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ON THE STEREOSELECTIVE SYNTHESIS OF ESTRONE

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WITH a view to building the estrone nucleus Banerjee *et al.*[1] prepared the model compound (Ia), which was also later reported by Turner.[2a] The methoxy derivative (Ib), obtained by Turner[2b] and by Johnson *et al.*,[3a,b] was stereoselectively converted into estrone by the latter workers. The route is the most practicable one for estrone except for the disadvantage that the key intermediate (Ib') is obtained as one of the two isomers in 43% yield.[3b] A more stereoselective preparation of the bicycle compound (Ib) by an ingenious method was reported by Bhattacharyya *et al.*[4] Recently a new stereoselective synthesis of estrone has been reported by Cole, Johnson,

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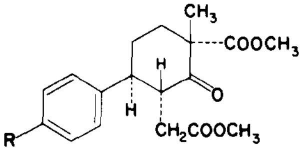
[1] J. Dutta and D.K. Banerjee, *Sci. & Cult.* **12**, 408 (1947).

[2a] D.L. Turner, *J. Amer. Chem. Soc.* **73**, 3017 (1951); [b] *Ibid.* **73**, 1284 (1951).

[3a] W.S. Johnson and R.G. Christiansen, *J. Amer. Chem. Soc.* **73**, 551 (1951); [b] W.S. Johnson, R.G. Christiansen and R.E. Ireland, *Ibid.* **79**, 1955 (1957).

[4] P. Sen Gupta and B.K. Bhattacharyya, *J. Indian Chem. Soc.* **31**, 337 (1954); cf. also J.O. Jilek, V. Simak and M. Protiva, *Chem. Listy* **47**, 874 (1953); *Chem. Abstr.* **49**, 197 (1955).

Robins and Walker.[5]



I a, R=H
b, R=OCH_3

In view of the reference[6] to an unpublished work of Johnson, Ireland and Tarney on the development of an improved method for the preparation of Ib, we place on record the experiments carried out by us for a stereospecific synthesis of the same keto diester. It appeared to us that reduction of the double bond in conjugation with the benzene nucleus present in the intermediates [2b,3b] at the earlier stages of preparation of Ib, led to a mixture of isomers. We, therefore, at first studied the stereospecific reduction of the unsaturated keto acids (Va and Vb), which were prepared by the following new method.

β-Dimethylamino-*p*-methoxypropiophenone hydrochloride (II) was condensed with the β-ketoadipic esters (IIIa and II. o) in presence of sodium and ethozide and dimethyl sulphate.[7] The resulting products (IVa and IVb) on

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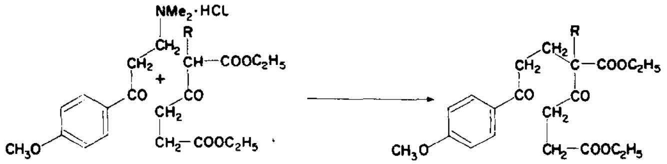
[5] J.E. Cole, Jr., W.S. Johnson, P.A. Robins and J. Walker, *Proc. Chem. Soc.* 114 (1958).

[6] L.F. Fieser and M. Fieser, *Steroids* p.500. Reinhold Publishing Corporation (1959).

[7] W.S. Johnson, J.S. Belew, L.J. Chinn and R.H. Hunt, *J. Amer. Chem. Soc.* **75**, 4995 (1953).

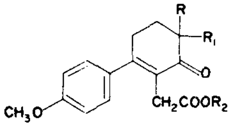
treatment with methanolic sodium methoxide furnished 1-p-anisyl-4-methoxycarbonyl-3-ketocyclohexene-2-acetic acid, m.p. 164°;[2b,3b] and 1-p-anisyl-4-methyl-4-methoxycarbonyl-3-ketocyclohexene-2-acetic acid, m.p. 127°.[3b] Hydrolysis of the aforementioned ester acids, as well as refluxing of IVa and IVb with 10% aqueous potassium hydroxide afforded the unsaturated keto acids (Va, m.p. 136°;[3b] and Vb, m.p. 146°), which on reduction with lithium and liquid ammonia[8] gave stereospecifically the saturated acids (VIa, m.p. 111°; yield 82%; and VIb, m.p. 136°, undepressed on admixture with an authentic sample;[4] yield 81%).

A stereospecific synthesis of the keto diester (Ib) starting from the saturated keto ester (VIc), m.p. 68°, was achieved via the isoxazole (VII),

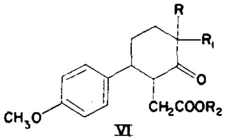


II III a, R=H
b, R=CH₃

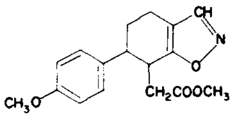
IV a, R=H
b, R=CH₃



V a, R=R₁=R₂=H
b, R=CH₃, R₁=R₂=H
c, R=R₁=H, R₂=CH₃
d, R=R₂=CH₃, R₁=CN
e, R=CH₃, R₁=CN, R₂=H



VI



VII

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[8] D.K. Banerjee, S. Chatterjee and S.P. Bhattacharya, J. Amer. Chem. Soc. 77, 408 (1955).

b.p. 145-150°/0.006 mm; yield 63%, and the methylated cyano keto ester (VId), m.p. 122°; yield 75%. Treatment of VId with methanolic hydrogen chloride gave Ib, m.p. 93°, undepressed on admixture with an authentic sample; yield 72%. Partial saponification of VId yielded the acid (VIe), m.p. 145°.

The unsaturated cyano keto acid (Ve), m.p. 126°, prepared from the unsaturated keto ester (Vc) via the corresponding isoxazole, m.p. 77-79°, on reduction with lithium and ammonia followed by treatment with methanolic hydrogen chloride also stereoselectively furnished the keto diester (Ib), but in lower yield.

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