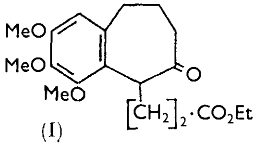
966. *Synthetical Studies Relating to Colchicine. Part IV.** *A Correction and Some Further Experiments with* 3′,4′,5′-*Trimethoxy*-1,2-*benzocyclohept*-1-*en*-3- *and* -4-*one*

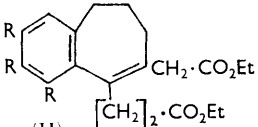
By J. D. Hardstone and K. Schofield

The Reformatsky reaction between ethyl β-(3′,4′,5′-trimethoxy-4-oxo-2-benzocyclohept-1-en-2-yl) propionate (I) and ethyl bromoacetate has been re-investigated, and experiments on some hydroxymethylene derivatives of 3′,4′,5′-trimethoxy-1,2-benzocyclohept-1-en-3- and-4-one are reported.

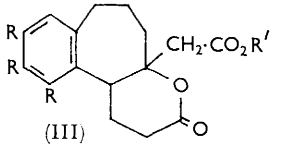
It was reported in Part II of this Series [1] that the Reformatsky reaction between (I) and ethyl bromoacetate gave (II; R = MeO) in 57% yield. We have failed to repeat this result, and from the Reformatsky conditions specified recovered only unchanged (I). Part of the evidence for identifying the earlier product as (II; R = MeO) was the ultraviolet (u.v.) absorption maximum at 272 mμ (log ε 3·75). Consideration of the three compounds (III; R = MeO, R′ = Et) ($\lambda_{max.}$ 280 mμ, log ε 3·09), (III; R = H, R′ = Et) ($\lambda_{max.}$ 263 mμ, log ε 2·51),[1] and (II; R = H) ($\lambda_{max.}$ 258 mμ, log ε 3·74) [1] suggests that the absorption intensity of (II; R = MeO) should be higher than that reported. If (II; R = MeO) was obtained, it was clearly impure.



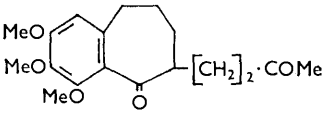
(I)



(II)



(III)



(IV)

Because of our failure, the Reformatsky reaction was repeated under other conditions.[2] The lactone (III; R = MeO, R′ = Et) was then isolated. The diffuse melting point of the compound, and the composition of the non-crystalline part of the product, show that both racemates of (III; R = MeO, R′ = Et) were formed. Like that of the lactone (III; R = H, R′ = Et) described earlier,[1] the infrared (i.r.) spectrum of this compound showed a single, sharp peak in the carbonyl region at 1725 cm.$^{-1}$, due presumably to the coincident frequencies of the two carbonyl functions. The hydroxy-diester corresponding to (III; R = MeO, R′ = Et) was probably present to a small extent in the product of the Reformatsky reaction. The methyl ester lactone (III; R = MeO, R′ = Me) was isolated by van Tamelen and his co-workers [3] from the Reformatsky reaction between methyl bromoacetate and the nitrile corresponding to (I).

The work relating to colchicine synthesis which we hitherto reported [1,4] was based on the use of 3′,4′,5′-trimethoxy-1,2-benzocyclohept-1-en-4-one. Another possible way of utilising this ketone was to construct from it a tricyclic compound having a six-membered ring c which could be ring-expanded. Accordingly, the ketone was converted into the 3-hydroxymethylene derivative. This, however, did not react with either methylaniline or methyl vinyl ketone, behaviour in contrast to that of the unmethoxylated hydroxymethylene ketone.[4] Similarly, the pyrrolidine enamine of the ketone did not react with methyl vinyl ketone.

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* Part III, J. D. Hardstone and K. Schofield, preceding Paper.

[1] T. A. Crabb and K. Schofield, *J.*, 1960 643.

[2] W. E. Bachman, W. Cole, and A. L. Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 824.

[3] E. E. van Tamelen, T. A. Spencer, D. S. Allen, and R. L. Orvis, *Tetrahedron*, 1961, **14**, 8.

[4] T. A. Crabb and K. Schofield, *J.*, 1958, 4276.

Like the 4-ketone, 3′,4′,5′-trimethoxy-1,2-benzocyclohept-1-en-3-one readily gave a hydroxymethylene derivative. With methyl vinyl ketone this gave the diketone (IV), which, however, could not be cyclised under any of a number of conditions.

3′,4′,5′-Trimethoxy-1,2-benzocyclohept-1-en-4-one is still not a very easily accessible compound.[1,3] In an attempt to modify its synthesis, 3′,4′,5′-trimethoxy-1,2-benzocyclohepta-1,3-diene was treated with diborane, and the product oxidised with chromic acid.[5] Surprisingly, the only ketone isolated was 3′,4′,5′-trimethoxy-1,2-benzocyclohept-1-en-3-one.

EXPERIMENTAL

Ultraviolet absorption spectra refer to solutions in 95% ethanol.

The Lactone (III; R = MeO, R′ = Et).—Ethyl bromoacetate (7·5 g.) and the keto-ester (4·6 g.) in 1 : 1 ether–benzene (100 ml.) were added dropwise to finely divided zinc (6 g.) activated with a crystal of iodine. When one-third of the solution had been added the mixture was boiled under reflux with stirring for 1 hr. Zinc (3 g.) and a crystal of iodine, together with a portion of the ester mixture, were added at hourly intervals for 3 hr. The resulting mixture was boiled for 3 hr. more, cooled, and treated with a mixture of acetic acid (10 ml.) and methanol (5 ml.), followed by water (250 ml.). Ether extracts of the mixture were washed with 5N-ammonium hydroxide and water, and dried ($MgSO_4$). The viscous red oil (3·92 g.), left after removal of ether, was dissolved in benzene and adsorbed on acid-washed alumina. Elution with ether gave, as the first major fraction, a viscous red liquid (2·51 g.). When triturated with ether this oil gave the *lactone* (0·67 g.). It formed needles, m. p. 138—145° (Found: C, 64·4; H, 7·2; alkoxyl as methoxyl, 17·0. $C_{21}H_{28}O_7$ requires C, 64·3; H, 7·2; alkoxyl as methoxyl, 16·3%) (from methanol). The remaining oil was distilled to give a viscous oil, b. p. 240—250°/0·15 mm. (Found: C, 64·2; H, 7·2%), probably a mixture of stereoisomeric lactones.

The second fraction, obtained from the alumina by elution with acetone, was a solid (0·28 g.), m. p. 65—73°. It could not be purified, but the i.r. spectrum (main peaks at 3440, 2944, 1723, 1625, 1600, 1523, 1455, 1306, and 1123 cm.$^{-1}$) suggested that it contained the hydroxy-diester corresponding to the lactone.

3-*Hydroxymethylene*-3′,4′,5′-*trimethoxy*-1,2-*benzocyclohept*-1-*en*-4-*one*.—Ethyl formate (0·74 g.) in benzene (9 ml.) was added to powdered sodium methoxide, prepared from sodium (0·25 g.), and baked at 220° for 3 hr. under reduced pressure under nitrogen. The mixture was cooled in an ice-bath, and the ketone (1·25 g.) in benzene (7·5 ml.) was added with stirring. The mixture was heated at 100° for 2 hr. Water was added to the cooled product, and the benzene layer was extracted with N-sodium hydroxide. Acidification gave an oil which was extracted with ether. Distillation gave the *hydroxymethylene compound* as an oil (1·07 g.), b. p. 155—160°/0·6 mm. (Found: C, 64·2; H, 6·5. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%), which gave a purple ferric chloride coloration. The i.r. spectrum (liquid film) showed strong bands at 2920, 2830, 1699, 1588, 1446, 1349, 1316, 1236, 1118, and 1000 cm.$^{-1}$.

4-*Hydroxymethylene*-3′,4′,5′-*trimethoxy*-1,2-*benzocyclohept*-1-*en*-3-*one*.—Obtained in 82% yield by the method described for the isomer, this *compound* formed needles, m. p. 110—112° (Found: C, 64·6; H, 6·6%) (from aqueous ethanol). It gave a blood-red ferric chloride coloration, and the i.r. spectrum (KBr disc) showed main peaks at 2939, 2854, 1620, 1596, 1490, 1458, 1321, 1250, 1203, 1132, and 1000 cm.$^{-1}$.

4-(3-*Oxobutyl*)-3′,4′,5′-*trimethoxy*-1,2-*benzocyclohept*-1-*en*-3-*one*.—The 4-hydroxymethylene-3-ketone (0·54 g.), freshly distilled methyl vinyl ketone (0·37 g.), triethylamine (30 mg.), and anhydrous methanol (10 ml.) were boiled under reflux for 6 hr. The solution was concentrated, diluted with water, and extracted with ether. Removal of the ether gave a viscous oil (0·42 g.) which solidified on cooling. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave the *diketone*, m. p. 53—55° (Found: C, 67·9; H, 7·7. $C_{18}H_{24}O_5$ requires C, 67·5; H, 7·6%). The i.r. spectrum (KBr disc) showed strong peaks at 1708 and 1689 cm.$^{-1}$.

Attempts to cyclise this compound using polyphosphoric acid, potassium t-butoxide, potassium hydroxide, and toluene-*p*-sulphonic acid failed, or converted it into the parent monoketone.

Hydroboration of 3′,4′,5′-*Trimethoxy*-1,2-*benzocyclohepta*-1,3-*diene*.—The diene was prepared by dehydration of the corresponding alcohol.[1] The m. p. of the latter was wrongly reported in Part II of this Series,[1] and is now corrected to 84—85°.

[5] H. C. Brown, *Tetrahedron*, 1961, **12**, 117.

The olefin (2·34 g.) in tetrahydrofuran (10 ml.) was treated at 0°, under nitrogen, with diborane generated from sodium borohydride (0·31 g.). Complete transfer of the diborane to the reaction flask was ensured by warming the generator to 70° and maintaining a gentle flow of nitrogen through the apparatus. The reaction solution was kept at room temperature for 2 hr., and excess hydride was then destroyed by the addition of water (3 ml.). To the resulting solution chromic acid, prepared from sodium dichromate (2·2 g.), conc. sulphuric acid (1·7 ml.), and water (7·5 ml.), was added with stirring during 10 min., so that the temperature remained at 20—25°. The mixture was stirred for 2 hr. and then extracted with ether. The washed extract was dried ($MgSO_4$) and evaporated, giving a viscous oil (1·76 g.), which consisted of starting material, and 3′,4′,5′-trimethoxy-1,2-benzocyclohept-1-en-3-one (0·56 g.), m. p. 100°, isolated by trituration with ether.

We are indebted to the Medical Research Council for a grant in support of this work.

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[*Received, April* 23*rd*, 1965.]