

447. Colchicine and Related Compounds. Part XV.*
Synthetic Studies.

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5-Acetamido-4-oxo-2':3':4'-trimethoxybenzocycloheptene (IX) has been synthesised by two routes from purpurogallin.

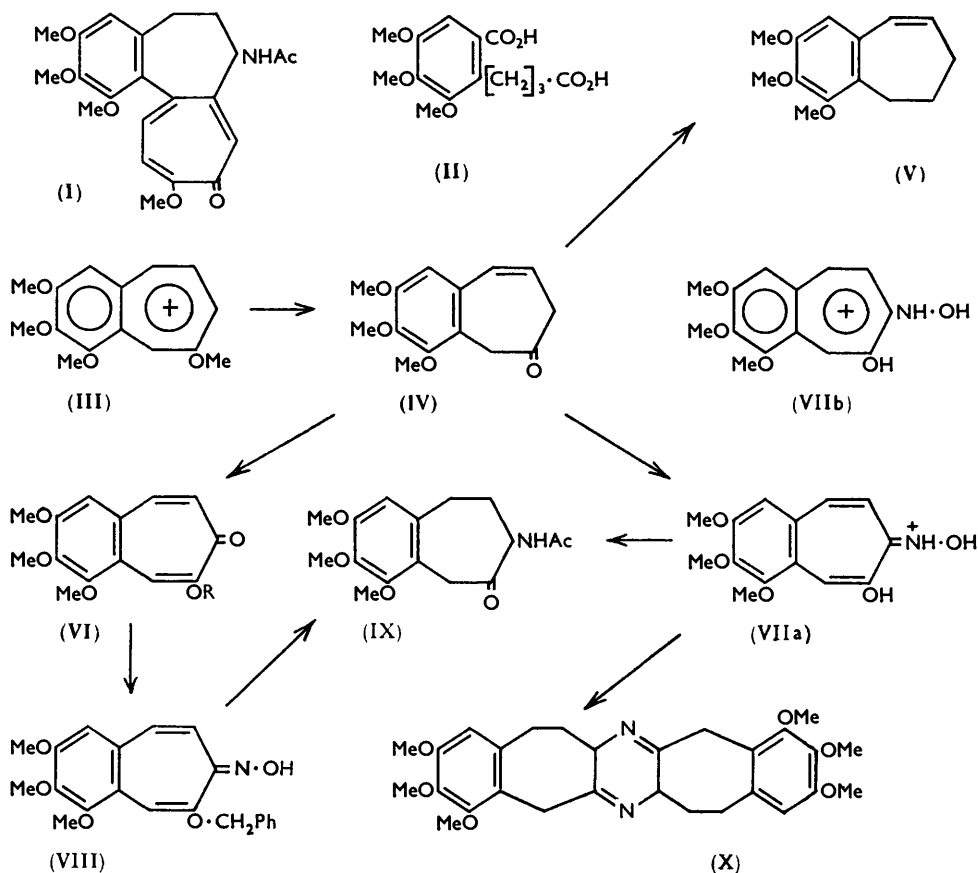
IN considering possible synthetical routes to colchicine (I) the ketone (IX) was chosen as the framework on which attempts to elaborate ring c would be made. This communication describes its synthesis.

Eschenmoser and his associates have described¹ the preparation of the tropylium cation (III) from purpurogallin, and its reduction to the ketone (IV). In our hands, the reduction proved to be capricious, and the expected ketone was separated from a non-ketonic oil by means of Girard's reagent P. That this oil was the styrene (V) followed from

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¹ Schaeppi, Schmidt, Heilbronner, and Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1874.

its analysis, and the virtual identity of its ultraviolet absorption spectrum with that of the ketone (IV). This assignment was supported by its reduction to a dihydro-compound and its oxidation with cold aqueous potassium permanganate to the acid (II), previously synthesised by Haworth, Moore, and Pauson.² The styrene is apparently formed by a



Clemmensen-like reaction from the ketone (IV) rather than by an alternative path from the ion (III), for we were able to convert (IV) into (V) under the conditions of the original reaction.

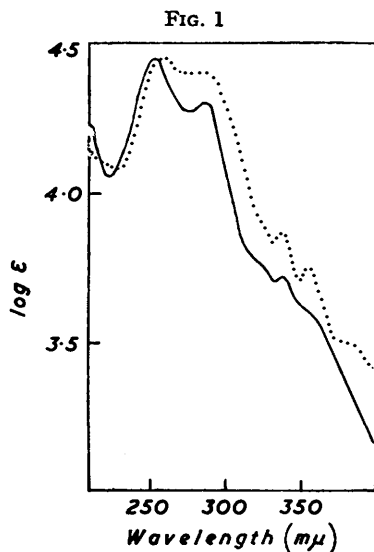
From Eschenmoser's work,¹ it appeared likely that those reactions of the ketone (IV) which involved enolisation, would occur at the allylic rather than at the benzylic methylene group, and it seemed feasible therefore to introduce the nitrogen atom at this stage. The ketone was accordingly nitrosated, yielding a bright yellow oxime hydrochloride, for which we prefer the structure (VIIa). Catalytic reduction of this substance yielded the crude amino-ketone hydrochloride. When treated with alkali, this gave the dihydropyrazine (X), but when warmed with acetic anhydride, it afforded the acetamido-ketone (IX) which was characterised at its 2 : 4-dinitrophenylhydrazone. It was still necessary to prove the orientation of the nitrogen atom, and an attempt was made to hydrolyse the oxime hydrochloride (VIIa) to the known¹ tropolone (VI; R = H). With dilute hydrochloric acid and aqueous formaldehyde³ a red product ($C_{15}H_{15}O_5N$) was isolated, but its structure has not been established. Its infrared spectrum shows neither O-H nor N-H bands.

² Haworth, Moore, and Pauson, *J.*, 1948, 1045.

³ Caunt, Crow and Haworth, *J.*, 1951, 1313.

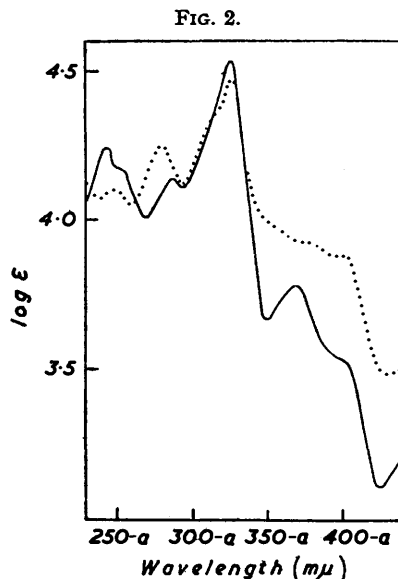
The structure of the acetamido-ketone (IX) was finally established by an unambiguous synthesis. The tropolone (VI; R = H), which can be obtained in poor yield from (IV), is already known¹ to be inactive towards carbonyl reagents, but its benzyl ether (VI; R = CH₂Ph) yielded an oxime (VIII) which on reduction in the presence of acetic anhydride afforded the ketone (IX). The latter was identified as its 2:4-dinitrophenylhydrazone, which was identical in m. p., mixed m. p., and infrared spectrum with the derivative described above.

The structure of the oxime hydrochloride (VII) deserves further comment. We originally expected that the molecule would be most adequately represented as (VIIb), with minor contribution from the structure (VIIa). In fact, the ultraviolet spectrum (Fig. 1) is very close to that of the tropolone ether oxime (VIII), and quite distinct from that of the tropylium ion (III) (Fig. 2). More surprisingly, we have observed that after



Full line, 4-Benzoyloxy-5-hydroxyimino-2':3':4'-trimethoxybenzocyclohepta-1:3:6-triene (VIII).
Broken line, 4-Hydroxy-5-hydroxyimino-2':3':4'-trimethoxybenzocyclohepta-1:3:6-triene hydrochloride (VII).

(Solvent: ethanol.)



Full line, 4:2':3':4'-Tetramethoxybenzocycloheptatrienylium sulphate (III) ($\alpha = 0$).
Broken line, 4-Hydroxy-5-hydroxyimino-2':3':4'-trimethoxybenzocyclohepta-1:3:6-triene (VII), in the presence of alkali ($\alpha = 10$).

(Solvent: ethanol.)

basification of (VII), the spectrum of the product is strikingly similar to that of the tropylium ion (III) (Fig. 2). In order to point the similarity in Fig. 2, the oxime curve is drawn with a bathochromic displacement of 10 m μ .

EXPERIMENTAL

Reduction of 4:2':3':4'-Tetramethoxybenzocycloheptatrienylium Sulphate (III).—The reduction was carried out as previously described¹ and the oily product (5.98 g.) was separated with Girard's reagent P into the ketone (IV) (1.8 g.), m. p. 70–72° (cyclohexane) [light absorption in ethanol; λ_{\max} (log ϵ), 224 (4.4), 258 m μ (3.98)], and the styrene (V) (1.6 g.) which was filtered through neutral alumina in benzene, and distilled at 165–170°/0.08 mm. as a colourless oil (Found: C, 71.4; H, 7.6. C₁₄H₁₆O₃ requires C, 71.8; H, 7.7%) [light absorption in ethanol: λ_{\max} (log ϵ), 223 (4.48), 263–264 m μ (4.05)].

2':3':4'-Trimethoxybenzocycloheptene.—The styrene (V) (300 mg.) rapidly absorbed 1 mol. of hydrogen in ethanol (15 ml.) in the presence of 2% Pd-CaCO₃ (200 mg.). After filtration,

concentration yielded the *dihydro-derivative*, b. p. 155—160° (bath)/0.3 mm., m. p. 44—48° (Found : C, 70.9; H, 7.7. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%). Light absorption : λ_{\max} (log ϵ) 274 μ (3.33).

Oxidation of 1' : 2' : 3'-Trimethoxybenzocyclohepta-1 : 3-diene (V).—The styrene (V) (500 mg.), in water (20 ml.), was shaken with portions of solid potassium permanganate until the mother liquors were permanently pink. After filtration, the filtrate was continuously extracted with ether for 4 hr. The product had m. p. 135—137° (from water) (Found : C, 56.6; H, 6.1%; equiv., 147. $C_{14}H_{18}O_7$ requires C, 56.4; H, 6.1%; equiv., 149). Light absorption : λ_{\max} (log ϵ), 252 (4.02), 294 μ (3.52). Mixed m. p. and infrared spectra showed it to be identical with a sample synthesised by Haworth's method.²

4-Hydroxy-5-hydroxyimino-2' : 3' : 4'-trimethoxybenzocyclohepta-1 : 3 : 6-triene (VII).—The ketone (IV) (3.6 g.) in ether (50 ml.) was cooled in ice and treated with dry hydrogen chloride, whilst pentyl nitrite (4 g.) in ether (20 ml.) was added dropwise. The yellow precipitate (2.69 g.) was filtered off; it had m. p. 206—208° (decomp.) (from ethanol) (Found : C, 53.6; H, 4.9; N, 4.5; Cl, 11.1%; equiv., 156. $C_{14}H_{16}O_5NCl$ requires C, 53.6; H, 5.1; N, 4.5; Cl, 11.3%; equiv., 157). Light absorption in ethanol : λ_{\max} (log ϵ), 258 (4.46), 338—339 (3.87), 355 (3.75), 383 μ (3.51); in alcoholic alkali, 241 (4.10), 271 (4.25), 321 (4.48), 391 (3.88), 460 μ (3.57).

When the hydrochloride (184 mg.) was warmed for 5 min. with aqueous formaldehyde (40%; 1.5 ml.), with or without 5N-hydrochloric acid, and finally diluted, there was formed a flocculent red precipitate (68 mg.). The *product* crystallised in small red needles from ethanol; it had m. p. 168—170° (Found : C, 62.0; H, 4.9; N, 5.1. $C_{15}H_{15}O_5N$ requires C, 62.3; H, 5.2; N, 4.8%). Light absorption in ethanol : λ_{\max} (log ϵ), 257 (4.45), 320 (4.54), 365 (4.12), 384 μ (4.16); in acidified ethanol, 258 (4.42), 320 (4.54), 365 (3.99), 383 (4.01), 436 μ (3.75).

5-Acetamido-4-oxo-2' : 3' : 4'-trimethoxybenzocycloheptene (IX).—(a) The hydrochloride (1 g.) in ethanol (20 ml.) containing Adams's platinum oxide catalyst (200 mg.) was shaken with hydrogen until 3 mols. had been absorbed, and was then filtered. Concentration of the filtrate yielded a dark glass which was warmed on the steam-bath for 10 min. with acetic anhydride (5 ml.), and concentrated *in vacuo*. The resulting dark oil afforded the *ketone* (IX) (617 mg.), m. p. 157—159°, as needles from acetone (Found : C, 62.6; H, 6.3; N, 4.9; MeO, 30.0; AcO, 13.5. $C_{16}H_{21}O_6N$ requires C, 62.5; H, 6.8; N, 4.6; 3MeO, 30.3; 1AcO, 14.0%). Light absorption : λ_{\max} (log ϵ), 278—280 μ (3.17) in ethanol; ν 1710 cm^{-1} , in Nujol. It gave a 2 : 4-dinitrophenylhydrazone, m. p. 260—261° (decomp.), as yellow prisms from acetic acid (Found : C, 54.5; H, 5.1; N, 14.5. $C_{22}H_{25}O_6N_5$ requires C, 54.2; H, 5.1; N, 14.4%).

When a small portion of the above glass, in ethanol, was treated with 5N-sodium hydroxide solution, a white precipitate formed. Rapid crystallisation from ethanol gave the *dihydro-pyrazine* (X) as prisms, m. p. 230° (decomp.) (Found : C, 67.8; H, 7.1; N, 5.4. $C_{28}H_{34}O_6N_2$ requires C, 68.0; H, 6.9; N, 5.7%). Light absorption in ethanol : λ_{\max} (log ϵ), 278 μ (3.47).

(b) The hydroxyimino-ether (VIII) (39 mg.) in acetic anhydride (2 ml.) was shaken with hydrogen in the presence of Adams's platinum oxide catalyst (11 mg.). After the absorption of 4 mols. of hydrogen the solution was filtered. Concentration gave an oil which furnished a 2 : 4-dinitrophenylhydrazone, identical in m. p. and mixed m. p. and in its infrared spectrum with that described above.

4-Benzoyloxy-5-hydroxyimino-2' : 3' : 4'-trimethoxybenzocyclohepta-1 : 3 : 6-triene (VIII).—The tropolone (VI; R = H) (120 mg.) was set aside overnight in methanol (15 ml.) containing sodium (11 mg.) and benzyl bromide (500 mg.). The solution was concentrated *in vacuo*, water added, and the suspension extracted with ethyl acetate. Concentration of the extract yielded an oil which was washed with petrol (b. p. 40—60°), and the residue crystallised from petrol (b. p. 60—80°), to give the *ether* (VI; R = CH_2Ph), m. p. 98—100° (Found : C, 71.25; H, 5.8. $C_{21}H_{20}O_5$ requires C, 71.6; H, 5.7%).

The ether was converted into the *oxime* (VIII), m. p. 171—172°, in the usual manner (Found : C, 68.8; H, 5.7; N, 4.0. $C_{21}H_{21}O_5N$ requires C, 68.65; H, 5.8; N, 3.8%). Light absorption in ethanol : λ_{\max} (log ϵ) 255 (4.55), 288 (4.30), 337 μ (3.72).

Microanalyses were carried out by Miss S. Watt and Mr. J. M. L. Cameron. The ultraviolet spectra were measured on a Unicam S.P. 500 spectrophotometer. One of us (J. K. S.) gratefully acknowledges a grant from D.S.I.R.