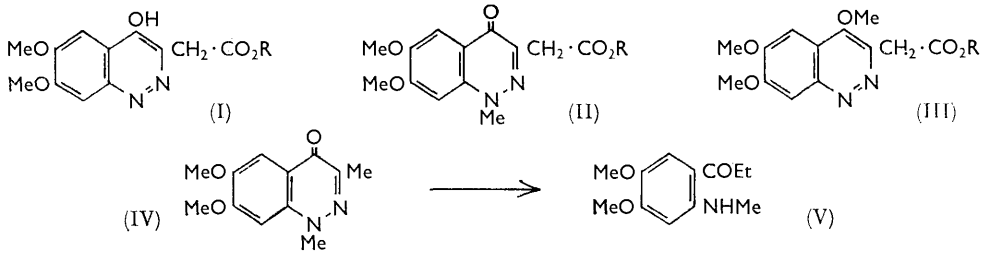
1128. *Cinnolines. Part VII.*[1] *Methylation of 4-Hydroxy-6,7-dimethoxycinnoline-3-acetic Acid*

By D. E. Ames and A. C. Lovesey

The α- and β-methylation products obtained by an earlier worker by action of dimethylsulphate and alkali on 4-hydroxy-6,7-dimethoxycinnoline-3-acetic acid are shown to be the 1- and 2-methyl derivatives, respectively.

Methylation of 4-hydroxy-6,7-dimethoxycinnoline-3-acetic acid (I; R = H) was examined by Simpson [2] who isolated two monomethylation products as the methyl esters. These compounds were designated α-ester, probably the *N*-methylcinnolone (II; R = Me), and β-ester, probably the *O*-methyl derivative (III; R = Me), on the basis of the following evidence. Both esters were readily hydrolysed with hydrochloric acid but the α-ester gave the α-acid whereas the β-ester yielded β-acid as hydrochloride, which, on recrystallisation from water, gave β-acid (thus the β-acid appeared to be more basic than the α-acid). The α-acid was decarboxylated at its melting point to give " α-ether " whereas the β-acid was stable well above its melting point. Zeisel determinations on " α-ether " and β-acid both gave values well below those for two methoxyl groups. It has recently been shown [1] that 4-hydroxycinnolines may be alkylated predominantly at position 2, and, in the case of the acid (I; R = H), alkylation might conceivably occur at the 3-methylene group. This reaction has therefore been re-examined in the hope of obtaining more decisive evidence for the structures of the products.



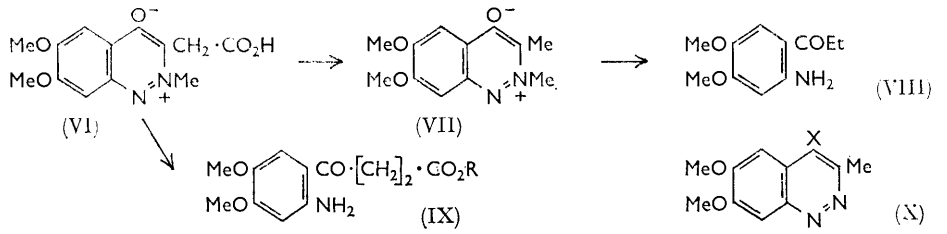
The structures assigned by Simpson [2] to the α-ether (IV), and consequently those of the α-ester (II; R = Me) and α-acid (II; R = H), have been confirmed by reduction of the compounds with zinc dust in acetic acid, or in aqueous ethanolic ammonia, to the *N*-methyl-amine (V) (compare reduction of *N*-methylcinnolones [3]). Amine (V) was also prepared by methylation of the toluene-*p*-sulphonyl derivative of the corresponding primary amine and subsequent acid hydrolysis.

Simpson [2] reported that acid (I; R = H) and the β-methyl acid could not be decarboxylated by heating alone or with quinoline and copper carbonate. We have now effected these decarboxylations by heating the acids with concentrated sulphuric acid at about 180°. The product obtained from the β-methyl acid is formulated as the anhydrobase of 4-hydroxy-6,7-dimethoxy-2,3-dimethylcinnolinium hydroxide (VII), since reduction with zinc in ammonia solution gave the primary amine 2-amino-4,5-dimethoxypropiophenone (VIII) (cf. ref. 3).

Structure (VI), which was therefore assigned to the β-acid, was confirmed by reduction of this acid with zinc and ammonia solution to β-(2-amino-4,5-dimethoxybenzoyl)propionic acid (IX; R = H).

[1] Part VI, D. E. Ames, R. F. Chapman, H. Z. Kucharska, and D. Waite, *J.*, 1965, 5391.
[2] J. C. E. Simpson, *J.*, 1946, 480.
[3] D. E. Ames and H. Z. Kucharska, *J.*, 1963, 4924.

Esterification of the acid (I; R = H) proved very difficult, presumably owing to its insolubility, but the methyl ester was eventually prepared by a modified Fischer–Speier process. This method was much more satisfactory than the alternative route, diazotisation of the amino-ester (IX; R = Me) (compare preparation of the ethyl ester [4]). The ester (I; R = Me) gave the corresponding 4-chloro-compound on treatment with phosphorus oxychloride, but attempts to convert this into the 3-methoxy-derivative were unsuccessful. As an alternative method for confirming that *O*-methylation had not occurred at the 4-hydroxyl group, the methylation of 4-hydroxy-6,7-dimethoxy-3-methylcinnoline (X; X = OH) was examined. Methylation with dimethyl sulphate and alkali gave a mixture of (IV) and (VII). Conversion of the cinnoline (X; X = OH) into the 4-chloro-compound (X; X = Cl), followed by treatment with sodium methoxide, gave 4,6,7-trimethoxy-3-methylcinnoline (X; X = OMe) which had a considerably lower melting point than the *N*-methyl products (IV) and VII).



Thus, the α- and β-methylation products derived from the acid (I; R = OH) are the 1- and 2-methyl derivatives, respectively, and no *O*-methyl product can be isolated; these results correspond to those obtained by alkylation of simpler 4-hydroxycinnolines.[1]

The ultraviolet spectra (Table) are consistent with the assigned structures (cf. ref. 5).

Ultraviolet absorption spectra (in ethanol)

	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
(I; R = H)	227	35,000	*285*	*2200*	343	18,100
	257	27,000			357	17,800
	265	28,000				
(I; R = Me)	228	26,500	*290*	*1000*	342	12,000
	257	19,100			357	11,800
	266	20,000				
(X; X = OH)	226	18,000	*286*	*2500*	344	10,100
	256	15,900			359	10,200
	264	16,600				
(IV) (" α-Ether ")	229	17,600	*283*	*2800*	350	11,000
	260	18,100	*292*	*2100*	365	11,100
	268	19,000				
(II; R = Me) (α-Ester)	235	25,000	*283*	*4400*	348	14,000
	261	20,500	*296*	*2400*	363	14,600
	269	20,600				
(II; R = H) (α-Acid)	235	26,000	*280*	*8000*	349	11,900
	260	19,500			363	13,800
	269	20,500				
(VII) (" β-Ether ")	239	23,300	271	11,500	361	10,100
			279	11,700	378	11,200
β-Ester	239	29,500	272	12,800	363	12,800
			281	12,100	379	14,000
(VI) (β-Acid)	239	30,100	272	13,400	362	13,100
			281	12,600	379	14,400
(X; X = OMe)	243	44,700	304	7400	—	—

Points of inflections are given in italics.

[4] K. Schofield and J. C. E. Simpson, *J.*, 1945, 520.
[5] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J.*, 1951, 3318.

Thus, the 1-methyl products (α-compounds) show two groups of bands, with maxima at about 230, 260, 270 mμ and 350, 360 mμ, respectively. One or two points of inflection occur in the region 280—296 mμ, corresponding to the weak pair of bands found in the spectra of cinnolones without the 6,7-dimethoxy-groups.[1] The similarity of the spectra of the 4-hydroxy-compounds to those of the 1-methyl derivatives suggests that the former exist in the tautomeric 4-cinnolone form, produced by protonation at position 1. In contrast, the 2-methyl products (β-compounds) show three groups of bands, with maxima at about 240, 270—280, and 360—380 mμ, the central band falling near the minimum for the α-compounds. The *O*-methyl derivative (4,6,7-trimethoxy-3-methylcinnoline) shows quite different absorption, with only two bands (243, 304 mμ), and there are no maxima at longer wavelengths corresponding to those of the *N*-methyl products.

Experimental

Evaporations were carried out under reduced pressure. Ultraviolet spectra were recorded on a Perkin-Elmer 137 spectrophotometer.

Methyl β-(2-*Amino*-4,5-*dimethoxybenzoyl*)*propionate*.—β-(2-Amino-4,5-dimethoxybenzoyl)-propionic acid [4] (10 g.), methanol (250 c.c.), and concentrated sulphuric acid (10 c.c.) were refluxed together for 4 hr. and diluted with water (300 c.c.); the mixture was neutralised with 2N- sodium hydrogen carbonate, warmed on a steam-bath, and set aside overnight. Filtration and crystallisation from aqueous methanol yielded the *amino-ester* (6·2 g.), yellow needles, m. p. 127—128° (Found: C, 59·0; H, 6·4; N, 5·0. $C_{13}H_{17}NO_5$ requires C, 58·5; H, 6·4; N, 5·2%).

Methyl 4-*Hydroxy*-6,7-*dimethoxycinnoline*-3-*acetate*.—(*a*) The amino-ester (1·5 g.), in ethanol (60 c.c.), was treated with hydrogen chloride (2 g.) at 0°. Sodium nitrite (0·4 g.) was added in portions during 2 hr. while the mixture was stirred at 0°. The mass was heated at 80° for 1 hr., cooled, and filtered, and the solid was washed repeatedly with sodium hydrogen carbonate solution. Repeated crystallisations from methanol gave the *ester* (0·5 g.), m. p. 315—316° (decomp.) (Found: C, 55·6; H, 5·2; N, 10·5. $C_{13}H_{14}N_2O_5$ requires C, 56·1; H, 5·0; N, 10·1%).

(*b*) Dry hydrogen chloride (40 g.) was passed into a suspension of 4-hydroxy-6,7-dimethoxycinnoline-3-acetic acid [2] (8 g.) in methanol, and the mixture was refluxed for 10 hr. After addition of concentrated sulphuric acid (10 c.c.) dropwise during 1 hr., refluxing was continued for a further 15 hr. The mixture was cooled and filtered; repeated recrystallisation from methanol gave the ester (7·0 g.), m. p. and mixed m. p. 315—316° (decomp.).

Methylation of Methyl 4-*Hydroxy*-6,7-*dimethoxycinnoline*-4-*acetate*.—Dimethyl sulphate (7 c.c.) was added during 15 min., with shaking, to the ester (5 g.) in 5% sodium hydroxide solution (60 c.c.) at 0°. The mixture was set aside overnight at room temperature, extracted with chloroform, and the extracts were evaporated. The residue (4·5 g.) was dissolved in benzene–chloroform (9 : 1) and applied to a 10 in. column of alumina (¾ in. diameter). Elution with the same solvent mixture gave α-ester [2] (II; R = Me) (2·7 g.), m. p. 182—183°. Further elution yielded β-ester (1·5 g.), m. p. 186—187°.

The same products were obtained (mixed m. p.) when the corresponding acid (I; R = H) was methylated and the products esterified as described by Simpson.[2]

Methyl 4-*Chloro*-6,7-*dimethoxycinnoline*-3-*acetate*.—A mixture of methyl 4-hydroxy-6,7-dimethoxycinnoline-3-acetate (0·5 g.) and phosphorus oxychloride (7 c.c.) was heated on a steam-bath for 15 min. and then poured into an ice-cold solution of sodium acetate (10 g.) in water (500 c.c.). Extraction with chloroform, evaporation, and recrystallisation from methanol gave the *chloro-compound* (0·3 g.), m. p. 151—152° (Found: C, 53·0; H, 4·3; Cl, 11·9; N, 9·4. $C_{13}H_{13}ClN_2O_4$ requires C, 52·6; H, 4·3; Cl, 11·9; N, 9·4%).

2-*Amino*-4,5-*dimethoxypropiophenone*.—4,5-Dimethoxy-2-nitropropiophenone [6] (18·6 g.), acetic acid (230 c.c.), and water (100 c.c.) were heated on a steam-bath and stirred vigorously while iron filings (30 g.) were added in small portions during 30 min. The mixture was heated for 6 hr., evaporated to small volume, and poured on to ice; some product was filtered off, and more was obtained from the filtrate by extraction with ethyl acetate followed by evaporation.

[6] H. Oelschläger, *Arch. Pharm.*, 1957, **290**, 587.

The *amino-ketone* (13·0 g.) formed yellow needles, m. p. 113—114° (from ethyl acetate) (Found: C, 63·4; H, 7·4; N, 6·7. $C_{11}H_{15}NO_3$ requires C, 63·2; H, 7·2; N, 6·7%).

4,5-Dimethoxy-2-toluene-p-sulphonamidopropiophenone.—The amine (6·0 g.) and toluene-*p*-sulphonyl chloride (12·0 g.) in pyridine (36 c.c.) were heated on a steam-bath for 45 min. and poured into water. Filtration and recrystallisation from ethanol gave the *sulphonamide* (9·1 g.), m. p. 140—141° (Found: C, 59·8; H, 5·4; N, 4·1; S, 8·8. $C_{18}H_{21}NO_5S$ requires C, 59·5; H, 5·7; N, 3·8; S, 8·8%).

4,5-Dimethoxy-2-methylaminopropiophenone.—The sulphonamide (7·5 g.) and methyl iodide (35 g.) were added successively to sodium methoxide solution [from sodium (6 g.) in methanol (750 c.c.)]. After the mixture had been refluxed for 28 hr., it was evaporated, and the residue was shaken with water (500 c.c.). Filtration, and recrystallisation from aqueous methanol, gave the N-*methyl derivative* (7·8 g.), m. p. 118—119° (Found: C, 59·6; H, 5·7; N, 3·9; S, 9·1. $C_{19}H_{23}NO_5S$ requires C, 60·0; H, 6·1; N, 3·7; S, 8·6%). This (3·5 g.), acetic acid (28 g.), and concentrated hydrochloric acid (76 g.) were refluxed for 10 hr. and basified with 5N-potassium hydroxide. Isolation with ether, and repeated recrystallisation from aqueous methanol, gave the *amine* (2·0 g.), yellow crystals, m. p. 87—88° (Found: C, 64·0; H, 7·6; N, 5·8. $C_{12}H_{17}NO_3$ requires C, 64·5; H, 7·7; N, 6·2%).

Reduction of 6,7-Dimethoxy,1,3-dimethyl-4-cinnolone.—The cinnolone ("α-ether")[2] (1 g.), in hot acetic acid (10 c.c.), was added to zinc dust (3 g.) in acetic acid (20 c.c.) containing 2 drops of concentrated hydrochloric acid. The mixture was refluxed for 5 hr., more zinc (1 g.) being added after 2 hr., and then filtered and the zinc washed with ethyl acetate. Basification of the filtrate with 5N-sodium hydroxide, and isolation with ethyl acetate, gave 4,5-dimethoxy-2-methylaminopropiophenone (0·4 g.), m. p. and mixed m. p. 86—87°. The toluene-*p*-sulphonamide had m. p. and mixed m. p. 117—118°.

In another experiment, a mixture of the cinnolone (1 g.), zinc dust (6 g.), and ethanol (50 c.c.) containing hydrobromic acid (48%; 6 drops) was warmed to 80°, and aqueous ammonia (20 c.c.; *d* 0·88) was added during 1 hr. The mixture was refluxed for 8 hr. and filtered; the solid was washed with ethyl acetate, and the combined filtrates were poured into water (500 c.c.). Isolation with ethyl acetate furnished an oil which was dissolved in hot methanol (5 c.c.). Hot water (10 c.c.) was added, and, on cooling, the amine separated, m. p. and mixed m. p. 85—86°; toluene-*p*-sulphonamide, m. p. and mixed m. p. 116—117°.

Decarboxylation Experiments.—(a) *4-Hydroxy-6,7-dimethoxycinnoline-3-acetic acid.* The acid (2 g.), concentrated sulphuric acid (60 c.c.), and water (20 c.c.) were heated at 200° (internal temperature) for 12·5 hr., cooled, poured into ice–water (500 g.), and neutralised with 2N-potassium carbonate. After one day, the liquid was filtered and the solid washed with cold water until free from sulphate. Dissolution of the residue in 2N-sodium hydroxide, boiling with charcoal, filtration, and acidification with 2N-hydrochloric acid gave 4-hydroxy-6,7-dimethoxy-3-methylcinnoline (0·8 g.), m. p. 338—339° (from 2-methoxyethanol). On admixture with 4-hydroxy-6,7-dimethoxycinnoline-3-acetic acid, the m. p. was depressed to 235—240°.

(b) *Anhydro-base of 3-carboxymethyl-4-hydroxy-6,7-dimethoxy-2-methylcinnolinium hydroxide* (β-*acid*). The acid (1·5 g.), in a mixture of concentrated sulphuric acid (25 c.c.) and water (5 c.c.), was heated at 185° for 2 hr., cooled, poured into ice–water (1000 c.c.), and basified with 5N-potassium hydroxide. Isolation with chloroform, and recrystallisation from methanol–ethyl acetate (1 : 1), afforded the anhydro-base of 4-hydroxy-6,7-dimethoxy-2,3-dimethylcinnolinium hydroxide ["β-ether" (VII)] (0·3 g.), m. p. 238—239° undepressd by admixture with the sample described below.

Reduction of Anhydro-base of 4-Hydroxy-6,7-dimethoxy-2,3-dimethylcinnolinium Hydroxide.—A mixture of zinc dust (3 g.), ethanol (25 c.c.), and hydrobromic acid (3 drops; 48%) was warmed to 90°. The anhydro-base (VII) (0·5 g.) was added, and aqueous ammonia (10 c.c.; *d* 0·88) was added in small portions during 8 hr. The liquid was filtered and the solid washed with hot ethyl acetate. Addition of water (200 c.c.) to the filtrates, and isolation with ethyl acetate, gave 2-amino-4,5-dimethoxypropiophenone (0·2 g.), m. p. and mixed m. p. 128—129° (toluene-*p*-sulphonyl derivative, m. p. and mixed m. p. 139—140°).

Similarly, the β-acid (VI) (1·0 g.) was added to a mixture of zinc dust (6 g.), ethanol (50 c.c.), and hydrobromic acid (6 drops; 48%) at 90°. Aqueous ammonia (20 c.c.; *d* 0·88) was added to the refluxing solution during 15 hr. The mixture was cooled and 2N-acetic acid added to adjust the pH to 6. Filtration, repeated extraction with ethyl acetate, and evaporation gave a mixture (0·8 g.) from which starting material (0·3 g.) was recovered by recrystallisation from

acetone. Evaporation of the mother-liquor to small volume, followed by recrystallisation from acetone, gave β-(2-amino-4,5-dimethoxybenzoyl)propionic acid (0·1 g.), m. p. 139—141°, identical with an authentic specimen [4] (mixed m. p. and infrared spectra).

4-*Hydroxy*-6,7-*dimethoxy*-3-*methylcinnoline*.—2-Amino-4,5-dimethoxypropiophenone (10 g.), in concentrated hydrochloric acid (100 c.c.) and water (12 c.c.), was diazotised at 0° with sodium nitrite (3·4 g.) in water 10 c.c.). The mixture was stirred at 0—2° for 1 hr. and left at room temperature for 2 days. After hydrochloric acid had been removed by distillation under reduced pressure, sodium acetate (10 g.) was added and the mixture was shaken for 10 min. and filtered, the solid being washed with cold water and methanol. This material (10 g.) was dissolved in 2N-sodium hydroxide; the solution was boiled with charcoal, cooled, and filtered. Acidification precipitated the product which was purified by reprecipitation in this manner until the filtrates were colourless (three times). Recrystallisation from 2-methoxyethanol gave colourless *needles*, m. p. 339—340° (decomp.) (Found: C, 60·1; H, 5·7; N, 12·4. $C_{11}H_{12}N_2O_3$ requires C, 60·0; H, 5·5; N, 12·7%). The m. p. was undepressed by admixture with material obtained by decarboxylation of the corresponding 3-acetic acid.

Methylation of 4-*Hydroxy*-6,7-*dimethoxy*-3-*methylcinnoline*.—Dimethyl sulphate (7 c.c.) was added in small portions, with shaking, to the hydroxycinnoline (5 g.) in water (60 c.c.) containing sodium hydroxide (4 g.) at 50°, and the solution was shaken for 15 min. Isolation with chloroform gave a mixture which was dissolved in benzene–chloroform (9 : 1) and applied to a 10 in. column of alumina (¾ in. diameter). Elution with the same solvent mixture yielded first 6,7-dimethoxy-1,3-dimethyl-4-cinnolone (IV) (2·9 g.), m. p. and mixed m. p. with α-ether [2] 229—230° (Found: C, 61·3; H, 6·0; N, 11·9. Calc. for $C_{12}H_{14}N_2O_3$: C, 61·5; H, 6·0; N, 11·9%).

Further elution with the same solvent mixture gave the anhydro-base of 4-hydroxy-6,7-dimethoxy-2,3-dimethylcinnolinium hydroxide (VII) (1·7 g.), m. p. and mixed m. p. with β-ether 240—241° (from methanol–ethyl acetate) (Found: C, 61·3; H, 6·0; N, 11·6%).

4-*Chloro*-6,7-*dimethoxy*-3-*methylcinnoline*.—4-Hydroxy-6,7-dimethoxy-3-methylcinnoline (5 g.) and phosphorus oxychloride (36 c.c.) were heated on a steam-bath for 1 hr. and then added dropwise to an ice-cold solution of sodium acetate. The product was extracted with chloroform, and the extracts were washed with sodium carbonate solution and water, dried (Na_2SO_4), and evaporated. Recrystallisation from ethyl acetate gave the *chloro-compound*, yellow crystals (4·0 g.), m. p. 222—223° (Found: C, 55·1; H, 4·7; Cl, 14·8; N, 11·7. $C_{11}H_{11}ClN_2O_2$ requires C, 55·3; H, 4·6; Cl, 14·8; N, 11·7%).

4,6,7-*Trimethoxy*-3-*methylcinnoline*.—The chloro-compound (4 g.) was added to sodium methoxide solution [from sodium (4 g.) in methanol (100 c.c.)], and the mixture was refluxed for 2·5 hr. and left at room temperature for 2 days. After evaporation (bath below 50°) and addition of water (20 c.c.), the solution was extracted repeatedly with ether. Evaporation of the extracts and repeated recrystallisation from ethyl acetate gave *the cinnoline*, pale yellow needles, m. p. 182—183° (3 g.) (Found: C, 61·8; H, 6·0; N, 11·7; $C_{12}H_{14}N_2O_3$ requires C, 61·5; H, 6·0; N, 11·9%).

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