[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

A Synthesis of Eucarvone

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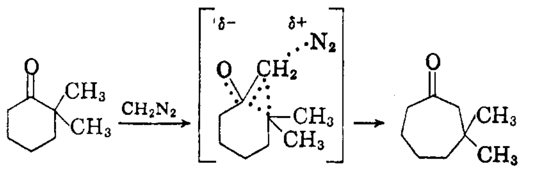
Eucarvone has been synthesized from 2,2-dimethylcyclohexanone by a procedure which should be useful for the preparation of other cycloheptadienones.

Both the reaction for preparing eucarvone (I) and its chemical behavior are sufficiently unique that the structure first suggested by Wallach[3] was accepted only with some reservations until confirming physical evidence was obtained.[4]

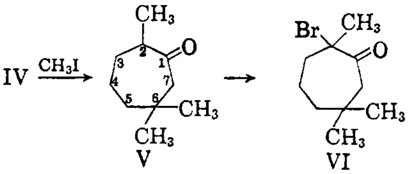
The synthesis reported here was developed in connection with work on the transformation of eucarvone to carvacrol.[5] It represents a route which could be used for preparing various alkylated eucarvones and unlike the original preparation[6] proceeds from an intermediate which already has a seven-membered ring.

The required starting material, 2,2-dimethylcyclohexanone (II), was prepared by methylation of 2-methylcyclohexanone and separation of II by the hydroxymethylene procedure of Bailey and Madoff.[7] The transformation of II to IV has been previously reported by Mousseron and Manon[8] but, as IV had been isolated by way of the semicarbazone derivative, which was obtained in unstated yield, it was not clear whether any of the isomeric ketone, 2,2-dimethylcycloheptanone, was also formed. The dimethylcycloheptanone fraction obtained in this work produced a single, sharp-melting 2,4-dinitrophenylhydrazone in good yield. Thus IV is certainly the major if not the exclusive rearrangement product. This must mean that the transition state, III, in which a tertiary carbon is migrating, is distinctly lower in energy than the alternate possibility in which a primary carbon would be migrating.



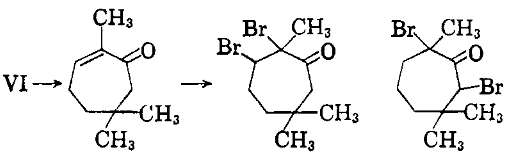
II III IV

The monomethylation of IV, which also might have produced a mixture, yielded a single ketone, V, in which the methyl group entered at C_7. Structure V was verified by comparison with an authentic sample prepared by reduction of eucarvone. The rate controlling step in the methylation is most likely the bimolecular displacement of the iodide ion by the enolate ion of IV. The *gem*-dimethyl group would certainly hinder any such process at C_7, and hence the enolate ion formed by loss of a proton at C_2, reacts most rapidly. In this connection it is interesting that ketone IV is also oxidized only at C_2; β,β-dimethylpimelic acid is the only product reported.[8]



V VI

The bromination of ketone V with either N-bromosuccinimide or bromine in acetic acid produced the same bromo ketone (VI), previously prepared by Wallach.[9] This bromo ketone is dehydrobrominated slowly by hot 2,6-lutidine to yield β-dihydroeucarvone (VII), thus indicating that structure VI is correct. For cycloheptane derivatives there appear to be quasi-axial (a′) and quasi-equatorial (e′) positions for substituents.[10] The configuration of the halogen of α-halocyclohexanones which are locked in one conformation by ring fusion may be assigned by observing the difference (Δλ) between the carbonyl frequency of the halo ketone and the unsubstituted ketone.[11] For nonrigid cyclanones the situation



VII VIII IX

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[1] Abstracted from a thesis presented by W. J. Houlihan to the Graduate School for the Ph.D. degree, August 1956.

[2] Colgate-Palmolive Fellow, 1954–1955.

[3] O. Wallach, *Ann.*, **305**, 245 (1899); O. Wallach, *Ann.*, **339**, 94 (1905).

[4] A. E. Gillam and T. F. West, *J. Chem. Soc.*, 483 (1942), measured the ultraviolet absorption of eucarvone; see also, E. J. Corey and H. J. Burke, *J. Am. Chem. Soc.*, **76**, 5257 (1954).

[5] These results will be published in a future communication.

[6] A. Baeyer, *Ber.*, **27**, 810 (1894).

[7] W. J. Bailey and M. Madoff, *J. Am. Chem. Soc.*, **76**, 2707 (1954).

[8] M. Mousseron and G. Manon, *Bull. Soc. chim. France.*, 392 (1949).

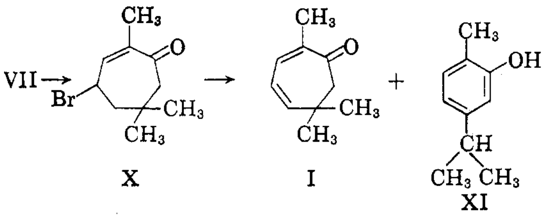
[9] O. Wallach, *Ann.*, **414**, 367 (1918).

[10] N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 232 (1959).

[11] R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

is much more complicated[12]; however, it is interesting to note that for bromo ketones VI and VIII, $\Delta\lambda$ is appreciably larger (13–14 cm.$^{-1}$) than for α-bromocycloheptanone ($\Delta\lambda$ 8 cm.$^{-1}$). This suggests that in the various conformations which are possible for these ketones the bromine atom of VI and VIII is in e′ positions to a greater extent than the bromine of α-bromocycloheptanone. An interesting comparison is provided by crystalline dibromide IX which has two distinct carbonyl bands ($\Delta\lambda$ 5 and 29 cm.$^{-1}$).

The synthesis was completed by bromination of VII with *N*-bromosuccinimide and elimination of hydrogen bromide from bromide X. There was a marked difference in stability between VI and X, as the latter compound lost hydrogen bromide slowly even at room temperature. In addition to the desired eucarvone, (I), the dehydrobromination of X produced considerable amounts of carvacrol (XI). The conditions reported here are certainly not optimal for transformation of X to I. From other results[5] it seems likely that I is formed in good yield but is then converted to XI.



EXPERIMENTAL[13]

2,2-Dimethylcyclohexanone (II). The procedure of Bailey and Madoff[7] was followed and from 2-methylcyclohexanone (132 g., 1.18 moles) there was obtained 65 g. (43%) of 2,2-dimethylcyclohexanone, which had b.p. 169° (765 mm.), and n_D^{22} 1.4450 (lit.[14] b.p. 163–170°/768 mm., n_D^{25} 1.4460). The infrared spectrum of this ketone had a doublet at 7.25 and 7.33 μ which is characteristic for *gem*-dimethyl groups.[15] The semicarbazone, recrystallized twice from ethanol, melted at 197–198° (lit.[14] m.p. 200–201°). The 2,4-dinitrophenylhydrazone melted at 141–142° (lit.[7,8] m.p. 140–142° and 125–126°).

3,3-Dimethylcycloheptanone (IV). 2,2-Dimethylcyclohexanone (60 g., 0.48 mole) and nitrosomethylurethane (60 g., 0.45 mole) were allowed to react as described by Mousseron and Manon.[8] There was obtained 54 g. of a ketone mixture which boiled at 50–52° at 10 mm. The mixture was fractionated at atmospheric pressure through a two-foot column packed with Raschig rings to yield three fractions: (1) unchanged 2,2-dimethylcyclohexanone, 17.5 g., b.p. 167–173°, n_D^{27} 1.4462, (2) mixed ketones, 13.2 g., b.p. 173–178°, n_D^{27} 1.4480 and (3) 3,3-dimethylcycloheptanone, 10.1 g., b.p. 178–180°, n_D^{27} 1.4494. Fraction 3 formed a semicarbazone which melted at 183–184° (lit.[7] m.p. 184–185°). The 2,4-dinitrophenylhydrazone melted at 143–145° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.52; H, 6.22. Found: C, 56.06; H, 6.09.

2,6,6-Trimethylcycloheptanone (*Tetrahydroeucarvone*) *V*. *A. From 3,3-Dimethylcycloheptanone.* A vigorously stirred slurry of finely ground sodamide (3.9 g., 0.1 mole) in dry benzene (50 ml.) was treated with 3,3-dimethylcycloheptanone (14 g., 0.1 mole) and the mixture refluxed for 26 hr. The resulting suspension of the sodium enolate was cooled in an ice bath and methyl iodide (14.2 g., 0.1 mole) was added dropwise during 2 hr. The mixture was finally allowed to stand overnight at room temperature. Ice water (50 ml.) was added cautiously and the benzene layer was separated, washed with water and dried. The solvent was removed *in vacuo* and the residue distilled through a Podbelniak concentric tube column at 18 mm. using a 10:1 reflux ratio. The following fractions were collected: (1) recovered 3,3-dimethylcycloheptanone, 3.3 g., b.p. 67.5–69.5°, n_D^{27} 1.4479, (2) mixed ketones, 2.3 g., b.p. 69.5–77°, n_D^{27} 1.4486–1.4503, (3) tetrahydroeucarvone, 1.7 g., b.p. 76–77°, n_D^{27} 1.4531 and (4) mixed ketones, 0.6 g., b.p. 77–79°, n_D^{27} 1.4539.

B. From eucarvone. Eucarvone (35 g., 0.24 mole) in absolute ethanol (30 ml.) was hydrogenated in the presence of Raney nickel catalyst (7 g.) using an initial hydrogen pressure of 40 p.s.i. The calculated amount of hydrogen (0.48 mole) was absorbed in 2.5 hr. The catalyst was filtered off and the filtrate distilled to yield 28.2 (74%) of tetrahydroeucarvone which boiled at 42–43.5° (0.4 ml.), n_D^{25} 1.4548, d_4^{25} 0.9069, MR_D calcd. 46.21, MR_D obs. 46.07 (lit.[16] b.p. 53°/mm., d_4^{20} 1.9063, n_D^{20} 1.455).

The infrared spectra of the tetrahydroeucarvone samples prepared in part A and B were identical and the semicarbazones were also identical by the criterion of a mixture melting point, 185–187°.[17]

The 2,4-dinitrophenylhydrazone melted at 117–130° after six recrystallizations from ethanol and was apparently an inseparable mixture of two forms. However, a solution refluxed for 20 hr. in ethanol was converted to one form, m.p. 134.5–137°.[18]

2-Bromo-2,6,6-trimethylcycloheptanone (VI). A slurry of tetrahydroeucarvone (6 g., 0.039 mole) was added to a suspension of *N*-bromosuccinimide (7 g., 0.039 mole) in dry carbon tetrachloride (50 ml.). Benzoyl peroxide (10 mg.) was added and the solution refluxed gently for 1.5 hr. The colorless solution was filtered and the solvent removed. The residue was distilled to yield 6.1 g. (65%) of bromide VI which boiled at 65–66° (1.0 mm.), $n_D^{29.5}$ 1.4932, $d_4^{29.5}$ 1.2300, MR_D calcd., 55.08, MR_D obsd., 55.15, characteristic infrared band (film) at 5.85 μ (1708 cm.$^{-1}$).

The same bromo ketone was obtained in 78% yield by the addition of bromine in acetic acid according to the procedure of Wallach.[9] Wallach observed the melting point of this ketone to be 32° but reported no other properties. The distilled ketone solidified on cooling but was largely melted at room temperature (*ca.* 27°).

β-Dihydroeucarvone (VII). *A.* Eucarvone (33 g.) in absolute ethanol (20 ml.) was hydrogenated using Raney nickel (7 g.)

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(12) N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958).

(13) Melting points were determined with the Kofler hot-stage and analyses were carried out by G. Robertson, Florham Park, N. J.

(14) P. S. Adamson, A. M. Marlow, and J. L. Simonsen, *J. Chem. Soc.*, 775 (1938).

(15) See R. T. O'Connor, *J. Am. Chem. Soc.*, **76**, 2372 (1954) and J. Plina and V. Herout, *Czech. Chem. Coll.*, **15**, 160 (1950), for further examples.

(16) Y. R. Naves and P. Ardizio, *Helv. Chim. Acta*, **32**, 329 (1949).

(17) Tetrahydroeucarvone has been reported (Ref. 16) to yield two different semicarbazones, m.p. 162–165° and 201–202° (Ref. 16); however, E. J. Corey and H. J. Burke [*J. Am. Chem. Soc.*, **78**, 174 (1956)] have also obtained what appears to be an inseparable mixture of the two, m.p. 187–192°.

(18) J. R. B. Campbell, A. M. Islam, and R. A. Raphael [*J. Chem. Soc.*, 4096 (1956)] isolated this isomer, m.p. 136–137.5°, by chromatography on a kieselguhr-bentonite column.

and hydrogen (45 p.s.i.). One mole of hydrogen was absorbed in 45 min. The catalyst was filtered, the solvent removed and the residue distilled to yield 25.4 g. (72%) of β-dihydroeucarvone which boiled 42.5–44° (0.1 mm.), $n_D^{24.5}$ 1.4741, d_4^{25} 0.9286, MR_D obsd., 46.26, $\lambda_{max}^{C_2H_5OH}$ 241 mμ (log ε, 3.85).

The semicarbazone of this ketone melted at 162–165° (lit.[16,18] m.p. 162–165° and 201–202°) after recrystallization from ethanol.

The 2,4-dinitrophenylhydrazone melted at 193–195° (lit.[18] m.p. 194–195°).

B. A mixture of bromo ketone VI (10 g., 0.043 mole) and 2,6-lutidine (9.6 g., 0.086) was refluxed for 10 hr. Dilute hydrochloric acid was added and then ether was used to extract the product. Fractionation of the residue remaining after evaporation of the ether, produced β-dihydroeucarvone, VII (1.8 g.), b.p. 44–46° (0.4 mm.) and recovered bromide, VI (6.0 g.), b.p. 66° (0.4 mm.). The infrared spectrum and other properties of the sample of VII obtained in this way were identical with those of the sample obtained in part A.

The addition of bromine in acetic acid to VII produced dibromide VIII, 6.2 g. (44%), m.p. 69–71° (lit.[19] m.p. 71–72°), infrared band (chloroform) at 5.85 μ (1709 cm.$^{-1}$), and a yellow oil which was distilled, b.p. 70–75°, $n_D^{26.5}$ 1.5030, d_4^{26} 1.284, infrared bands (film) at 6.00 and 6.13 μ, $\lambda_{max}^{C_2H_5OH}$ 238 μ (log ε, 3.48). These properties suggested that this substance was the unsaturated ketone resulting from loss of hydrogen bromide from dibromide VIII; however, it decomposed rather rapidly at room temperature and was not investigated further.

2,7-Dibromo-2,6,6-trimethylcycloheptanone (IX). The bromination of ketone V by the procedure of Wallach[9] produced IX in 73% yield as white needles, m.p. 65–67°, infrared bands (chloroform) at 5.80 (1724 cm.$^{-1}$) and 5.88 μ (1700 cm.$^{-1}$), (reported, lit.,[9] m.p. 68°).

Eucarvone (I). A slurry of ketone VII (7.6 g., 0.05 mole), *N*-bromosuccinimide (8.9 g., 0.05 mole) and carbon tetrachloride (50 ml.) was heated at reflux temperature for 3 hr. The succinimide was filtered, the solution washed with sodium bicarbonate, and water, and dried. The solvent was removed *in vacuo* and the residue (8.8 g.) was mixed with dry 2,6-lutidine (10.8 g., 0.10 mole) and heated at 85–90° for 3 hr. The reaction mixture was processed as in the preparation of VII from bromide VI. The first fraction (1.3 g.) was identified as eucarvone, b.p. 42–44° (1 mm.), $n_D^{24.8}$ 1.5051, $\lambda_{max}^{C_2H_5OH}$ 303 mμ (log ε, 3.83). The infrared spectrum was identical with that of a sample of eucarvone prepared from carvone.[4,6] Also the 2,4-dinitrophenylhydrazone melted at 151–153° alone or when mixed with an authentic derivative.

The second fraction from this reaction was carvacrol, XI, (3.2 g.), b.p. 52–53° (1 mm.), $n_D^{24.8}$ 1.5196, $\lambda_{max}^{C_2H_5OH}$ 278 mμ (log ε, 3.28). The identity of this product was established by comparison with an authentic sample of carvacrol obtained from the palladium catalyzed isomerization[20] of carvone.

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(19) O. Wallach, *Ann.*, 418, 58 (1919).

(20) R. P. Linstead, K. O. A. Michaelis, and S. L. S. Thomas, *J. Chem. Soc.*, 1139 (1940).

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE & CO.]

The Synthesis of Steroid Ring-E Pyrroles and Pyrrolidines

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The direct transformation of kryptogenin to pentacyclic heterocycles containing nitrogen in ring E has been achieved by the use of anhydrous ammonia and ammonium or amine salts of formic or acetic acids.

Ring closure of the 1,4-diketone system of sarsasapogenoic acid and 5,6-dihydrokryptogenin, by hydrogenation of the dioximes, to form steroid pyrrolidines analogous to the dihydrosapogenins was first reported by Uhle and Jacobs.[1] Uhle and Sallmann[2] recently published an alternate method, involving zinc and acetic-acid reduction of kryptogenin 16-phenylhydrazones, affording the pyrrolidine as well as an interesting pyrroline intermediate. We wish to direct attention to our earlier experiments in this field[3] which were apparently overlooked in the latter publication. Our methods permit preparation of either the pyrrole or the pyrrolidine and we offer them as useful adjuncts to the synthesis of 16,22-iminocholestane derivatives.

By the Leuckart reaction[4] kryptogenin was converted to 3β,26-dihydroxy-16β,22-imino-5-cholestene, II. The latter and its *O,O,N*-triacetyl derivative appear to be identical with the same structures lately reported[2]; we also prepared a crystalline hydrochloride. The melting point of our Leuckart product V agrees fairly well with the 3β,27-dihydroxy-16β,22-methylimino-5-cholestene of Uhle and Sallmann, who reported no optical rotation value, however.

These authors suggested an α-configuration for the C_{-22} hydrogen atom, relative to the projected plane of the molecule, by virtue of catalytic and borohydride reduction of their pyrroline to the pyrrolidine through "attack from the rear."[5] To this we would add the hypothesis that chemical reduction by Leuckart conditions, leading from I to II and to V, would also take place through rear side attack, giving rise to pyrrolidines possessing C_{-16} and C_{-22} hydrogens α-oriented with respect to the

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(1) F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, 160, 243 (1945).

(2) F. C. Uhle and F. Sallmann, *J. Am. Chem. Soc.*, 82, 1190 (1960).

(3) G. P. Mueller, U. S. Patent 2,740,781; *Chem. Abstr.*, 50, 10804a (1956).

(4) M. L. Moore, *Org. Reactions*, V, 301 (1949).