried, and the solvent removed. The residue was sublimed at 100—110°/0·02 mm. and the combined sublimates were percolated for a short time with ether in order to remove a more soluble yellow compound (see below). The non-volatile fraction remaining after the sublimation was treated separately (see below). The portion of the sublimate insoluble in cold methanol was then extracted with boiling methanol (Soxhlet), and the extract on concentration yielded crude *ethyl O-methyl stipitatate*, which was purified by recrystallisation from the same solvent. The ether-ester (200 mg.) formed pale yellow needles, m. p. 154—156° (Found, in a sample dried at 60° for 3 hours in a vacuum: C, 58·4, 58·9; H, 5·4, 5·3. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). The ultra-violet absorption spectrum in 95% methanol showed maxima at 2610 and 3500 (broad) A.; log $\varepsilon_{max.}$ 4·32 and 3·56, respectively.

The ether-soluble fraction of the crude sublimate was combined with the mother-liquors from the crystallisation of ethyl *O*-methylstipitatate and after fractional crystallisation from methanol, a *substance* was obtained which crystallised in bright yellow needles (30 mg.), m. p. 182—184° (slight decomp.) (Found, in a sample dried overnight at room temperature in a vacuum: C, 56·9; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). The ultra-violet absorption spectrum of an ethanol solution showed maxima at 2430, 3360, and 4040 A.; $E^{1\%}_{1\,cm.}$ 1230, 367, and 345, respectively.

The non-volatile residues from the sublimations were combined and triturated with cold methanol, and the insoluble residue crystallised from hot methanol (charcoal) to give pale yellow plates of *ethyl stipitatate* (40 mg.), m. p. 240° (decomp.), raised to 244° (decomp.) on recrystallisation from the same solvent and undepressed in admixture with a sample of the ester prepared from the natural acid (see below) (Found, in a sample dried overnight at room temperature in a vacuum: C, 57·1; H, 4·6. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). The ultra-violet absorption spectrum of an ethanol solution showed maxima at 2640, 3640, and 3700 A.; log $\varepsilon_{max.}$ 4·48, 3·61, and 3·61, respectively.

O-*Methylstipitatic Acid.*—Hydrolysis of the ethyl ester with N/10-aqueous potassium hydroxide at 50° for 1 hour gave almost quantitative yields of *O*-methylstipitatic acid, crystallising from methanol in pale yellow flat needles, m. p. 262—264° (decomp.), alone or mixed with an authentic specimen prepared from stipitatic acid (Birkinshaw, Chambers, and Raistrick, *loc. cit.*) [Found, in a sample dried overnight at room temperature in a vacuum: C, 55·6; H, 4·0; OMe (Zeisel), 15·6. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1; 1OMe, 15·8%]. The ultra-violet absorption spectrum showed maxima at 2580, 3160, and 3560 A.; log $\varepsilon_{max.}$ 4·48, 3·53, and 3·61, respectively.

Stipitatic Acid.—(*a*) *O*-Methylstipitatic acid (40 mg.) in hydrobromic acid (1 c.c. of 48%) was heated at 110° for 12 hours. Stipitatic acid crystallised out from the cooled reaction mixture and was recrystallised from boiling water, forming small pale yellow plates (55 mg.), m. p. 280° (decomp. with previous darkening) alone and mixed with an authentic specimen. For analysis, it was sublimed at 180°/2 × 10^{-4} mm., the m. p. being thereby raised to 282° (Found: C, 53·0; H, 3·5. Calc. for $C_8H_6O_5$: C, 52·7; H, 3·3%).

(*b*) Hydrolysis of ethyl stipitatate with N/10-aqueous potassium hydroxide at 50° for 1 hour gave stipitatic acid, m. p. 282° (decomp.), identical with the product obtained in (*a*) (Found: C, 52·5; H, 3·6%). The ferric colours of stipitatic acid, its *O*-methyl ether, ethyl ester, and *O*-methyl ether ethyl ester, as determined with alcoholic solutions and excess of the reagent, were all green.

Ethyl Stipitatate.—Stipitatic acid (30 mg.) was heated under reflux with absolute ethanol (5 c.c.) containing concentrated sulphuric acid (3 drops) for 2 hours. After dilution and extraction with ether in the usual way, *ethyl stipitatate* was obtained as pale yellow plates, m. p. 244—246° (decomp.) (from methanol) (Found, in a sample dried overnight at 50° in a vacuum: C, 57·4; H, 5·0. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

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