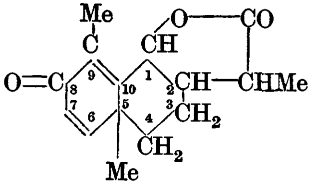
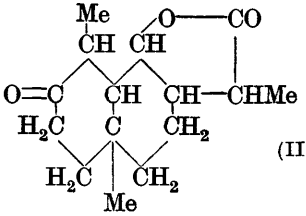
CCCXL.—*The Constitution of Santonin. Part III. Proof of the Positions of the Methyl Groups.*

By GEORGE ROGER CLEMO and ROBERT DOWNS HAWORTH.

IN Parts I and II (J., 1929, 2368; this vol., p. 1110) the hitherto undetermined positions of the *iso*propyl side-chain and of the lactone ring were settled by the synthesis of *dl*-santanous acid and of *desmotropo*santonin respectively, and the new formula (I) was advanced for santonin itself.



(I.)

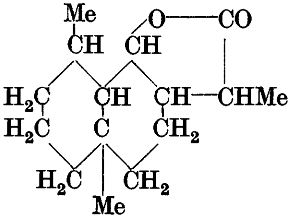


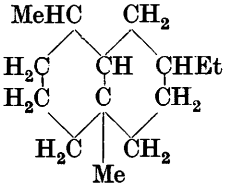
(II.)

The one point outstanding in connexion with this structure was to prove the 5-position of the second methyl group, and the present paper describes experiments carried out for this purpose.

In Part I it was suggested that the production of phenolic derivatives from santonin was due to the migration of a methyl group from position 5 to 6 and in order to prevent this change it was decided to reduce the compound to tetrahydrosantonin (II) (compare Asahina, *Ber.*, 1913, **46**, 1775; Wienhaus and Oettingen, *Annalen*, 1913, **397**, 219). The ketonic group in tetrahydrosantonin was then reduced by means of amalgamated zinc and concentrated hydrochloric acid, and *deoxytetrahydrosantonin* (III) obtained. As in the first of the above reductions three new asymmetric centres are introduced into the molecule, and the second involves long treatment with hot concentrated mineral acid, it was only to be expected that stereoisomeric problems should arise; no attempt, however, has been made fully to resolve them.

(III.)





(IV.)

The lactone (III) was reduced with red phosphorus and hydriodic acid; when the oily iodine-containing product was treated with sodium amalgam and then distilled with soda–lime, 1 : 4(a)-*dimethyl*-7-*ethyldecalin* (IV) was obtained. Several attempts were made to dehydrogenate this characteristically smelling liquid with selenium and also with sulphur, but the results were unsatisfactory, and although analysis indicated some loss of hydrogen, attempts to prepare a pure crystalline picrate were unsuccessful.

As the failure of the dehydrogenation process was doubtless due to the volatility of (IV), the action of selenium on the lactone (III) was next investigated; a hydrocarbon was then obtained which readily formed a picrate, m. p. 96—97°. This proved to be identical with the picrate of 1-methyl-7-ethylnaphthalene which Professor Heilbron kindly sent to us. The loss of the methyl group during the selenium treatment establishes the 5-position of the second methyl group in santonin, and it is hoped to submit confirmatory synthetic work at a later date.

EXPERIMENTAL.

Tetrahydrosantonin (II).—Santonin (20 g.) in glacial acetic acid (150 c.c.) was mixed with 2% palladium chloride solution (added in three portions of 5 c.c. each during the reduction) and an aqueous solution of gum arabic (3 g.) and stirred in an atmosphere of hydrogen for 24 hours; reduction was then complete. The liquid was filtered, and evaporated under reduced pressure, and the residue crystallised from aqueous methyl alcohol and then from absolute alcohol. Tetrahydrosantonin separated as colourless plates, m. p. 156—157° (compare Asahina, *loc. cit.*; Wienhaus and Oettingen, *loc. cit.*) (Found: C, 72·0; H, 8·8. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·8%).

Deoxytetrahydrosantonin (III).—Tetrahydrosantonin (10 g.), amalgamated zinc (50 g.), and concentrated hydrochloric acid (75 c.c.) were refluxed for 24 hours. The reduction product, which solidified on cooling, was decanted from the residual zinc. The solid was collected and crystallised from methyl alcohol, already used to extract the zinc, colourless plates (5 g.), m. p. 140—141°, raised to 141—142° by crystallisation from ethyl alcohol, being obtained (Found: C, 76·2; H, 10·4. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%).

1 : 4(a)-*Dimethyl*-7-*ethyldecalin* (IV).—Deoxytetrahydrosantonin (8 g.), hydriodic acid (*d* 1·7; 40 c.c.), and red phosphorus (8 g.) were refluxed for 24 hours; the mixture was then diluted with water and extracted with ether. The extract was washed with sodium bisulphite solution and dried, and the solvent removed. The oily iodine-containing residue (7·5 g.) was dissolved in boiling ethyl alcohol (100 c.c.) and reduced with sodium amalgam (30 g. of 4%) for 12 hours. The solution was diluted, acidified, and extracted with ether. The extract was dried, the solvent removed, and the residual iodine-free oil (6 g.) mixed with soda–lime (8 g.) and distilled at a dull red heat. The oily distillate was separated from water by extraction with ether, the extract dried, the solvent removed, and the residue distilled in a vacuum; 1 : 4(a)-*dimethyl*-7-*ethyldecalin* was then obtained as a colourless oil with characteristic odour, b. p. 120—125°/20 mm. (Found: C, 86·7; H, 12·9. $C_{14}H_{26}$ requires C, 86·6; H, 13·4%).

1 : 4(a)-Dimethyl-7-ethyldecalin was heated with an equal weight of selenium in a metal-bath at 320° for 30 hours, and it was observed that most of the hydrocarbon refluxed above the surface of the selenium. As the oil gave no crystalline picrate, it was heated with sulphur at 200° for 24 hours. The resulting oil was purified by distillation over sodium; b. p. 120—125°/20 mm. (Found: C, 88·1; H, 12·8%). The oil was treated with picric acid in alcohol–ether, the solvent removed, and the residue fractionally crystallised. The first fractions were unchanged picric acid; a small amount of yellow needles, m. p. 103—104°, was isolated from the mother-liquors, but these liberated picric acid, possibly by dissociation, during attempts at purification.

1-*Methyl*-7-*ethylnaphthalene*.—Deoxytetrahydrosantonin (2 g.) and finely powdered selenium (2 g.) were heated in a metal-bath at 280—320° for 40 hours, the pressure then being reduced to 1 mm. The oil that passed over was steam-distilled and the volatile oil was extracted with ether, dried, and distilled twice over sodium, 0·5 g. of an oil, b. p. 95—99°/1 mm., being obtained (Found : C, 89·9; H, 9·3%). When treated with picric acid in absolute alcoholic solution, it yielded a picrate which separated from alcohol in orange-coloured needles, m. p. 96—97° (Found : C, 57·1; H, 4·3. Calc. for $C_{19}H_{17}O_7N_3$: C, 57·1; H, 4·3%). This picrate was identified as the picrate of 1-methyl-7-ethylnaphthalene by comparison with a synthetic specimen (Harvey, Heilbron, and Wilkinson, this vol., p. 423).

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Addendum. Whilst this paper was in course of preparation we were surprised to find that Ruzicka and Eichenberger (*Helv. Chim. Acta*, 1930, **13**, 1117), after using at length the arguments we gave in Part I, had added a proof of the 5-position of the second methyl group. Their attack on the position of this group is very similar to our own and is clearly based on our earlier work. Hexahydrosantonin, presumably the fully saturated alcohol, was dehydrogenated and 1-methyl-7-ethylnaphthalene isolated as picrate. It may be added that not a single yield is stated.

The work we now describe was far advanced last July when Professor Heilbron sent us the specimen of picrate for mixed melting-point purposes, but it was then interrupted for some weeks and has only recently been finished. Had it been realised that we could not expect even a few months in which to establish the last point in the formula we had advanced for santonin, the work would have been finished and submitted for publication in July.—G. R. C.; R. D. H.