SYNTHESIS OF COMPOUNDS RELATED TO SANTONIN

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Santonin, the lactone of 1-hydroxy-7-keto-8-10-dimethyl $\Delta^{5:8}$-hexahydro-naphthyl-2-propionic acid (A), the well-known naturally occurring anthelmintic, has been recently synthesised by us.[1] The anthelmintic action of santonin is generally attributed to the lactonic and ketonic groups in it. It will be interesting to see whether the methyl groups in 8 and 10 positions in santonin have any marked effect on the anthelmintic action. We have, therefore, synthesised the following compounds related to santonin by the series of reactions given below :—

(1) Lactone of 1-hydroxy-7-keto-$\Delta^{5:8}$ hexahydro naphthyl 2-propionic acid (B).

(2) Lactone of 1-hydroxy-7-keto-8-methyl $\Delta^{5:8}$-hexahydro-naphthyl-2-propionic acid (C).

(3) Lactone of 1-hydroxy-7-keto-10-methyl $\Delta^{5:8}$-hexahydro-naphthyl-2-propionic acid (D).

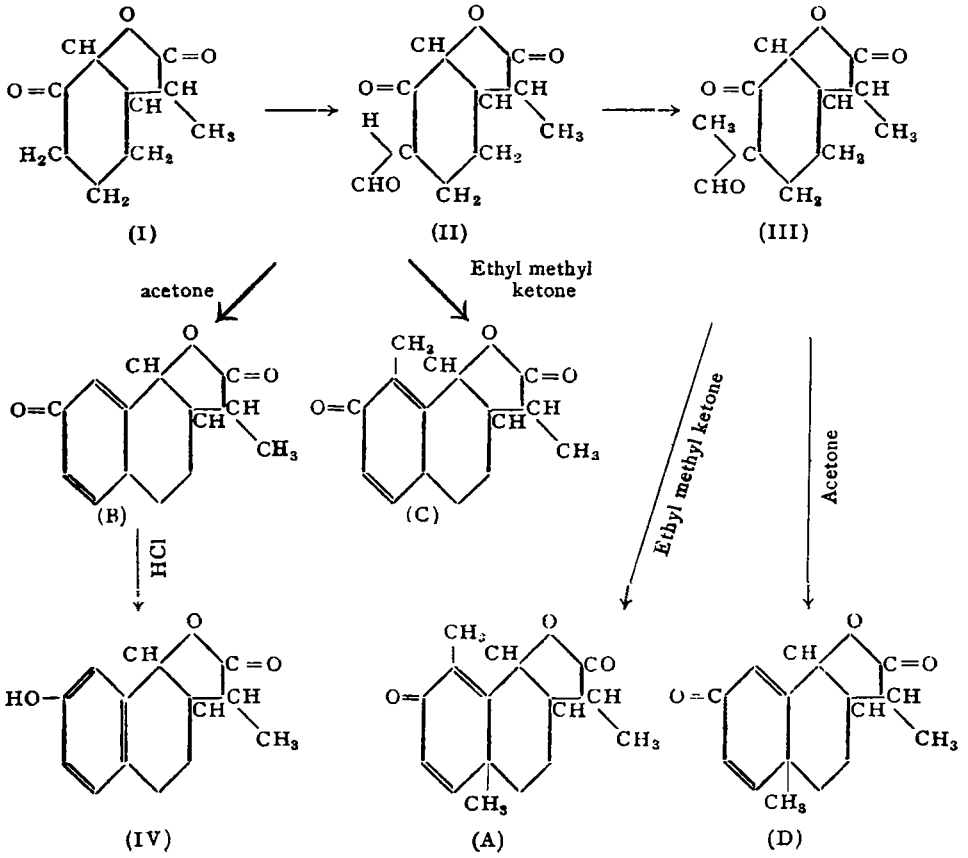
Condensation of 6-keto-2-chloro-Δ^{1}-cyclohexene[3] with diethyl sodio-mono-methyl-malonate, followed by hydrolysis gives the lactone of α-(2-hydroxy-3-keto-cyclohexyl) propionic acid (I). This keto lactone (I) on condensation with ethyl formate in the presence of sodium gives the lactone of α-(2-hydroxy-3-keto-4-formyl-cyclohexyl) propionic acid (II). Condensation of this keto-formyl lactone (II) with acetone and ethyl methyl ketone furnished the lactones (B) and (C) respectively.

The lactone (B) on treatment with fuming hydrochloric acid was converted into the lactone of 1-7-dihydroxy-tetrahydro-naphthyl propionic acid IV, identical with the lactone obtained from 7-methoxy tetralone by Paranjape, Phalnikar and Nargund.[4] It may be noted that the transformation of (B) into (IV) is a reaction analogous to the conversion of santonin into desmotroposantonin.

Condensation of this keto-formyl-lactone (II) with ethyl methyl ketone gave (C). Ethyl methyl ketone may condense with the lactone (II) in two different ways and may give either 8-methyl or 6-methyl lactone. It has been shown by us[1] that ethyl methyl ketone condenses with 2-formyl-cyclo-hexanone to give 7-keto-8-methyl-hexahydro-naphthalene. On similar lines it is assumed that ethyl methyl ketone will condense with the lactone (II) and give a 8-methyl compound (C) and not the 6-methyl one.

The sodio salt of the lactone (II) when treated with methyl iodide under pressure undergoes methylation and the methylated product (III) when condensed with acetone in the presence of sodium ethoxide gives the lactone (D).

It will be noted that these lactones (B), (C) and (D) differ from santonin in the fact that they contain two or one methyl group less than in santonin. The pharmacological actions of these lactones has been studied and will be reported later.



These compounds contain asymmetric carbon atoms. Details regarding their optical properties will be reported in another communication. A preliminary account of these properties however has been recently published.[2]

Experimental

The preparation of the lactone of α-(2-hydroxy-3-keto-cyclohexyl) propionic acid (I), the lactone of α-(2-hydroxy-3-keto-4-formyl-cyclohexyl) propionic acid (II) and the lactone of α-(2-hydroxy-3-keto-4-formyl-4-methyl cyclohexyl) propionic acid (III) has been described by us.[1]

Lactone of 1-*hydroxy*-7-*keto*-$\Delta^{5:8}$-*hexahydro-naphthyl*-2-*propionic acid* (*B*).—The lactone of α-(2-hydroxy-3-keto-4-formyl-cyclohexyl) propionic acid (II) (8 gm.) was mixed with acetone (2 gm.) and the mixture was added to sodium ethoxide prepared from sodium (3·2 gm.) and absolute alcohol (40 c.c.) and was allowed to stand overnight. Alcohol was then removed on a water-bath and the reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The ether layer was washed with water, dried over calcium chloride (anhydrous) and ether removed. The residue containing the lactone of 1-hydroxy-7-keto-$\Delta^{5:8}$-hexahydro-naphthyl-propionic acid (B) was a semisolid, which on crystallisation from benzene was obtained as fine needles and melted at 91°.

[Found: C, 71·7; H, 6·5 per cent. Equi. wt. (by back titration), 217·7; $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4 per cent. and Equi. wt. 218·0.] It gives a semicarbazone, m.p. 145°.

On keeping this lactone with fuming hydrochloric acid in a sealed tube for 21 days, it was transformed into the lactone of 1-7-dihydroxy-tetrahydro-naphthyl propionic acid (IV), m.p. 111° C. identical with the lactone prepared by Paranjape, Phalnikar and Nargund[4] from -7-methoxy-tetralone.

Lactone of 1-*hydroxy*-7-*keto*-8-*methyl*-$\Delta^{5:8}$-*hexahydro-naphthyl*-2-*propionic acid* (*C*):—The lactone (II) was similarly condensed with ethyl methyl ketone in the presence of sodium ethoxide and was worked up as in the above case. The lactone of 1-hydroxy-7-keto-8-methyl-$\Delta^{5:8}$-hexahydro-naphthyl-2-propionic acid (C) thus obtained, crystallised from alcohol and had m.p. 111°.

[Found: C, 72·7; H, 6·9 per cent. Equi. wt. (by back titration), 232·1; $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9 per cent. and Equi. wt. 232·0.]

Lactone of 1-*hydroxy*-7-*keto*-10-*methyl*-$\Delta^{5:8}$-*hexahydro-naphthyl*-2-*propionic acid* (*D*).—Condensation of the lactone of α-(2-hydroxy-3-keto-4-formyl-4-methyl cyclohexyl)-propionic acid (III) with acetone was carried out as

in the above case. The lactone of 1-hydroxy-7-keto-10-methyl-$\Delta^{5:8}$-hexahydro-naphthyl-2-propionic acid (D) was first obtained as a syrupy liquid but on purification and crystallisation from alcohol it was obtained as a solid, m.p. 141°. It gave a semicarbazone, m.p. 201° C.

[Found: C, 72·8; H, 6·9 per cent. and Equi. wt. (by back titration), 231·8; $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9 per cent. and Equi. wt. 232·0.]

Summary

Following the methods used in the synthesis of santonin the synthesis of compounds related to santonin has been described.

REFERENCES

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2. ———— .. *Current Science*, 1943, **12**, 307.
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