[CONTRIBUTION FROM THE ISRAELI MINISTRY OF DEFENSE AND THE WEIZMANN INSTITUTE OF SCIENCE]

The Condensation of 2-Hydroxy- and 2-Acetoxycyclohexanone with 1-Diethylamino-3-pentanone

BY JACOB SZMUSZKOVICZ AND HARRY BORN

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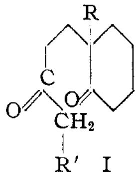
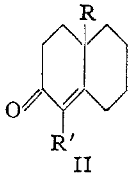
Previous work has demonstrated that alkyl vinyl ketones undergo the Michael condensation with 2-substituted cyclohexanones in the 2-position. It has now been shown that also in the case of 2-hydroxy- and 2-acetoxycyclohexanone, the condensation takes place at C_2.

The condensation of simple 2-substituted cyclohexanones with methyl and ethyl vinyl ketone, respectively, has been investigated fairly extensively, *e.g.*, in the case of the 2-methyl,[1] 2-carbethoxy,[1,2] 2-acetyl,[3] 2-formyl,[4] 2-phenyl[5] compounds.

In every case the condensation occurs at the already substituted 2- and not at the free 6-position, so that compounds of type I with a quaternary carbon atom and—after cyclization—substances of the general formula II containing an angular substituent, are obtained.



I



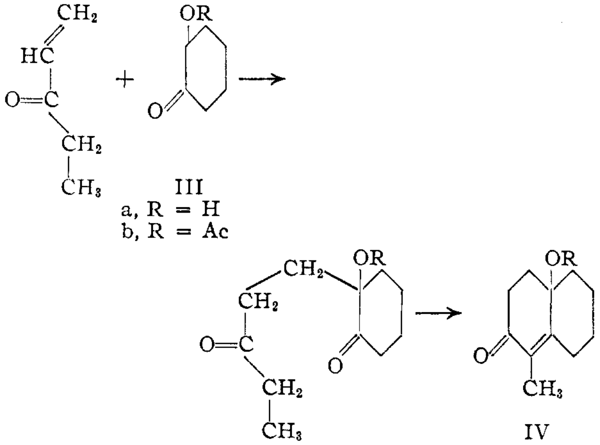
II

It has now been found that 2-hydroxycyclohexanone (IIIa) behaves like other substituted cyclohexanones. Condensed with the methiodide of 1-diethylamino-3-pentanone (as source of ethyl vinyl ketone) under the conditions described by Cornforth and Robinson[6] (but using sodium methoxide in place of potassium ethoxide), IIIa gives a good yield of 1-methyl-10-hydroxy-$\Delta^{1:9}$-octalone-2 (IVa).

The reaction conforms to this scheme, at least preponderantly, as from crude IVa the semicarbazone could be isolated in a yield of 70% (calcd. on III). The ultraviolet absorption spectra of IVa (λ_{max} 244, 312 mμ; log E 4.14, 1.90) and its semicarbazone (λ_{max} 270 mμ; log E 4.46) conform to those of an α,β-unsaturated ketone of the proposed structure.[7] Dehydration of IVa with oxalic acid in toluene gave rise to 1-methyl-2-keto-2,3,4,6,7,8-hexahydronaphthalene (V), λ_{max} 290 mμ, log E 3.95 (semicarbazone, λ_{max} 298 mμ, log E 4.51).

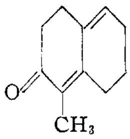
From the absorption spectrum of the crude dehydration product, one can conclude that the latter contains at least 75% of V. Dehydrogenation of V with palladium afforded 1-methyl-2-naphthol (VI) in 80% yield.

The reaction of 2-acetoxycyclohexanone (IIIb) with the methiodide of 1-diethylamino-3-pentanone follows a similar course as that of IIIa. When the crude reaction product was distilled, acetic acid was eliminated and a mixture of V and the known 1-methyl-5,6,7,8-tetrahydro-2-naphthol (VII) was obtained.

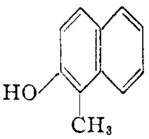


III
a, R = H
b, R = Ac

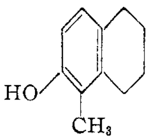
IV
a, R = H
b, R = Ac



V



IV



VII

The structure of V could be established beyond doubt; the compound was identical with a substance obtained by Birch[8] from 6-methoxy-1-tetralol by Oppenauer oxidation, methylation and lithium aluminum hydride reduction. The identification was carried out by determination of the ultraviolet spectrum, the mixed melting point, the crystallographic properties and the X-ray powder diagram of the two samples as 2,4-dinitrophenylhydrazone derivatives.

Although Birch did not prove the structure of his compound, which was a by-product in the synthesis, the position of the double bond (C_5–C_{10}) follows from the fact that it arises from the reduced carbonyl group at C_5 (C_1 in 6-methoxy-1-tetralone), and no other formula except V can explain the formation of the same substance by the two routes of synthesis.

Acknowledgment.—The authors are indebted to Dr. E. D. Bergmann, Prof. A. L. Wilds and Dr. R. Pappo for valuable discussions.

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[1] E. C. Du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937).

[2] F. J. McQuillin and R. Robinson, *ibid.*, 586 (1941).

[3] G. Büchi, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948).

[4] C. H. Shunk and A. L. Wilds, THIS JOURNAL, **71**, 3946 (1949); A. L. Wilds and C. H. Shunk, *ibid.*, **72**, 2388 (1950).

[5] V. Boekelheide, *ibid.*, **69**, 790 (1947).

[6] J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

[7] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Pub. Corp., New York, N. Y., 1949, p. 190.

[8] A. J. Birch, J. A. K. Quartey and H. Smith, *J. Chem. Soc.*, 1768 (1952).

Experimental[9]

2-Hydroxycyclohexanone.—2-Chlorocyclohexanone was hydrolyzed with potassium carbonate[10] to the corresponding hydroxy compound. The solid dimer of the latter was converted into the oily monomer by distillation *in vacuo*, immediately before use.[11]

2-Acetoxycyclohexanone.—This was prepared by refluxing the solid dimer (134 g.) of 2-hydroxycyclohexanone with 766 ml. of acetic anhydride for one hour. The reaction mixture was allowed to stand at room temperature for seven hours and the solvent distilled off at reduced pressure. Ether was added and the solution filtered and distilled. Thus, 154 g. (86%) of a white oil, b.p. 104.5–105° (8 mm.),[12] was obtained and crystallized on standing in the cold. Recrystallization from petroleum ether (b.p. 40–60°) afforded large prisms, m.p. 35–36°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.2; H, 7.5.

1-Methyl-10-hydroxy-$\Delta^{1:9}$-octalone-2 (IVa).—The reaction between 15.7 g. (0.1 mole) of diethylaminopentanone,[13] 14.2 g. (0.1 mole) of methyl iodide, 11.4 g. (0.1 mole) of 2-hydroxycyclohexanone in 90 ml. of anhydrous benzene and 3.45 g. (0.15 mole) of sodium in 90 ml. of absolute methanol (dried over magnesium methoxide) was carried out according to the directions of Cornforth and Robinson.[6] Acidification of the sodium hydroxide extract of the reaction mixture afforded no water-insoluble material. Upon evaporation of the ethereal solution, 17 g. of a viscous yellow oil was obtained which crystallized on standing in the cold; m.p. 54–56°. The sample for analysis was prepared by washing the crystals with petroleum ether (b.p. 40–60°); prisms, m.p. 54–56°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.9. Found: C, 73.8; H, 8.9.

Semicarbazone (prepared with semicarbazide acetate in dilute ethanol), m.p. (crude) 190°, after two recrystallizations from ethanol (white microscopic prisms) 192–193° (dec.).

Anal. Calcd. for $C_{12}H_{19}N_3O_2$: C, 60.8; H, 8.0; N, 17.7. Found: C, 60.6; H, 8.2; N, 17.8.

The **dinitrophenylhydrazone** was prepared at room temperature. Recrystallization from ethanol–chloroform afforded deep purple plates, m.p. 197–198°. This compound was identical with the dinitrophenylhydrazone prepared from the dienone V as shown below.

Anal. Calcd. for $C_{17}H_{18}N_4O_4$: C, 59.7; H, 5.3. Found: C, 59.7; H, 5.2.

The ultraviolet spectrum was measured in chloroform and showed maxima at 403 mμ (4.55), 312.5 mμ (4.17), 265 mμ (4.26).

1-Methyl-2-keto-2,3,4,6,7,8-hexahydronaphthalene (V). (**a**).—The semicarbazone of IVa (60 mg.), oxalic acid (0.5 g.) and 6 ml. of water were refluxed for one half hour. The resulting yellow solution was extracted with ether, and the ethereal layer washed with water, dried through anhydrous sodium sulfate and evaporated. The residual oil was treated with 0.2 g. of semicarbazide hydrochloride and 0.3 g. of sodium acetate in dilute ethanol. After a few hours, the solution was evaporated (40 mg.) and recrystallized from dilute ethanol. Pale yellow needles of the semicarbazone of V, m.p. 213–214° (dec.), were obtained.

Anal. Calcd. for $C_{12}H_{17}N_3O$: C, 65.7; H, 7.8. Found: C, 66.1; H, 7.9.

(**b**).—A mixture of crude IVa (1 g.), anhydrous oxalic acid (0.1 g.) and toluene (20 ml.) was distilled azeotropically for one hour. The reaction mixture was diluted with ether and the ethereal layer washed with water, dried through sodium sulfate and evaporated (*in vacuo*, during the later stage). The semicarbazone was prepared as above, m.p. and mixed m.p. 213–214° (dec.). The crude yellow oil (0.92 g.) was evaporatively distilled at 120° (1 mm.) and crystallized overnight. Trituration with petroleum ether (b.p. 40–60°) afforded prisms, m.p. 59–61°.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.3; H, 8.7.

The dinitrophenylhydrazone melted at 197–198° and was identical with the sample prepared from IVa.

1-Methyl-2-naphthol (VI).[14]—The crude dienone (V) (0.515 g.) was heated under reflux with 5 ml. of *p*-cymene (B.D.H., analytical grade) and 0.15 g. of 30% palladium-charcoal[15] for 2.5 hours. The mixture was filtered while still warm, the catalyst washed with ether, and the combined solution evaporated *in vacuo*. The residue crystallized immediately but retained tenaciously traces of *p*-cymene. Recrystallization from petroleum ether (b.p. 60–80°) afforded needles, m.p. 109–111° (0.325 g., 65% yield). One further recrystallization raised the melting point to 111–112° (reported m.p. 110°,[16] and 111°[17]). The mother liquor afforded a second crop, m.p. 109–111° (0.075 g., 15%).

Preparation of the picrate was attempted in ethanol, but no crystalline product separated. The solution was, therefore, evaporated to dryness and the residue recrystallized from a mixture of benzene and petroleum ether (b.p. 60–80°); red needles, m.p. 163–165° (reported 163–164°[17]).

The acetate (boiling acetic anhydride, anhydrous sodium acetate, two hours) formed prisms from petroleum ether, m.p. 66–67° (reported m.p. 66°[16]).

Condensation of 2-Acetoxycyclohexanone (IIIb) with 1-Diethylamino-3-pentanone.—The reaction between 1-diethylamino-3-pentanone (11.5 g.), methyl iodide (10.4 g.) and 2-acetoxycyclohexanone (11.5 g.) in 70 ml. of benzene, and 2.53 g. of sodium in 70 ml. of absolute methanol was carried out as in the case of 2-hydroxycyclohexanone. The product, a yellow oil, was distilled at 1 mm. through a seven-inch column packed with Pyrex glass beads (outside jacket temperature 190–195°). The first fraction (0.9 g.), b.p. 113–120°, was not investigated any further. The second fraction (2.5 g.), b.p. 120–125°, crystallized on standing, m.p. 59–61°. Trituration with petroleum ether (b.p. 40–60°) afforded prisms, m.p. and mixed m.p. with V, 59–61°.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.5; H, 8.7.

The third fraction (3.5 g.), b.p. 125–128°, crystallized immediately and after one recrystallization from petroleum ether (b.p. 60–80°), afforded elongated needles, m.p. 112–114°. Recrystallization from the same solvent gave 1-methyl-5,6,7,8-tetrahydro-2-naphthol (VII) of m.p. 113–114° (reported m.p. 113.5–114.5°[18]).

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.4; H, 8.4.

The methyl ether (dimethyl sulfate in dilute sodium hydroxide solution) showed a melting point of 48–50°, which was raised by recrystallization from dilute methanol to 50.5–51.5°. The substance formed colorless plates. Mixed melting point with the authentic sample (m.p. 50.5–51°[18]) showed no depression.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.8; H, 9.1. Found: C, 81.8; H, 8.9.

Synthesis of V According to Birch.[8]—The directions given by Birch were followed closely. From the intermediate 1,2,3,4,5,8-hexahydro-1-hydroxy-6-methoxynaphthalene, the dinitrophenylhydrazone of 2-keto-2,3,4,6,7,8-hexahydronaphthalene was prepared. It formed deep red plates from chloroform, m.p. 187–188°, λ_{max} 301 mμ (4.16), 402 mμ (4.56) in chloroform.

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[9] All melting points are uncorrected. The ultraviolet absorption spectra were determined by Dr. Y. Hirshberg and Mr. Ch. Eger with a Beckman quartz spectrophotometer; 95% ethanol was employed as solvent unless otherwise stated.

[10] P. D. Bartlett and G. F. Woods, This Journal, **62**, 2933 (1940).

[11] J. C. Sheehan, R. C. O'Neill and M. A. White, *ibid.*, **72**, 3376 (1950).

[12] L. P. Kyrides, *C. A.*, **38**, 1531 (1944), U. S. Patent 2,331,329; A. B. Boese and F. G. Young, *C. A.*, **40**, 3130 (1946), U. S. Patent 2,395,800; M. S. Newman, B. J. Magerlein and W. B. Wheatley, This Journal, **68**, 2112 (1946); W. Treibs and H. Bast, *Ann.*, **561**, 165 (1949).

[13] Prepared in 69% yield using McMahon's procedure (E. M. McMahon, J. N. Roper, W. P. Utermohlen, R. H. Hasek, R. C. Harris and J. H. Brant, This Journal, **70**, 2971 (1948)), as modified by Wilds (private communication, 1950).

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[15] R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

[16] K. Fries and E. Hübner, *Ber.*, **39**, 435 (1906); R. Robinson and F. Weygand, *J. Chem. Soc.*, 386 (1941).

[17] K. Dziewonski and C. Dragan, *Chem. Zentr.*, **106**, 2529 (1935).

[18] R. H. Martin and R. Robinson, *J. Chem. Soc.*, 491 (1943).

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: N, 17.1. Found: N, 17.0.

The **dinitrophenylhydrazone** of V melted at 193.5–195° (deep purple prisms from chloroform). Mixed m.p. with our sample was 194–196°. The ultraviolet spectrum was determined in chloroform and was identical with that of our sample.

The crystallographic investigation[19] gave the following result.

Both samples consisted of birefringent crystal plates bounded, in general, by three pairs of edges of unequal prominence at approximately 120° to each other. Both showed oblique extinction at an angle of about 25° to the longest edge.

The samples were proved to be crystallographically identical by 20-hour Debye–Scherrer photographs of finely powdered specimens with nickel-filtered copper K radiation. The identification was accomplished by visual inspection of the powder diagrams, in which at least eight prominent lines were clearly visible.

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[19] Kindly carried out by Mr. F. Hirshfeld, Laboratory of X-Ray Crystallography, Weizmann Institute of Science, Rehovoth, Israel.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Position of the Double Bond in Pseudosantonin

BY WILLIAM G. DAUBEN AND PAUL D. HANCE

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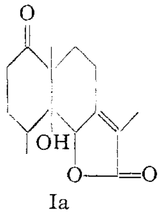
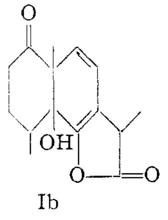
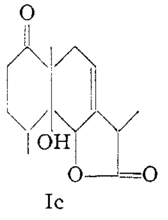
Pseudosantonin and its dihydro and tetrahydro derivatives have been studied spectroscopically and compared with model unsaturated esters and lactones. Examination of the ultraviolet and infrared spectra strongly suggests a β-γ'-type of unsaturation in pseudosantonin and its related compounds.

Since the reported isolation in 1935 of pseudosantonin, a constituent of the sesquiterpenic lactones obtained from *Artemisa maritima*, the structure and the chemistry of the compound has been the subject of considerable investigation.[1–7] On the basis of these researches, three isomeric structures (Ia, Ib, Ic) have been considered and prior to 1952 the structure Ic was thought to offer the most satisfactory explanation of the wide variety of reactions this sesquiterpenic lactone undergoes.

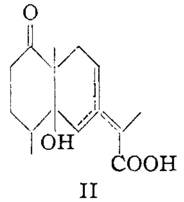
Early in 1952, Cocker, Cross and Hayes[8] reported evidence which led them to favor the alternate structure Ia. They found that pseudosantonin, in the infrared region, possessed an absorption band at 1745 cm.$^{-1}$, a value characteristic for $\Delta^{\alpha,\beta}$-butenolides[9] and, in the ultraviolet region, displayed a maximum of high intensity at 206 mμ, a distinctive feature for an isolated tetrasubstituted olefinic double bond.[10] They also reported that the acidic mixture obtained upon decomposition of the ozonide of pseudosantonin probably contained pyruvic acid, an acid only capable of being formed from a compound of structure Ia. The structure of this sesquiterpenic lactone also has been investigated in this Laboratory and we should like to report a detailed study of the spectra of pseudosantonin and its related hydrogenation products which was undertaken to establish the position of the double bond in the natural product.

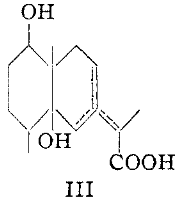

Ia

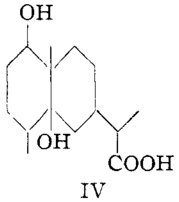

Ib


Ic

It has been shown[1] that when pseudosantonin (I) is hydrogenated in the presence of palladium in acetic acid the lactone ring undergoes hydrogenolysis and an acid, dihydropseudosantonin (II), is formed. When this dihydro derivative is allowed to react with sodium amalgam, reduction of the carbonyl group occurs and the resulting tetrahydropseudosantonin (III) is obtained. Further reduction of the tetrahydro derivative with platinum in acetic acid yields hexahydropseudosantonin (IV) which can also be obtained directly from pseudosantonin under the same conditions.


II


III


IV

The ultraviolet spectra of pseudosantonin and its hydrogenated derivatives are shown in Fig. 1. It was found that none of these compounds displayed a distinct maxima in the 205–250 mμ region.[11] The value of the extinction coefficients at 210 and 220 mμ are: pseudosantonin, 8300, 3500; dihydropseudosantonin, 4480, 2080; tetrahydropseudosantonin, 3680, 320; hexahydropseudosantonin, 160, 70, respectively.

The ultraviolet spectra of α,β- and β,γ-unsatu-

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[1] G. R. Clemo and W. Cocker, *J. Chem. Soc.*, 30 (1946).

[2] W. Cocker, *ibid.*, 36 (1946).

[3] W. Cocker and C. Lipman, *ibid.*, 553 (1947); see *ibid.*, 1519 (1950), for correction.

[4] W. Cocker and S. Hornsby, *ibid.*, 1157 (1947).

[5] W. Cocker, B. E. Cross and C. Lipman, *ibid.*, 959 (1949).

[6] W. Cocker and C. Lipman, *ibid.*, 1170 (1949).

[7] W. Cocker, B. E. Cross, A. K. Fateen, C. Lipman, E. R. Stuart, W. H. Thompson and R. R. A. Whyte, *ibid.*, 1781 (1950).

[8] W. Cocker, B. E. Cross and D. H. Hayes, *Chemistry and Industry*, 314 (1952).

[9] J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

[10] P. Bladon, H. B. Henbest and G. W. Wood, *ibid.*, 2737 (1952).

[11] As pointed out by Bladon, Henbest and Wood,[10] the maxima reported in the region of 205 mμ are only "apparent maxima" and are due to the contribution of false-energy factors which will vary with the instrument and the intensity of the light source. The maximum reported by Cocker and his co-workers obviously is such an "apparent maximum" and as such has no real significance.