

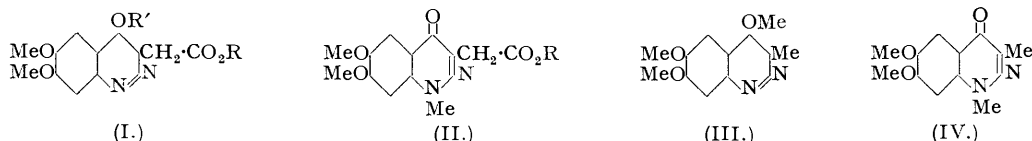
93. Cinnolines. Part VI. Derivatives of 4-Hydroxy-6:7-dimethoxycinnoline-3-acetic Acid.

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A few simple functional derivatives of 4-hydroxy-6:7-dimethoxycinnoline-3-acetic acid are described. Both *O*- and *N*-methyl ethers are formed by the action of methyl sulphate and alkali on the acid; these are produced in approximately equal amounts, and are converted by esterification into the corresponding *ether-esters*. The two isomeric series are designated α - and β -, and, although corresponding members differ markedly in chemical properties (basicity, ease of decarboxylation), it has not proved possible to distinguish with certainty between the alternative structures for each substance.

THE preparation of the substance named in the title has already been described (Schofield and Simpson, *J.*, 1945, 520), but the study of its reactions originally planned has had to be postponed after the derivatives described below had been prepared.

Treatment of the acid (I; R = R' = H) with methyl sulphate and alkali gave a mixture of two isomeric *ether-acids*, (I; R = H; R' = Me) and (II; R = H), designated for convenience α - and β -, from which only the α -compound, m. p. 260° (decomp.), could be obtained pure. Esterification of the mixture with methyl alcohol and sulphuric acid yielded the corresponding mixture of *ether-esters* (I; R = R' = Me) and (II; R = Me), which was separated without difficulty into the pure α - and β -isomers. Each of these was readily hydrolysed by dilute hydrochloric acid, but whereas the α -ether-acid separated directly from the reaction solution, hydrolysis of the β -compound gave a well-defined *hydrochloride* of the β -ether-acid. This salt was soluble in hot water, and from the solution the pure β -ether-acid separated after a few minutes; re-esterification of this acid yielded the parent ester, identical with that prepared by fractionation of the original mixture of ether-esters. The α - and β -ether-acids also behaved differently when heated; the β -compound was stable well above its melting point, but the α -isomer readily lost carbon dioxide at the melting point and yielded a *base* (III or IV), which is provisionally designated the " α -ether." This substance formed a hydrochloride, and a slight degree of quaternisation seemed to occur when it was refluxed with ethyl iodide in alcoholic solution.



It was hoped that methoxyl determinations would enable definite structures to be assigned to substances of the α - and β -series by virtue of the ease with which *O*-dealkylation is usually effected as compared with *N*-dealkylation. However, estimations on the substance (III or IV) and on the β -ether-acid, as representatives of each series, were unsatisfactory, being appreciably below the theoretical value for two methoxyl groups. No systematic study appears to have been made of the factors which affect the reactivity of methoxyl groups on C₄ in nitrogen heterocyclic compounds, but the inertness encountered here, both in the Zeisel estimations and in the acid hydrolysis of the α - and β -ether-esters, contrasts sharply with the extreme reactivity displayed by C₄ alkoxy groups in various quinazoline derivatives (Bogert and May, *J. Amer. Chem. Soc.*, 1909, **31**, 507; Lange and Sheibley, *ibid.*, 1932, **54**, 1994, 4305; 1933, **55**, 1188).

The available chemical evidence, although favouring the *N*-methylcinnolone structure for the α -series, is not decisive. The greater basicity of the β - as compared with the α -ether-acid cannot be used as evidence of the *O*-ether structure for the latter by analogy with the absence of basic properties in the hydroxy-acid (I; R = R' = H) of similar fine structure (Schofield and Simpson, *loc. cit.*), because 4-methoxycinnoline is decidedly more basic than 4-hydroxycinnoline (a suspension of the former in cold water dissolves immediately on addition of a drop of 2*N*-hydrochloric acid, but the hydroxycinnoline dissolves only slowly on warming with 2*N*-acid), and it is therefore probable that a similar difference would be found between the two acids (I; R = R' = H) and (I; R = H, R' = Me). Fusion of the α -ether with phthalic anhydride, both with and without zinc chloride [the C₃-methyl group should be reactive in a substance of structure (IV), but not in one of structure (III)], gave no positive result. Attempted diagnosis of the structure of this substance by means of a mixture of phosphorus pentachloride and phosphorus oxychloride was also unsuccessful; it is well established (Fischer and Guthmann, *J. pr. Chem.*, 1916, **93**, 379; Thielepape, *Ber.*, 1922, **55**, 127; Thielepape and Fulde, *ibid.*, 1939, **72**, 1432) that *N*-methyl- α -quinolones are smoothly converted into α -chloroquinolines by these reagents, but, in the present case, almost the whole of the material was converted into a highly-coloured water-soluble product after basification of the diluted reaction-mixture. This behaviour is not obviously explicable on the basis of structure (III), but could be explained on the assumption that the reaction with (IV) gives the 4-chloromethochloride as primary product, as a number of 4-substituted quaternary cinnolinium salts have been observed in this laboratory to yield intensely coloured solutions on treatment with alkali (unpublished). Finally, the extreme ease with which the α -ether acid undergoes decarboxylation also points to the *N*-ether structure for the α -series, because the acid (I, R = R' = H), although of higher decomposition point, does not behave similarly, and a crystalline product could not be obtained when decarboxylation of the acid was attempted with quinoline and copper carbonate.

EXPERIMENTAL.

(Melting points are uncorrected.)

Preparation of Mixed α - and β -Ether-acids.—A solution of 4-hydroxy-6:7-dimethoxycinnoline-3-acetic acid (50 g.) in 10% sodium hydroxide (400 c.c.) and water (200 c.c.) was treated with methyl sulphate (70 c.c.), added in portions with shaking in a stoppered flask at 50–60°. Excess of sodium hydroxide solution was then added, after which the clear solution was cooled somewhat and made acid to Congo red with dilute hydrochloric acid. The solid product, which invariably separated in two distinct crops, was collected and washed (yield, 40.5 g.). Several crystallisations of a portion of this material from aqueous acetic acid gave the pure α -ether-acid as minute colourless needles, m. p. 260–261° (efferv.) (dependent on the rate of heating) (Found: C, 55.2; H, 5.1. $C_{13}H_{14}O_5N_2$ requires C, 56.1; H, 5.1%). The acid was easily soluble in cold aqueous sodium carbonate and not appreciably soluble in hot alcohol or hot 2N-nitric acid. The acidified filtrate from the mixed isomers was combined with that from a 25 g. experiment (which gave 20.5 g. of mixed solids), and excess of sodium acetate was added, followed, after evaporation to about 400 c.c., by 12 g. of picric acid; the mixture of picrates (14.5 g.; m. p. 255–260°) which separated was not investigated.

Preparation of α - and β -Ether-esters.—The foregoing mixture of ether-acids (40.5 g.) was refluxed for 3½ hours with methanol (500 c.c.) and concentrated sulphuric acid (20 c.c.). Excess of solid sodium bicarbonate was then added, and most of the methanol removed by evaporation. The residue, after dilution with water and a little aqueous sodium carbonate, was extracted four times with chloroform. The extract was dried (sodium sulphate) and evaporated, and the residue crystallised from alcohol, yielding 18.1 g. of almost pure α -ether-ester, m. p. 185–186°. An analytical sample formed long, pale yellow needles, m. p. 186–187°, only moderately soluble in hot alcohol, and appreciably soluble in hot water (Found: C, 57.5; H, 5.3. $C_{14}H_{16}O_5N_2$ requires C, 57.5; H, 5.5%). For hydrolysis, the ester (15 g.) was heated on the steam-bath with 2N-hydrochloric acid (240 c.c.) for 1 hour. The solid rapidly dissolved, and this was soon followed by crystallisation of the product, which was filtered cold, washed and dried; yield, 13.4 g., m. p. 261–262° (efferv.) alone and mixed with the α -ether-acid already described.

The alcoholic filtrate from the α -ether-ester was combined with that from a similar experiment, in which 21.5 g. of mixed ether-acids had been esterified, and the solvent was removed. Crystallisation of the residue from acetone readily yielded the pure β -ether-ester (20.8 g.) as brittle yellow prismatic needles, m. p. 184–185° (160–170° when mixed with the α -isomer); occasionally this substance separated from acetone, in which it was rather sparingly soluble, as sheaves of long, silky needles, m. p. 188–189° (Found: C, 57.95; H, 5.3. $C_{14}H_{16}O_5N_2$ requires C, 57.5; H, 5.5%).

Preparation of β -Ether-acid.—The β -ether-ester dissolved rapidly at room temperature in 30 parts of 2N-hydrochloric acid. The ester (10 g.) was heated for ¾ hour on the steam-bath with the acid (100 c.c.) and crystallisation of the product (9 g.) was induced by adding 30 c.c. of concentrated hydrochloric acid (the same product also separated from 2N-acid alone, but the yield was apt to be lower). This hydrochloride of the β -ether-acid formed small, colourless, glassy cubes, m. p. 252–253° (decomp.). For analysis it was recrystallised from a mixture of dilute and a little concentrated hydrochloric acid, and washed with alcohol (Found: C, 49.6; H, 4.7; N, 9.15; Cl, 12.05. $C_{13}H_{15}O_5N_2Cl$ requires C, 49.6; H, 4.8; N, 8.9; Cl, 11.3%). When the salt (9 g.) was warmed with water (ca. 100 c.c.) it dissolved to a clear yellow solution, which quickly deposited a mass of needles (8 g.) of the free β -ether-acid, m. p. 241–243°. An analytical sample of this substance separated from dilute acetic acid in small, soft, colourless needles, m. p. 244–245° (230–235° when mixed with the α -isomer), not appreciably soluble in hot water, acetone, chloroform, or alcohol, and easily soluble in pyridine, glacial acetic acid, aqueous sodium carbonate, and aqueous sodium acetate. The acid showed no tendency to lose carbon dioxide, and was stable even when heated to 310° [Found: C, 55.6; H, 5.0; N, 10.35; OMe, 20.9. $C_{13}H_{14}O_5N_2$ requires C, 56.1; H, 5.1; N, 10.1; OMe (2), 22.3%]. Esterification by the method described for the mixed ether-acids gave the β -ether-ester as sole product (identified by m. p. and mixed m. p.).

Preparation of α -Ether from α -Ether-acid.—(a) The acid (1 g.) was heated in an open tube in an oil-bath; decarboxylation set in suddenly at 280° (bath temp.) and was complete in a few minutes. The brown melt set to a hard crystalline mass on cooling, a solution of which in alcohol yielded 0.6 g. of discoloured stout prismatic needles, m. p. 228–230°, of the α -ether. An analytical sample formed small yellow prisms, m. p. 229–230°; the substance sometimes separated from supersaturated solutions in fine soft needles [Found: C, 60.85; H, 5.8; N, 12.15; OMe, 23.7. $C_{12}H_{14}O_3N_2$ requires C, 61.5; H, 6.0; N, 12.0; OMe (2), 26.5%]. The substance was fairly easily soluble in hot alcohol, and insoluble in ether, water, alkalis, and dilute acids. When it was heated with a mixture of acetic acid and 6N-hydrochloric acid, a sparingly soluble hydrochloride, m. p. 229–230° (decomp.) (220–225° when mixed with the original substance), separated on cooling. That this was the hydrochloride, and not the product of any further reaction, was shown by suspending it in water and adding aqueous ammonia; the solid dissolved almost completely, followed by crystallisation of the original base, m. p. and mixed m. p. 230–231°. After the base (0.2 g.) had been refluxed for 4½ hours with ethyl iodide (2 c.c.) and alcohol (4 c.c.), the product which separated on cooling had m. p. 205° (efferv.), but gave no depression when mixed with the original material.

(b) The acid (1.1 g.) was heated with benzophenone (3.3 g.) (cf. Schofield and Simpson, *loc. cit.*) in an open tube in an oil-bath. The solid remained in suspension until a bath temperature of 260–270° was reached; decarboxylation then occurred and a clear yellow solution was formed, which quickly turned brown. After a further 5 minutes the product was isolated from the cooled melt by digestion with ether; yield 0.75 g., m. p. 226–228° alone and when mixed with a sample prepared by method (a).

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