233. *The Constitution of Some Cadalene Derivatives.*

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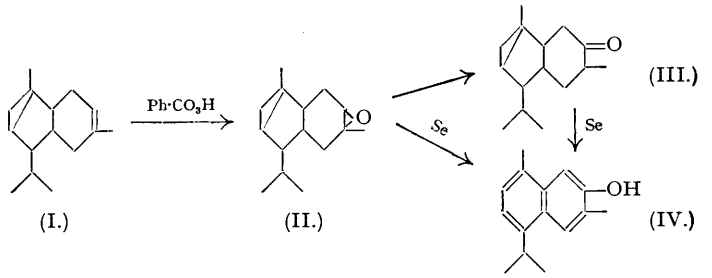
The constitution of a number of monosubstitution products of cadalene, previously believed by Gripenberg to be 2-derivatives, has been confirmed by relating them to the known 1 : 2 : 6-trimethyl-4-*iso*propylnaphthalene. A synthesis of 7-hydroxy-1 : 6-dimethyl-4-*iso*propylnaphthalene (7-hydroxycadalene) has shown it to be identical with a product from copæne and supports the constitution of the latter recently proposed by two of us (L. H. B. and W. I. T.). A compound alleged by Gripenberg to have the same constitution must now be assigned some other, still unknown structure.

In experiments on the constitution of copæne (I) (Briggs and Taylor, *J.*, 1947, 1338) a phenolic compound, $C_{15}H_{18}O$, was isolated which, it was suggested, was probably the previously unknown 7-hydroxy-1 : 6-dimethyl-4-*iso*propylnaphthalene (7-hydroxycadalene) (IV) arising from the dehydrogenation of copæne oxide (II) or its isomeric ketone (III).



(I.) (II.) (III.) (IV.)

However, in an earlier publication (*Ann. Acad. Sci. Fennicæ, Ser. A*, 1943, **59**, No. 41), which appeared in abstract form only after this work was completed, Gripenberg described a compound arising from the alkali fusion of a cadalene sulphonic acid which, he suggested, had the structure (IV). Gripenberg also described a number of monosubstitution products of cadalene alleged to have the 2-configuration, including the 2-hydroxy-compound. The isomeric 5-hydroxycadalene is also known, having been synthesised by Plattner and Magyar (*Helv. Chim. Acta*, 1941, **24**, 191) by an unambiguous route. The phenolic compound from copæne, however, appeared not to be identical with any of these substances.

The structures for Gripenberg's 2- and 7-hydroxy-isomers were, however, based solely on inductive reasoning, and, although we concur completely with his deductions even to the structure of his alleged 7-hydroxy-isomer, we felt a more rigid proof of the configuration of his compounds to be necessary in elucidating the structure of the copæne by-product.

We have concluded the proof of the 2-substituted compounds of cadalene through the *chloromethyl* derivative obtained by direct chloromethylation of cadalene. Oxidation, on the one hand, *via* the *aldehyde*, affords a cadalenecarboxylic acid, identical with that obtained by Gripenberg from both bromocadalene and acetylcadalene (these products being obtained from cadalene by direct bromination and the action of acetyl chloride in the Friedel and Crafts reaction, respectively) and having the suggested 2-configuration. Reduction, on the other hand, gave the 1 : 2 : 6-trimethyl-4-*iso*propylnaphthalene which was synthesised by Campbell and Soffer (*J. Amer. Chem. Soc.*, 1942, **64**, 417) by an unambiguous method. Since the 2-hydroxy-isomer of cadalene can be directly related to the above bromo- and acetyl derivatives (*q.v.*) its structure is confirmed.*

We attempted to establish the structure of the alleged 7-hydroxy-derivatives first from cadalene itself. We have prepared cadalenesulphonic acid and from it the corresponding naphthol and confirmed their properties given by Gripenberg. The naphthol considerably depresses the melting point of the copæne isomer, thus eliminating the possibility of their being dimorphic forms.

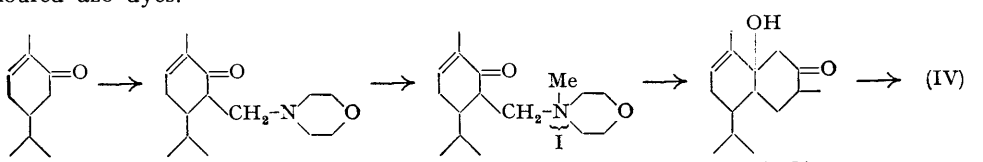
Oxidation of the sulphonic acid with permanganate should ultimately break the ring to which the sulphonic acid group is not attached, but the only product isolated from an experiment designed for this purpose was trimellitic acid in very small yield. As the corresponding

* Since this work has been completed, Dr. Gripenberg has informed us that he had already, in unpublished work, proved the configuration of the 2-derivatives by converting the bromo-derivative ***via*** its Grignard compound and orthoformic ester into the corresponding aldehyde, reduction of which gave 1 : 2 : 6-trimethyl-4-*iso*propylnaphthalene.

sulphonamide should behave similarly and the products should be easier to characterise, the corresponding sulphonamide was oxidised in a similar manner; it afforded, in small yield, (*a*) a viscous, liquid acid, giving a liquid methyl ester, and (*b*) a solid acid, $C_{15}H_{17}O_4NS$, characterised as its solid methyl ester and containing a sulphonamide group and all the original carbon atoms, one of which is oxidised to carboxyl. The liquid acid could correspond in properties to 4-sulphonamidotrimellitic acid (Jacobsen, *Ber.*, 1883, **16**, 192), but the solid acid is new and throws no light on the problem.

It seemed at this point that a simpler approach might be made synthetically, and 7-hydroxycadalene has now been synthesised unequivocally by the following series of reactions.

Carvotanacetone (V) was converted by paraformaldehyde and morpholine hydrochloride into the Mannich base (VI) (probably a mixture of stereoisomers), and the methiodide (VII) was condensed with ethyl sodio-α-acetylpropionate in absolute alcohol. Hydrolysis with potassium hydroxide solution then afforded 9-hydroxy-7-keto-1 : 6-dimethyl-4-*iso*propyl-Δ^1-octalin (VIII). Although hydroxy-ketones are usually dehydrated under such experimental conditions, Mannich, Koch, and Borkowsky (*Ber.*, 1937, **70**, *B*, 355) isolated a similar compound in their synthesis of β-octalone. Dehydration, reduction, and dehydrogenation of the hydroxy-ketone was achieved in one step by heating it with palladised charcoal in boiling diphenyl ether (cf. Horning and Horning, *J. Amer. Chem. Soc.*, 1947, **69**, 1360). The resultant 7-hydroxy-1 : 6-dimethyl-4-*iso*propylnaphthalene (7-hydroxycadalene) (IV), m. p. 119°, was characterised as the picrate and trinitrobenzene compound and shown by direct comparison to be identical with the naphthol from copæne, m. p. 116°, thus confirming the structure of copæne proposed by two of us (L. H. B. and W. I. T.). It couples with diazotised amines in alkaline solution to form dark-coloured azo dyes.



(V.) (VI.) (VII.) (VIII.)

Gripenberg's " 7-hydroxy "-isomer must therefore have some other structure. Sulphonation of naphthalene derivatives at 135°, as in his experiment, usually affords a β-sulphonic acid, in this case theoretically the 2-, 3-, or 7-derivative. That the acid occupies a β-position is shown by the fact that it is unchanged by attempted reduction with sodium amalgam, a diagnostic test introduced by Friedlaender and Lucht (*Ber.*, 1893, **26**, 3028) who showed that α-sulphonic acids, unlike the β-acids, are hydrolysed by this reagent. The 2- and 7-isomers may now be eliminated from the experiments described above. The 3-isomer, however, is unlikely since sulphonation usually proceeds in the less alkylated ring and also because the corresponding naphthol with no free adjacent α-position should not couple with diazotised amines, which it does. Possibly, in this case, wandering of an alkyl group occurs. This is common in heavily alkylated benzene and naphthalene derivatives, although it would not normally be expected in this case.

Experimental.

Preparation of Cadalene.—Crude cadinene (250 g., b. p. 120—140°/10 mm.), obtained by the distillation of oil of cade, was dehydrogenated with selenium (220 g.) for 70 hours at 300°. The crude cadalene fraction (120 g., b. p. 140—160°/10 mm.) was converted into the picrate, which was purified by crystallisation from alcohol to a constant m. p. 116—117° (yield 85 g.). The hydrocarbon was regenerated by decomposition with aqueous ammonia and extraction with ether, from which distillation afforded pure cadalene, b. p. 155—158°/10 mm.

Bromination of Cadalene.—To ice-cold cadalene (4·13 g.) in carbon tetrachloride (5 c.c.) ice-cold bromine (2·48 g.) in the same solvent (4 c.c.) was slowly added. After being kept for a day the solution was washed with alkali and water, and dried (Na_2SO_4), and the solvent was removed. Distillation then afforded crude 2-bromocadalene, b. p. 170—172°/8 mm. (4·3 g.). After it had been kept for some days in the refrigerator, pure 2-bromocadalene crystallised in plates, which after recrystallisation from methyl alcohol and alcohol had m. p. 39° (Found : Br, 28·4. Calc. for $C_{15}H_{17}Br$: Br, 28·9%). We could not confirm the m. p. 52—52·5° given to this compound by Gripenberg. The picrate, long orange needles, m. p. 114—115°, from alcohol, and the trinitrobenzene complex, yellow needles, m. p. 125—126°, from absolute alcohol, agreed in properties with those of Gripenberg (m. p. 113—113·5° and 124·5—125° respectively). The trinitrotoluene complex crystallised well, from methyl alcohol, in yellow needles, m. p. 87°.

The residue from the distillation of 2-bromocadalene was extracted with boiling alcohol (charcoal)

and yielded a small quantity of a dibromocadalene, needles, m. p. 121—122° (Found: Br, 44·6. $C_{15}H_{16}Br_2$ requires Br, 44·9%), which failed to yield derivatives with picric acid and trinitrobenzene.

When an attempt was made to convert 2-bromocadalene into the 2-methyl derivative *via* the Grignard product and methyl sulphate, cadalene (trinitrobenzoate, m. p. and mixed m. p. 113°) was the only product isolated.

Chloromethylation of Cadalene.—Cadalene (3 g.), paraformaldehyde (1 g.), glacial acetic acid (4·5 c.c.), concentrated hydrochloric acid (5 c.c.), and syrupy phosphoric acid (0·85 c.c.) were vigorously stirred at 100° for 6 hours. After dilution with water (30 c.c.), the product yielded to ether after washing (dilute sodium hydroxide solution) and drying (Na_2SO_4) an oil giving the following fractions on distillation: (*a*) solid, m. p. 84°, b. p. 100—180°/10 mm., 1·5 g., (*b*) semi-solid, b. p. 180—230°/10 mm., 0·34 g., and (*c*) solid, m. p. 154—156°, b. p. *ca.* 230/0·01 mm., 0·85 g. Fraction (*a*), *2-chloromethylcadalene*, crystallised readily from alcohol, in aggregates of small needles, m. p. 87° (Found: C, 77·7; H, 7·8. $C_{16}H_{19}Cl$ requires C, 77·9; H, 7·8).

The picrate was unstable, but the *trinitrobenzene* complex crystallised from absolute alcohol in yellow needles, m. p. 91—92° (Found: N, 9·7. $C_{16}H_{19}Cl,C_6H_3O_6N_3$ requires N, 9·2%).

Fraction (*c*), *2 : 2′-dicadalylmethane*, almost insoluble in boiling alcohol, methyl alcohol, and acetone, crystallised from glacial acetic acid in stout rods, m. p. 154—156° (Found: C, 91·2; H, 9·2. $C_{31}H_{36}$ requires C, 91·1; H, 8·9%). The picrate formed from the hydrocarbon (1 mol.) and picric acid (2 mols.) crystallised from glacial acetic acid in stout rods, m. p. 124—126°, but decomposed in alcohol and benzene.

When 2-chloromethylcadalene was chloromethylated as described above, besides unchanged material, a small yield (35 mg. from 500 mg.) of a *bischloromethylcadalene* was obtained which, after repeated crystallisation from alcohol, formed needles, m. p. 139—140° (Found: Cl, 22·6. $C_{17}H_{20}Cl_2$ requires Cl, 23·0%), and failed to yield a picrate or trinitrobenzene complex.

Cadalene-2-aldehyde.—2-Chloromethylcadalene (650 mg.) and hexamine (350 mg.) in alcohol (7 c.c.) were heated under reflux for 6 hours. The solution was diluted with water (10 c.c.), the alcohol removed by distillation, and the aqueous solution treated with saturated sodium hydrogen sulphite solution. The solid bisulphite compound, which formed in a few minutes, was washed with a little water and alcohol, and the recovered aldehyde was distilled. The fraction, b. p. *ca.* 120°/10 mm. (120 mg.), solidified in colourless needles which, after recrystallisation from alcohol, melted at 84° (Found: C, 84·2; H, 7·9. $C_{16}H_{18}O$ requires C, 84·9; H, 8·0%). The 2 : 4-dinitrophenylhydrazone was insoluble in the usual solvents, but crystallised from pyridine in rosettes of bright red needles, m. p. 270—271°. The semicarbazone crystallised from 80% alcohol in clusters of irregular plates, m. p. 206—207·5°.

Cadalene-2-carboxylic acid.—A solution of cadalene-2-aldehyde (34 mg.), potassium permanganate (16 mg.), and excess of sodium bicarbonate in acetone (3 c.c.) was allowed to stand until decolourised. The solution was filtered, and the residue extracted with boiling water (1 c.c.). Acidification of the combined filtrates yielded a colourless acid, purified by sublimation at 180°/1 mm. or by crystallisation from glacial acetic acid. The final product had m. p. 193°, slightly lower than that (195—196°) recorded by Gripenberg (Found: C, 79·5; H, 7·3. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·5%).

1 : 2 : 6-*Trimethyl*-4-iso*propylnaphthalene.*—2-Chloromethylcadalene (230 mg.) and zinc (300 mg.) in glacial acetic acid (10 c.c.) were heated on the water-bath and saturated with hydrogen chloride. The acetic acid was removed by vacuum-distillation; the residue after extraction with ether yielded an oil, b. p. *ca.* 160°/10 mm. (60 mg.), the picrate and trinitrobenzene complex of which formed red needles, m. p. 142°, from alcohol, and yellow needles, m. p. 167°, from absolute alcohol, respectively, m. p.s which agree with those recorded by Campbell and Soffer (*J. Amer. Chem. Soc.*, 1942, **64**, 417) for the derivatives of 2-methylcadalene.

Cadalenesulphonic acid was prepared at 100° by a method similar to that described by Gripenberg, the free acid crystallising in plates from benzene, m. p. 121—122° (Gripenberg records m. p. 124—125°). The 5-benzyl-ψ-thiouronium salt had m. p. 228° after repeated crystallisation from alcohol (Gripenberg recorded m. p. 222—223°).

Cadalenesulphonamide.—Sodium cadalenesulphonate (500 mg.) and phosphorus pentachloride (600 mg.) were heated at 100° for 45 minutes. After cooling, the melt was triturated with water, and the crude sulphonyl chloride then heated under reflux with concentrated ammonia (20 c.c.) for 1½ hours. The sulphonamide produced, after crystallisation from alcohol, formed colourless needles, m. p. 157—158°, unchanged by further recrystallisation (Found: N, 4·8. Calc. for $C_{15}H_{19}O_2NS$: N, 5·05%). We could not confirm the m. p. 175·5—176° given to this compound by Gripenberg.

The Hydroxycadalene from Cadalenesulphonic Acid.—Sodium cadalenesulphonate (600 mg.) was fused with potassium hydroxide (1 g.) at 310° for 35 minutes with continuous stirring. After cooling, the melt was dissolved in water, acidified, and extracted with ether. After being washed with sodium bicarbonate solution and dried (Na_2SO_4), the extract yielded a viscous red oil, b. p. *ca.* 200°/10 mm. (150 mg.), which partly solidified when kept in the refrigerator. Crystallisation from 50% alcohol gave the pure hydroxycadalene, m. p. 89°, corresponding to the product, m. p. 90°, described by Gripenberg. The m. p. was depressed to 74° after admixture with a specimen of 7-hydroxycadalene, m. p. 116°, derived from copæne.

Oxidation of Cadalenesulphonic Acid.—Potassium permanganate (27 g.; 26 atoms of oxygen) was slowly added to potassium cadalenesulphonate (4·0 g., 1 mol.) in water (200 c.c.). After a rapid initial oxidation, the mixture was heated on the water-bath for 3 days. Manganese dioxide was then filtered off, and lead acetate (25 c.c. of a 25% solution) added to the filtrate acidified with acetic acid. After concentration of the solution to *ca.* 50 c.c., a solid crystallised out in rods (yield, *ca.* 1 g.). This was suspended in water, saturated with hydrogen sulphide, and filtered; the solution, when evaporated to dryness, gave a white solid, freely soluble in water. Fusion of this product with potassium hydroxide at 160—170° for 15 minutes and working up in the usual way failed to give a phenolic product. However, extraction, with ether, of the original oxidation mother-liquors yielded trimellitic acid (15 mg.), m. p. 210—216°, characterised by its anhydride, m. p. 158°, which was undepressed by an authentic specimen prepared from ψ-cumene.

Oxidation of Cadalenesulphonamide.—A mixture of cadalenesulphonamide (3·68 g.), potassium permanganate (21 g., 24 atoms of oxygen), and potassium carbonate (6 g.) in acetone (150 c.c.) was heated under reflux for 24 hours. The acetone-insoluble portion was extracted with boiling water (100 c.c.), and this on acidification with dilute sulphuric acid gave a sticky solid (*A*), whilst exhaustive extraction with ether afforded a further quantity of oily material (*B*).

(*A*) was dissolved in dilute sodium carbonate solution, any neutral component extracted with ether, and the solution acidified. A semi-solid mixture of acids was obtained, separated by crystallisation from alcohol into needles (69 mg.) and an oil (200 mg.). The crystalline *acid* had m. p. 254—255° (Found : C, 58·5; H, 5·3; N, 4·6. $C_{15}H_{17}O_4NS$ requires C, 58·6; H, 5·6; N, 4·6%) and with diazomethane furnished a methyl ester, m. p. 157—158°. The solid acid exhibits a purple fluorescence in alcohol. The oil was dissolved in dry acetone, chromatographed on charcoal, and eluted with the same solvent. The major part of the eluate furnished an oil, but the final fractions yielded a further 35 mg. of the above acid.

Similar chromatography of (*B*) and elution failed to yield a solid product, whilst a methyl ester prepared by the action of diazomethane, although semi-solid, could not be induced to crystallise.

Synthesis of 7-Hydroxycadalene.—(a) *3-Morpholinomethylcarvotanacetone methiodide.* A mixture of carvotanacetone (25·4 g., 1/6 mol.), morpholine hydrochloride (21·7 g., 1/6 mol.), paraformaldehyde (1·7 g.), and absolute alcohol (30 c.c.) was heated under reflux. At the end of each half-hour, further additions of paraformaldehyde (1·7 g.) were made until a total of 6·8 g. had been added, and the boiling was continued for 4 hours in all; the mixture was then homogeneous. As no crystalline hydrochloride separated after cooling the mixture, some of the alcohol was removed and the residue diluted with water. Unchanged ketone was removed with ether, and the free Mannich base liberated from the aqueous solution by treatment with ice-cold sodium hydroxide solution (8 g. in 25 c.c.). The free base was obtained as a dark oil (30 g.) by extraction with ether. Methyl iodide (28 g., 20% excess) was added to a solution of the base (41 g.) in dry ether, and the mixture set aside overnight. The methiodide separated as a brownish-yellow gum (58 g.) which, however, could not be induced to crystallise.

(b) *9-Hydroxy-7-keto-1 : 6-dimethyl-4-isopropyl-*Δ^1*-octalin.* A solution of ethyl sodio-α-acetylpropionate was prepared from ethyl α-acetylpropionate (31·3 g.) and sodium (5·1 g.) in absolute alcohol (130 c.c.). The solution was then added to the methiodide (57 g.), dissolved in dry alcohol, which was possible with mechanical shaking if the methiodide had not been allowed to stand too long. Otherwise, it was added to the methiodide, and the mixture gently warmed in an oil-bath, with shaking, until the gum left the walls of the flask. The mixture was then heated under reflux for 5 hours. In order to hydrolyse the ester so formed, potassium hydroxide solution (9 g. in 20 c.c.) was added, and the heating under reflux continued for a further 4 hours. Most of the alcohol was then distilled off, and sufficient water added to dissolve the sodium iodide formed in the reaction and to cause the oily product to separate. The oil, removed by ether extraction, furnished *9-hydroxy-7-keto-1 : 6-dimethyl-4-isopropyl-*Δ^1*-octalin* as a yellow oil, b. p. 150—154°/1—2 mm. (yield 16·1 g.) (Found : C, 74·9; H, 9·7. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). The *2 : 4-dinitrophenylhydrazone* crystallised from alcohol in orange needles, m. p. 167° (Found : N, 13·4. $C_{21}H_{28}O_5N_4$ requires N, 13·5%). The *semicarbazone* crystallised from alcohol in colourless needles, m. p. 208·5° (Found : N, 14·3. $C_{16}H_{27}O_2N_3$ requires N, 14·3%).

(c) *7-Hydroxycadalene.* Palladium–charcoal catalyst (1·5 g.) was added to 9-hydroxy-7-keto-1 : 6-dimethyl-4-*iso*propyl-Δ^1-octalin (5 g.) in diphenyl ether (15 c.c.), and the mixture heated at *ca.* 270° for 2 hours. After removal of the catalyst, the naphthol was extracted with Claisen solution according to the method of Horning and Horning (*J. Amer. Chem. Soc.*, 1947, **69**, 1360). After acidification of the alkaline extract with concentrated hydrochloric acid, the product was removed with ether and distilled. The viscous oil obtained, b. p. 172°/1 mm. (bath-temperature, 300°), solidified when scratched. Recrystallisation from light petroleum (b. p. below 60°) yielded colourless needles, m. p. 119°, undepressed on admixture with the naphthol from copæne (Found : C, 83·2; H, 8·6. Calc. for $C_{15}H_{18}O$: C, 84·1; H, 8·5%). The picrate formed reddish-brown needles, m. p. 138°, and decomposed on long storage; the trinitrobenzene complex crystallised from alcohol in orange-red needles, m. p. 140—140·5°. Neither product depressed the m. p. (139° and 139—140°, respectively) of the corresponding derivatives from the copæne naphthol.

The analyses are by Drs. Weiler and Strauss, Oxford, and Miss J. E. Fildes, University of Sydney.

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