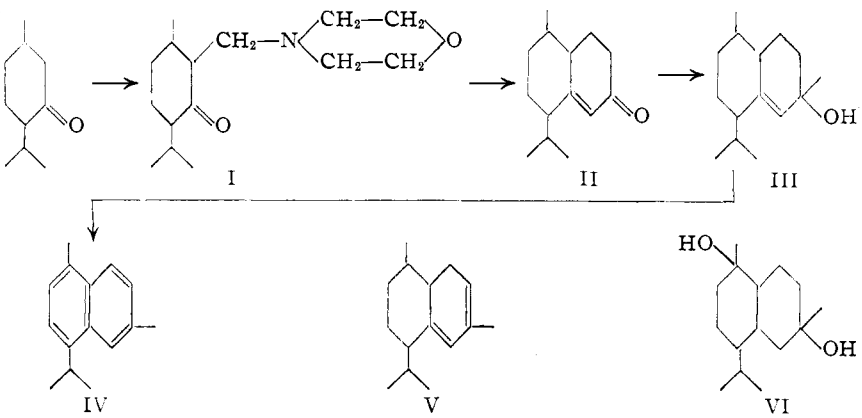
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SYDNEY]

A Convenient Synthesis of Cadalene

BY NAIDA S. GILL[1] AND FRANCIS LIONS

Cadalene has been synthesized previously by various series of reactions involving from seven to eleven steps,[2] the best being probably that of Johnson and Jones which gives an over-all yield of 25% in six steps. The present paper describes yet another synthesis with an over-all yield of 27% or better, which is probably the most convenient of all.

Reaction of l-menthone with morpholine hydrochloride and paraformaldehyde in boiling ethanol yielded a gum which was probably a mixture of stereoisomeric Mannich base hydrochlorides.[3] The oily bases (I) obtained from it with cold alkali gave a crystalline methiodide which condensed readily in dry ethanol with ethyl sodioacetoacetate to a product from which by alkaline decarbethoxylation 1-methyl-4-isopropyl-6-keto-$\Delta^{5,10}$-octalin (II) was obtained as a partially crystalline oil. Interaction of II with methylmagnesium iodide yielded oily 1,6-dimethyl-4-isopropyl-6-hydroxy-$\Delta^{5,10}$-octalin (III, again probably a mixture of stereoisomers) and simultaneous dehydration and dehydrogenation of this to cadalene (IV) was effected by heating with sulfur, the purified hydrocarbon being characterized as its picrate and trinitrotoluate.



It is worth noting that dehydrogenation of tertiary alcohols of the formula III should give dienes of the formula V, *i. e.*, $C_{15}H_{24}$ hydrocarbon isomers of naturally occurring sesquiterpenes. In order to prepare pure synthetic hydrocarbons it would first be essential to separate into optically pure forms the Mannich bases I before proceeding further. There are also potentialities for the synthesis of naturally occurring sesquiterpenes of cadinene type by similar methods. Thus starting from 1-hydroxy-*p*-menthanone-3[4] it should be possible to prepare at least some of the diols of formula VI. Replacement of the hydroxyl groups of the correct isomers by chlorine atoms would yield cadinene dihydrochloride.

Experimental

2-Morpholinomethyl Menthone Methiodide.—A mixture of *l*-menthone (51.3 g.), morpholine hydrochloride (43 g.), paraformaldehyde (3.3 g.) and absolute ethanol (60 ml.) was refluxed (oil-bath) for thirty minutes. Three further lots of paraformaldehyde (3.3 g.) were added at half-hour intervals, refluxing being continued. After each addition more morpholine hydrochloride dissolved until eventually (three and one-half hours) a homogeneous solution was obtained. Most of the alcohol was distilled off, water added and unchanged menthone removed with ether. The aqueous solution was carefully basified at 0° with sodium hydroxide solution, the liberated Mannich bases being taken up in ether, dried and the solvent removed (64 g.). About an equal volume of dry ether and then methyl iodide (43 g., 20% excess) were added. The liquid clouded almost immediately owing to separation of quaternary salt. After standing overnight the white crystalline methiodide (79 g., 60%) was collected, washed with dry ether and dried *in vacuo* at room temperature. It recrystallized from ethanol in colorless leaflets, m. p. 234° (dec.) when rapidly heated.

Anal. Calcd. for $C_{16}H_{30}O_2NI$: C, 48.6; H, 7.6; N, 3.5. Found: C, 48.2; H, 7.6; N, 3.6.

1-Methyl-4-isopropyl-6-keto-$\Delta^{5,10}$-octalin (II).—Ethyl acetoacetate (21.8 g.) was added to a solution of sodium (3.8 g.) in absolute ethanol (180 ml.). 2-Morpholinomethyl menthone methiodide (43 g.) was added and the mixture gently refluxed (oil-bath). The methiodide gradually went into solution and sodium iodide precipitated. After four hours a solution of potassium hydroxide (7 g.) in water (20 ml.) was added and refluxing continued for a further four hours. The alcohol was then distilled off and water added after cooling. The separated dark oil was taken up, washed and dried in ether, the solvent removed and the residue distilled *in vacuo*. A pale yellow oil (18.5 g., 82%) b. p. 134–137° (1 mm.) (bath temperature 185–190°) was collected. On cooling this ketone partially crystallized in leaflets which after draining on a porous tile and careful recrystallization from alcohol, in which they were very soluble, had m. p. 70°.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.5; H, 10.8. Found: C, 81.0; H, 10.8.

The **2,4-dinitrophenylhydrazone** formed red needles (from ethanol) m. p. 152–153°.

Anal. Calcd. for $C_{20}H_{26}O_4N_4$: N, 14.5. Found: N, 14.5.

Attempts to prepare a crystalline semicarbazone all resulted in the production of gums.

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(2) *Cf.* Johnson and Jones, THIS JOURNAL, **69**, 792, footnote 3 (1947); Colonge and Chambion, *Compt. rend.*, **222**, 557 (1946); Dev and Guha, *Science and Culture*, **13**, 73 (1947).

(3) *Cf.* Mannich and Honig, *Arch. Pharm.*, **265**, 598 (1927).

(4) *Cf.* Read and Swann, *J. Chem. Soc.*, 237 (1937).

1,6-Dimethyl-4-isopropyl-6-hydroxy-$\Delta^{5,10}$-octalin (III).—A solution of II (15 g.) in dry ether was gradually added to a solution of methylmagnesium iodide from methyl iodide (12.4 g.) and magnesium (2.1 g.), a vigorous reaction occurring. The mixture was then gently refluxed for ninety minutes, cooled and poured into a mixture of cracked ice and ammonium chloride solution. The ether layer was removed and the aqueous layer extracted with ether several times. The solvent was removed from the united ether extracts after drying and the residual oil distilled *in vacuo*. A fraction (10.2 g., 63%) b. p. 110–114° (1 mm.) (bath temperature 160°) was collected.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.1; H, 11.7. Found: C, 81.0; H, 11.8.

1,6-Dimethyl-4-isopropylnaphthalene (Cadalene, IV).—A mixture of III (6 g.) and powdered sulfur (2.7 g.) was heated for four hours at 200–250° in an oil-bath. The resultant very dark product was distilled with steam, the cadalene coming over as a yellow-brown oil which was collected and dried in ether and eventually distilled *in vacuo*, being thus obtained as a pale yellow oil (4.8 g., 81%) b. p. 163–164° (18 mm.) (literature,[5] b. p. 157–158° (12 mm.)). The **picrate** formed orange needles (from ethanol) m. p. 116° (literature,[2] m. p. 114–116°).

Anal. Calcd. for $C_{21}H_{21}O_7N_3$: N, 9.8. Found: N, 10.1.

The trinitrotoluate formed yellow needles (from methanol) m. p. 82.5° (literature,[6] m. p. 83°).

Anal. Calcd. for $C_{22}H_{23}O_6N_3$: N, 9.9. Found: N, 9.9.

Acknowledgment.—We are indebted to Miss Joyce Fildes for the combustion micro-analyses recorded in this paper.

Summary

A convenient, relatively high-yielding synthesis of cadalene from l-menthone involving use of the Mannich reaction is described.

(5) Ruzicka and Meyer, *Helv. Chim. Acta*, **4**, 508 (1921).

(6) Briggs and Taylor, THIS JOURNAL, **69**, 716 (1947).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Addition Reactions of Chalcones. I. The Preparation of Some γ-Ketosulfones

BY HENRY GILMAN AND LOUIS F. CASON

In connection with the search for new chemotherapeutic agents[1] we prepared a number of γ-ketosulfones by means of the addition of sulfinic acids to chalcones.

$$RCH{=}CHCOR' + R''SO_2H \longrightarrow RCH(SO_2R'')CH_2COR'$$

R, R′, R″ are aromatic

The 1,4-addition of certain sulfur compounds and other unsymmetrical reagents to chalcones has been known since the rather early development of the chemistry of conjugated systems. Posner[2] treated thiols with benzalacetophenone in the presence of hydrogen chloride and/or zinc chloride in ethanol or acetic acid. The products were trialkylmercapto derivatives of 1,3-diphenylpropane resulting from the addition of one molecule of the thiol to the α,β-unsaturated linkage and the condensation of two molecules with the carbonyl group of the ketone. These compounds generally lost two molecules of the thiol upon oxidation and were converted into the corresponding γ-ketosulfone. From benzenethiol and the ketone, however, there was obtained only the 1,4-addition product which readily underwent oxidation to the ketosulfone identical with that obtained from the addition of benzenesulfinic acid to benzalacetophenone.[3] Later Ruhemann[4] showed that thiols undergo 1,4-addition to chalcones in the presence of the basic catalysts piperidine or sodium methoxide. In more recent studies, Nicolet[5] showed that these addition reactions are reversible, the equilibrium being shifted far to the left in the presence of alkalies. He demonstrated that *p*-toluenethiol and α-toluenethiol add smoothly to chalcone without the aid of a catalyst.[6] Gilman and King[7] obtained identical products by the addition and subsequent hydrolysis of *p*-tolylthiomagnesium iodide to benzalacetophenone. In some later investigations, γ-ketosulfides have been prepared in excellent yields from chalcones and aliphatic thiols.[8]

γ-Ketosulfones have been previously prepared by the 1,4-addition of sulfinic acids to chalcones[3,9,10a,10b] and from the interaction of aromatic hydrocarbons and sulfur dioxide with chalcones in the presence of anhydrous aluminum chloride.[11] According to Kohler and Reimer,[9] the products are crystalline and stable under ordinary conditions but are decomposed by bases. Addition products of this type have been used to identify small amounts of sulfinic acids obtained from the cleavage and rearrangement of certain sulfones.[10a]

Several new chalcones and related α,β-unsaturated ketones (listed in Table I) were prepared as intermediates in this study by the known procedures of Claisen,[12] and of Kohler and

(1) Gilman and Broadbent, THIS JOURNAL, **69**, 2053 (1947), mention several important sulfones and related compounds which have shown promise in antituberculous and antimalarial tests.

(2) Posner, *Ber.*, **34**, 1395 (1901).

(3) Posner, *ibid.*, **35**, 799 (1902).

(4) Ruhemann, *J. Chem. Soc.*, **87**, 17, 461 (1905).

(5) Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(6) Nicolet, *ibid.*, **57**, 1098 (1935).

(7) Gilman and King, *ibid.*, **47**, 1136 (1925).

(8) Frank and Smith, *ibid.*, **68**, 2103 (1946); Frank, Drake, Smith and Stevens, *J. Polymer Sci.*, **3**, 50 (1948) [*C. A.*, **42**, 4385 (1948)]; Kipnis and Ornfelt, THIS JOURNAL, **71**, 3554 (1949).

(9) Kohler and Reimer, *Am. Chem. J.*, **31**, 163 (1904).

(10) (a) Martin, *Iowa State Coll. J. Sci.*, **21**, 38 (1946) [*C. A.*, **41**, 952 (1947)]; (b) Goldberg, Hein mann, and Grier, *Jubilee Vol. Emil Barell*, 341 (1946) [*C. A.*, **41**, 4153 (1947)].

(11) Vorländer and Friedberg, *Ber.*, **56**, 1144 (1923).

(12) Claisen, *ibid.*, **20**, 657 (1887).