227. *Cinnolines. Part VIII. Esters of 4-Hydroxy-cinnoline- and -quinoline-3-carboxylic Acids.*

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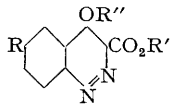
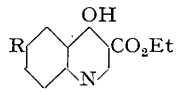
The preparation and properties of ethyl esters of 4-hydroxy-cinnoline- and -quinoline-3-carboxylic acids are described.

For the purpose of investigating the properties of functional derivatives of 4-hydroxycinnoline-3-carboxylic acid (I; R = R′ = R″ = H), obvious advantages would attend the development of a practical method of selectively substituting either the carboxyl or the hydroxyl group. Earlier experiments in this direction (Schofield and Simpson, *J.*, 1945, 512) were not successful, but it has now been found that the *esters* (I; R = H and OMe; R′ = Et; R″ = H) can be prepared in about 25% yield by esterification of the corresponding acids with alcohol and either 100% sulphuric acid or 20% oleum (cf. Newman, *J. Amer. Chem. Soc.*, 1941, **63**, 2431; Baxter and Spring, *J.*, 1945, 232). Application of the same method to the appropriate quinoline acids gave about 15% of the corresponding esters (II; R = H and OMe), identical with those prepared by pyrolysis of ethyl arylaminomethylenemalonates (preceding paper).



(I.)



(II.)

These cinnoline and quinoline esters are all readily hydrolysed to the parent acids, but are sharply differentiated in other respects. Thus the cinnoline esters, in contrast to the quinoline analogues, are appreciably acidic. Further, whereas the cinnoline derivatives were readily acetylated to yield (I; R = H and OMe; R′ = Et; R″ = Ac), similar treatment of the esters (II; R = H and OMe) was without effect; (II; R = H) also resisted more drastic treatment, but (II; R = OMe) was slowly converted under these conditions into the 4-*acetoxy*-derivative.

The contrast between the facile acetylation of the cinnoline hydroxy-esters and the resistance of the analogous quinoline derivatives is in harmony with the general behaviour, in this respect, of 4-hydroxy-compounds in the two heterocyclic series, although no really clear-cut conclusions regarding the latter group can be drawn from the somewhat confused literature on the subject. A more detailed discussion of this point, and of its theoretical implications, is reserved for a future communication.

Experimental.

(Melting points are uncorrected.)

Preparation of Esters.—The cinnoline acids were crude and used without further purification (Schofield and Simpson, *loc. cit.*); the quinoline acids were purified by crystallisation from, or digestion with, acetic acid. The general esterific

ation procedure followed those of Newman and of Baxter and Spring (*locc. cit.*), the finely-powdered acid (1 part) being dissolved in 20% oleum (5—7 parts by volume) with cooling, and the solution so obtained added to absolute alcohol (20—30 parts by volume). After 15—20 minutes' heating on the steam-bath, the mixtures were cooled, poured into excess of aqueous sodium carbonate, acidified with acetic acid, and then neutralised with sodium bicarbonate solution. (To ensure separation from unchanged acid, the solutions containing the quinoline esters were finally made alkaline with sodium carbonate, but in the case of the cinnoline esters alkalinity was avoided because of their acidic nature.) Alcohol was driven off, and the solid which had separated was filtered cold and washed with water. All the hydroxy-esters, and also 4-hydroxycinnoline, gave reddish colorations with ferric chloride (cf. Camps, *Ber.*, 1901, **34**, 2703); the derived acetoxy-esters gave negative reactions.

Quinoline Esters.—Ethyl 4-hydroxyquinoline-3-carboxylate (yield, 0·15 g. from 1 g. of acid) crystallised from acetic acid in soft, colourless needles, m. p. 275—276° alone and when mixed with the sample described in the preceding paper; all samples showed some shrinking at about 240°. Unesterified acid (0·7 g., identified by m. p. and mixed m. p.) was recovered from the alkaline mother-liquor. Unchanged ester was the sole product after it (100 mg.) had been heated at 95° for 2½ hours with 1 c.c. of a mixture of pyridine (1 c.c.) and acetic anhydride (1·5 c.c.), as also after 1 hour's refluxing of its suspension in acetic anhydride (15 parts) (solvent removed and total residue examined).

Ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (yield, 15%) had m. p. 280—281° alone and mixed with an authentic sample (preceding paper) after crystallisation from aqueous acetic acid. The original alkaline filtrate yielded 40% of unesterified acid. The solubility of the ester in boiling 3% aqueous sodium bicarbonate (*ca.* 0·1%) was several times greater than in boiling water, but the product which separated from the alkaline solution was slightly impure ester and not a sodium salt. This behaviour appears to indicate very weakly acidic properties for the compound, which, however, is sharply differentiated from the cinnoline esters (below). The ester was unaffected by a mixture of pyridine and acetic anhydride at 95°, but when it (0·5 g.) was refluxed with acetic anhydride (6 c.c.), a clear solution resulted after 3 hours. After a further 2 hours' refluxing, solvent was removed (evacuated desiccator); a solution of the residue in hot ligroin (b. p. 60—80°), after filtration from a little insoluble matter, deposited *ethyl 4-acetoxy-6-methoxyquinoline-3-carboxylate*, which formed long, silky, colourless needles, m. p. 124—125°, from benzene–ligroin (b. p. 60—80°) (Found: C, 62·3; H, 5·2; N, 4·9. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8%).

Cinnoline Esters.—*Ethyl 4-hydroxycinnoline-3-carboxylate* was sparingly soluble in hot water and crystallised in long, silky, colourless needles, m. p. 191—192° after previous shrinking (Found: C, 60·7; H, 4·6; N, 13·35. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%). It dissolved easily in hot alcohol and in warm aqueous sodium bicarbonate (for this reason it was sometimes isolated in part as the sodium salt, m. p. 229—230°, converted into the free ester by very dilute hydrochloric acid). 2 G. of acid yielded 0·35 g. of ester, 0·35 g. of pure unchanged acid, and 0·32 g. of a mixture (presumed ester and acid); from 1 g., 0·55 g. of a mixture of ester and sodium salt was obtained. The use of 100% sulphuric acid instead of 20% oleum gave essentially similar results. When the ester was refluxed with hydrochloric acid (5N, 40 parts), it was rapidly and quantitatively hydrolysed to the parent acid, identified by m. p. and mixed m. p. *Ethyl 4-acetoxycinnoline-3-carboxylate* (yield, 80%) was formed when the ester was either refluxed with acetic anhydride (5 parts) or heated with 10 parts of a mixture of pyridine and the anhydride (2 : 3) for ½ hour at 95°. Removal of the solvent in an evacuated desiccator left an oil which crystallised on trituration with a little water. The acetoxy-ester formed long colourless needles, m. p. 82—83°, from aqueous alcohol [Found: C, 59·75; H, 4·6; N (mean of three), 11·55. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·65; N, 10·8%]; it was extremely soluble in alcohol, and insoluble in aqueous sodium bicarbonate. It dissolved slowly in cold 4N-ammonia, and underwent selective hydrolysis of the 4-acetoxy-group when warmed for 5 minutes at 95° with 0·4N-ammonia (30 parts), the hydroxy-ester (identified by m. p. and mixed m. p.) crystallising as the sole product when the solution was acidified with acetic acid.

Ethyl 4-hydroxy-6-methoxycinnoline-3-carboxylate, very sparingly soluble in hot water, formed soft, almost colourless, flattened needles, m. p. 233—234°, from aqueous acetic acid (Found: C, 57·5; H, 5·0; N, 11·65. $C_{12}H_{12}O_4N_2$ requires C, 58·0; H, 4·9; N, 11·3%), and, like its analogue, was soluble in warm aqueous sodium bicarbonate. Hydrolysis with boiling 2N-hydrochloric acid regenerated the parent acid (m. p. and mixed m. p.). When the ester was heated at 95° for ½ hour with 20 parts of a mixture of pyridine and acetic anhydride (2 : 3), a crystalline residue of *ethyl 4-acetoxy-6-methoxycinnoline-3-carboxylate* was formed after removal of solvents in an evacuated desiccator; this substance crystallised from alcohol in long, pale saffron-coloured brittle rods, m. p. 152—153° (Found: C, 57·6; H, 5·15; N, 10·1. $C_{14}H_{14}O_5N_2$ requires C, 57·9; H, 4·85; N, 9·65%), and, like its methoxyl-free analogue, was quantitatively hydrolysed to the parent hydroxy-ester when warmed for a few minutes with dilute ammonia, the product being isolated by addition of acetic acid, and identified by m. p. and mixed m. p.

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