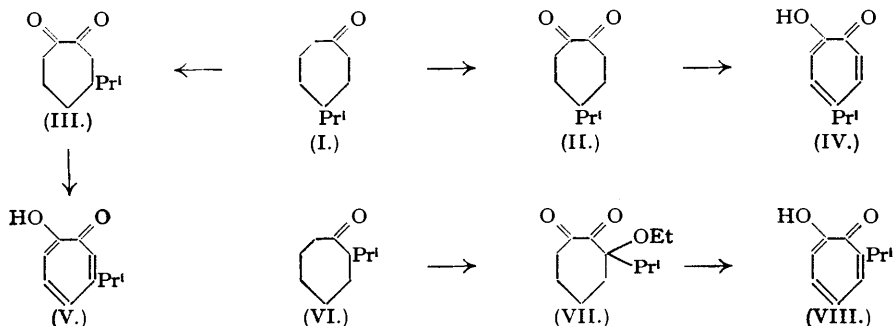


149. Tropolones. Part II. The Synthesis of α -, β -, and γ -Thujaplicins.

By J. W. COOK, R. A. RAPHAEL, and A. I. SCOTT.

By extension of the methods described in Part I (*J.*, 1951, 503) to 2- and 4-isopropylcycloheptanones the naturally occurring tropolones, α -, β -, and γ -thujaplicin, have been synthesised.

THE first naturally occurring compounds to be conclusively characterised as monocyclic tropolones were the α -, β -, and γ -thujaplicins isolated from the heart-wood of Swedish and American Western red cedar (*Thuja plicata* D. Don). The constitutions of these substances were rigidly established as α -, β -, and γ -isopropyltropolones (VIII, V, and IV) respectively by the degradative work of Erdtman, Gripenberg, and Anderson (*Acta Chem. Scand.*, 1948, **2**, 625, 639, 644; *Nature*, 1948, **161**, 719; cf. also Aulin-Erdtman, *Acta Chem. Scand.*, 1950, **4**, 1031).



The antibiotic properties of these compounds, which evidently confer on the heart-wood its resistance to decay, have aroused interest (*idem, ibid.*; Southam, *Proc. Soc. expt. Biol.*, N.Y., 1946, **40**, 4409; Baillie, Freeman, Cook, and Somerville, *Nature*, 1950, **166**, 65). Erdtman has suggested that the occurrence of the thujaplicins might be of use botanically as a taxonomic criterion.

The successful conversion of *cycloheptanone* into *tropolone* suggested extension of the method to the synthesis of the *thujaplicins*, by use of appropriate homologues of *cycloheptanone*. One of these homologues, 4-*isopropylcycloheptanone* (I), was readily obtained by diazomethane ring expansion of 4-*isopropylcyclohexanone*. From the product of this reaction there were obtained roughly equal amounts of two isomeric semicarbazones differing widely in solubility and melting point; separate regeneration from the derivatives gave two samples of ketone, each of which gave only the semicarbazone from which it had been prepared. The thiosemicarbazones of the two samples were also different. On the other hand, the 2:4-dinitrophenylhydrazones and the bis-*p*-nitrobenzylidene compounds derived from the two samples were identical. The infra-red absorption spectra of the two ketones were kindly determined by Dr. F. Sondheimer at Harvard University who reported that the curves were almost identical and gave the following band assignments: An intense C=O absorption occurs at 1694 cm^{-1} with an overtone at 3390 cm^{-1} ; the situation of the former band at a frequency rather lower than that exhibited by other examples of saturated ketones (*ca.* 1725—1710 cm^{-1}) may be due to a steric property of the seven-membered ring. The expected methylene frequency occurs at 2874 cm^{-1} , and a doublet appearing at 1387 and 1370 cm^{-1} is probably due to the C-Me grouping which is known in other compounds to give rise to absorption at *ca.* 1390—1370 cm^{-1} .

Geometrical isomerism about the C=N bond seems to us the most probable interpretation of the formation of isomeric semicarbazones although this does not satisfactorily explain the exclusive formation of each from its parent ketone. Similar isomeric semicarbazones were obtained from 4-methylcycloheptanone by Quدرات-I-Khuda and Ghosh (*J. Indian Chem. Soc.*, 1940, 17, 19) who regarded them as derived from stereoisomeric forms of the parent ketones. However, it seems highly improbable that such conformations of the *cycloheptane* ring (corresponding to the boat and chair forms of *cyclohexane*) could exist as discrete chemical entities.

Selenium dioxide oxidation of the ketone (I) gave the expected mixture of two α -diketones (II) and (III). These were not separated, but were brominated together to give, after sodium hydroxide treatment, a mixture of sodium bromo- β - and - γ -*thujaplicins*. Hydrogenolysis of the latter pair led to a mixture of β - and γ -*thujaplicins* (V and IV) which were separated by fractional crystallisation from light petroleum.

A convenient method of preparing 2-*isopropylcycloheptanone* (VI) was found in the ring expansion of *cyclohexanone* with diazoisobutane (*cf.* Adamson and Kenner, *J.*, 1939, 181). Selenium dioxide oxidation of (VI) in ethanolic solution brought about attack on both positions α to the carbonyl group, with formation of 3-ethoxy-3-*isopropylcycloheptane*-1:2-dione (VII). Such dual oxidations have been noted before, especially with compounds where a tertiary carbon atom is vicinal to the initial carbonyl group (Cauquil *et al.*, *Compt. rend.*, 1938, 208, 1156; 1936, 202, 326). Treatment of (VII) with bromine followed by sodium hydroxide gave sodium bromo- α -*thujaplicin* (presumably the ethoxyl group is replaced by bromine by virtue of its ready metathesis with the hydrogen bromide formed in the reaction). The usual hydrogenolysis procedure then yielded α -*thujaplicin* (VIII).

The synthetic *thujaplicins* did not depress the melting points of the corresponding naturally occurring compounds and gave the same *tropolone* reactions (green colour with ferric chloride and chloroform-soluble copper salt formation).

EXPERIMENTAL.

4-*isopropylcyclohexanone* was prepared from *p*-*isopropylphenol* (Cook, Philip, and Somerville, *J.*, 1948, 164) by the method of Frank, Berry, and Shotwell (*J. Amer. Chem. Soc.*, 1949, 71, 3891); it had b. p. 97—99°/15 mm. (*lit.*, 90—91°/13 mm.) and gave a semicarbazone, m. p. 187—188° (*lit.*, m. p. 187—188°).

4-*isopropylcycloheptanone* (I).—To a stirred mixture of 4-*isopropylcyclohexanone* (45 g.), methanol (50 c.c.), and powdered anhydrous sodium carbonate (1 g.) was added *N*-nitrosomethylurethane (1 c.c.). After a few seconds a vigorous reaction ensued and the temperature rose sharply. Nitrosomethylurethane (78 g.) was then added dropwise during 1½ hours, the temperature being kept at 20—25° by ice-water cooling. After the addition the mixture was stirred for 1 hour and set aside at room temperature for 16 hours. Filtration, removal of solvent, and fractionation gave crude 4-*isopropylcycloheptanone* (34.5 g.), b. p. 110—114°/18 mm.

A solution of the crude ketone (52 g.) in ethanol (50 c.c.) was warmed to 50° and treated with warm ethanolic semicarbazide acetate solution [from semicarbazide hydrochloride (82 g.), potassium acetate (120 g.), and ethanol (400 c.c.)]. The crop of crystals which separated on cooling was filtered off and crystallised from aqueous ethanol; *semicarbazone*-A (33 g.) formed plates, m. p. 180—182° (strongly depressed on admixture with the semicarbazone of 4-*isopropylcyclohexanone*) (Found: C, 63.0; H, 9.7; N, 19.5. $\text{C}_{11}\text{H}_{21}\text{ON}_3$ requires C, 62.6; H, 9.95; N, 19.9%). When the mother-liquors from this compound were diluted with water a further quantity of solid separated. Repeated crystallisation

from aqueous ethanol gave the isomeric *semicarbazone-B* (24 g.) as tiny plates, m. p. 135—137° (Found : C, 62.8; H, 10.4; N, 19.7%). A mixture of the two semicarbazones melted indefinitely over the whole range between the m. p.s of the individual constituents.

Heating *semicarbazone-A* with strong aqueous oxalic acid in the usual manner quantitatively regenerated the parent ketone as a liquid with a pleasant odour, b. p. 115—117°/18 mm., n_D^{20} 1.4708 (Found : C, 77.6; H, 11.6. $C_{16}H_{18}O$ requires C, 77.9; H, 11.7%). Treatment of a small sample of this ketone with semicarbazide acetate furnished in good yield only *semicarbazone-A* with no detectable amount of the *B*-isomer. The *thiosemicarbazone-A*, prepared in the usual manner, crystallised from aqueous ethanol in tiny platelets, m. p. 156° (Found : C, 58.3; H, 9.5. $C_{11}H_{21}N_3S$ requires C, 58.15; H, 9.3%).

Similar regeneration from *semicarbazone-B* furnished the parent ketone, b. p. 114—117°/18 mm., n_D^{20} 1.4690 (Found : C, 77.6; H, 11.9%), which yielded only *semicarbazone-B* on appropriate treatment. The *thiosemicarbazone-B* formed plates, m. p. 174° (from aqueous ethanol) (Found : C, 58.35; H, 9.5%).

Both samples of ketone (*i.e.*, from *semicarbazones-A* and *-B*) on treatment with aqueous alcoholic 2 : 4-dinitrophenylhydrazine sulphate gave the same hydrated 2 : 4-dinitrophenylhydrazone crystallising from ethanol in yellow plates, m. p. 93—95° (Found : C, 47.7; H, 7.1; N, 13.6. $C_{16}H_{22}O_4N_4 \cdot 4H_2O$ requires C, 47.35; H, 7.4; N, 13.8%); under reduced pressure the crystals lost water to give the anhydrous compound as a liquid which resolidified to the hydrate on being exposed to moist air. Reaction of both samples of ketone with *p*-nitrobenzaldehyde in the presence of ethanolic sodium ethoxide produced the same *bis-p-nitrobenzylidene* compound, crystallising in prisms, m. p. 151°, from *n*-butanol (Found : N, 7.1. $C_{24}H_{24}O_5N_2$ requires N, 6.7%).

Sodium Bromo- β - and γ -thujaplicins.—To a boiling solution of 4-isopropylcycloheptanone (9.1 g.) in ethanol (98%; 15 c.c.) was added dropwise during 1 hour a solution of selenium dioxide (7.2 g.) in ethanol (98%; 45 c.c.). Heating under reflux was continued for 6 hours after the final addition and the mixture was then kept at room temperature overnight. Removal of precipitated selenium and solvent followed by distillation gave a mixture of the diones (II) and (III) as a pale yellow liquid, *v.* p. 135—145°/18 mm. (7.2 g.).

A stirred solution of the diones (7.2 g.) in glacial acetic acid (8 c.c.) was cooled to 0° and treated dropwise during 1 hour with bromine (14.4 g.). The resulting deep-red solution was kept at room temperature overnight and then heated by steam until evolution of hydrogen bromide ceased (1½ hours). The acetic acid was removed by distillation in steam and the residue was extracted with ether. The ethereal extract was filtered from insoluble tarry material and then shaken with sodium hydroxide solution (6N.; 10 c.c.); the precipitated yellow sodium salts (1.2 g.) were filtered off and purified by crystallisation from water. Like the analogous sodium bromotropolone the salts contained two molecules of water of crystallisation (Found : C, 39.0; H, 4.2. $C_{10}H_{10}O_2BrNa \cdot 2H_2O$ requires C, 39.3; H, 4.6%).

β - and γ -Thujaplicins (V and IV).—The mixture of isomeric sodium salts (626 mg.) was dissolved in methanol (25 c.c.) and stirred under hydrogen with palladium-charcoal (10%; 150 mg.) until 1 mole of hydrogen had been absorbed. Removal of catalyst and solvent furnished a red oil which was extracted with boiling light petroleum (b. p. 40—60°). After being treated with charcoal the extract was evaporated to small bulk (*ca.* 10 c.c.) and cooled to -15°. The slightly sticky crystalline solid thus obtained was sublimed at 80° (bath-temp.)/10⁻³ mm. and the hard cream-coloured sublimate was crystallised from light petroleum (b. p. 40—60°). The resulting prismatic needles (120 mg.) had m. p. 79.5°, undepressed on admixture with naturally occurring γ -thujaplicin (m. p. 79°). Treatment with ethereal diazomethane yielded γ -thujaplicin methyl ether as a liquid, which readily yielded a *picrate* crystallising from ethanol in yellow needles, m. p. 148—149° (Found : C, 50.3; H, 4.6. $C_{17}H_{17}O_9N_3$ requires C, 50.1; H, 4.2%).

The petroleum mother-liquors from the above preparation were evaporated to dryness, leaving an oil which was distilled at 80° (bath-temp.)/10⁻³ mm. The distillate was dissolved in a small quantity of light petroleum (b. p. 40—60°), cooled to -15°, and seeded with a trace of β -thujaplicin. The solution deposited prisms, m. p. 46—47° (12 mg.) undepressed on admixture with natural β -thujaplicin (m. p. 47°).

Both β - and γ -thujaplicin were obtained in this way, not only from the mixture of ketones formed by ring-enlargement of 4-isopropylcyclohexanone, but also from each of the samples regenerated from the pure semicarbazones (A and B).

N-Nitrosoisobutylurethane.—To a stirred, cooled mixture of isobutylamine (40 g.), ether (200 c.c.), and water (100 c.c.), ethyl chloroformate (30 g.) was added dropwise, the reaction mixture being kept below 5°. A further portion of chloroformate (30 g.) and a cold solution of sodium hydroxide (22 g. in 30 c.c. of water) were then separately added dropwise at the same rate. Thirty minutes after the last addition the ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal extracts were dried (K_2CO_3); removal of solvent followed by distillation furnished isobutylurethane (67 g., 85%), b. p. 110°/30 mm., n_D^{20} 1.4290 (Found : N, 9.1. $C_7H_{13}O_2N$ requires N, 9.6%).

To a gently shaken mixture of the urethane (67 g.), ether (150 c.c.), sodium nitrite (150 g.), ice (46 g.), and water (230 c.c.) was added dropwise during 1 hour dilute ice-cold nitric acid [from concentrated acid (100 c.c.) and water (150 c.c.)], the temperature being kept below 15°. When the ethereal layer had become green it was separated, washed with water and potassium carbonate solution, and dried (K_2CO_3). Removal of the solvent under reduced pressure gave the *N-nitrosoisobutylurethane* (80 g.) as a pink oil which was used without further purification for the next stage.

2-isopropylcycloheptanone (VI).—A mixture of cyclohexanone (47 g.), methanol (50 c.c.), and sodium carbonate (1 g.) was treated with *N-nitrosoisobutylurethane* (80 g.) in a manner analogous to the cognate preparation described above. Fractionation of the product yielded 2-isopropylcycloheptanone (23 g.), b. p. 93—95°/18 mm., n_D^{20} 1.4555 (Found : C, 77.4; H, 11.6. $C_{10}H_{18}O$ requires C, 77.9; H, 11.7%).

The *semicarbazone* crystallised from aqueous ethanol in plates, m. p. 175—176° (Found : C, 62.5; H, 10.3; N, 19.95. $C_{11}H_{21}ON_3$ requires C, 62.6; H, 9.95; N, 19.9%).

3-Ethoxy-3-isopropylcycloheptane-1:2-dione (VII).—To a boiling solution of *2-isopropylcycloheptanone* (23 g.) in ethanol (98%; 30 c.c.) was added dropwise during 2 hours a solution of selenium dioxide (18 g.) in ethanol (98%; 110 c.c.). After 6 hours' heating under reflux the mixture was set aside overnight and worked up as described above. Fractional distillation of the product gave the *ethoxy-dione* (VII) (13 g.) as a pale yellow oil, b. p. 130°/22 mm., n_D^{25} 1.4785 (Found : C, 68.3, 67.5; H, 9.2, 9.2; OEt, 20.7. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5; OEt, 21.2%). The *mono-2:4-dinitrophenylhydrazone*, after preliminary purification by chromatography in benzene over alumina, crystallised from ethanol in orange rosettes, m. p. 118° (Found : N, 15.0. $C_{18}H_{24}O_6N_4$ requires N, 14.3%).

Sodium Bromo- α -thujaplicin.—A solution of the ethoxy-dione (VII) (10 g.) in glacial acetic acid (10 c.c.) was treated with bromine (20 g.) and worked up as described above. The *sodium bromo- α -thujaplicin* (2.1 g.) thus obtained crystallised from water in yellow nodules decomposing at 300° (Found : C, 40.6; H, 4.25. $C_{10}H_{10}O_2BrNa \cdot 1.5H_2O$ requires C, 40.5; H, 4.4%). Heating the sesquihydrate to 150° *in vacuo* for 6 hours did not result in complete dehydration, only the monohydrate being formed (Found : C, 42.6; H, 4.1. $C_{10}H_{10}O_2BrNa \cdot H_2O$ requires C, 42.45; H, 4.25%).

α -Thujaplicin (VIII).—A solution of the above sodium salt (400 mg.) in methanol (25 c.c.) was stirred under hydrogen in the presence of palladium-charcoal (10%; 100 mg.) until one mole of hydrogen had been absorbed. Removal of catalyst and solvent followed by extraction with boiling light petroleum (b. p. 40—60°) and evaporation gave an oil which distilled at 80° (bath-temp.)/10⁻³ mm. The distillate solidified to a feathery, frost-like mass on being cooled to 0°; crystallisation from a small volume of light petroleum (b. p. 40—60°) at -15° gave prisms of *α -thujaplicin* (78 mg.), m. p. 26—27° undepressed on admixture with an authentic specimen (m. p. 27—28.5°). The oily methyl ether gave a poor yield of the *picrate*, yellow needles, m. p. 110° (decomp.) (from ethanol) (Found : N, 10.6. $C_{17}H_{17}O_9N_3$ requires N, 10.3%). As the mother-liquors of this preparation furnished much unchanged liquid ether it is probable that only one of the two expected *α -thujaplicin* methyl ethers forms a picrate.

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THE UNIVERSITY, GLASGOW, W.2.

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