[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XIV.[1] Bromination and Dehydrobromination of *cis*- and *trans*-2,9-Dimethyl-3-Decalones

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The *trans*-ketone (Ib) mentioned in the title was prepared by formylation-hydrogenation of *trans*-9-methyl-3-decalone. Monobromination of the isomeric ketones (Ia and Ib) afforded the corresponding 2-bromo compounds (IIa and IIb), which were converted to the *cis*- and *trans*-Δ^1-ketones (IIIa and IIIb), respectively. The dibromo compounds (IVa and IVb) of these ketones were dehydrobrominated to the same dienone (V), which underwent rearrangement to the phenol (VII). The latter was unequivocally established by synthesis. A possible mechanism for explaining differences in behavior toward dehydrobromination between the 2-bromo derivatives of 9-methyl- and 2,9-dimethyl-3-decalones is proposed.

In previous communications[2-4] from our laboratory, striking differences between 9-methyl- and 4,9-dimethyl-3-decalones in their behavior on bromination-dehydrobromination were disclosed. The former ketones, both *cis* and *trans*, gave the corresponding 2-bromo derivatives, which underwent rearrangement to the same Δ^4-ketone on collidine treatment. On the contrary, the isomers of 4,9-dimethyl-3-decalone were brominated at the 4-position and a normal dehydrobromination took place to yield the Δ^4-ketone. The 2,4-dibromo derivatives of these ketones were reacted with bases to give the expected cross-conjugated dienones, except that of *trans*-9-methyl ketone which was dehydrobrominated to the rearranged linear-conjugated dienone.

In the present work, these reactions were extended to *cis*- and *trans*-2,9-dimethyl-3-decalones (Ia and Ib). In view of the above results, it may be safely predicted that these two ketones with bromine would afford the corresponding 2-bromo and 2,4-dibromo compounds. It seemed of interest, however, to examine whether dehydrobromination of these bromo compounds is attended with rearrangement, as reported for some of the bromo compounds.

The *cis*-ketone (Ia)[4] with one equivalent of bromine gave a monobromo compound (IIa) which was treated with a variety of bases. There was always obtained the same unsaturated ketone (IIIa), which was characterized as its 2,4-dinitrophenylhydrazone. The Mattox-Kendall procedure[5] furnished the same hydrazone derivative. The location of the double bond at the 1- and 2-positions in IIIa rests mainly on the ultraviolet absorption spectrum, $\lambda_{\max}^{\text{EtOH}}$ 238 mμ (log ε 4.08), characteristic of an α,β-unsaturated ketone with two substituents.[6] Catalytic hydrogenation of the Δ^1-3-ketone gave only the starting *cis*-ketone (Ia) of steric homogeneity, probably supporting the structure (IIIa). Since reaction of the *cis*-monobromo ketone (IIa) with bases led invariably to the Δ^1-compound (IIIa), it is obvious that no rearrangements took place during dehydrobromination reactions of II. Therefore, this bromo ketone, as anticipated, can be assigned the 2-bromo structure (IIa).

Treatment of the *cis*-ketone (Ia) with two equivalents of bromine readily yielded a 2,4-dibromo compound (IVa), which was dehydrobrominated to the dienone (V), characterized as its 2,4-dinitrophenylhydrazone. The dienone had $\lambda_{\max}^{\text{EtOH}}$ 244 mμ (log ε 3.94), in agreement with the value expected for an α,β,α,'β'-unsaturated ketone.[6]

The *trans*-2,9-dimethyl ketone (Ib) was prepared by formylation and hydrogenation of *trans*-9-methyl-3-decalone[7] as reported for the *cis*-isomer (Ia).[4] The hydroxymethylene compound (VI), obtained in 70% yield as a solid, readily absorbed two equivalents of hydrogen over palladium-charcoal to furnish Ib in almost quantitative yield. The location of the newly introduced methyl group at the 2-position was evidenced by the non-identity with *trans*-4,9-dimethyl-3-decalone which was previously reported.[4]

Catalytic hydrogenation of 9-methyl-Δ^4-3-octalone (XXII) presents a convenient method for preparing *cis*-9-methyl-3-decalone on a laboratory scale.[8,9] From the hydrogenation mixture, the predominant *cis*-9-methylketone was isolated as crystals of low melting point, usually in 40–50% yield. Further separation of the mother oil, which has not

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(1) Paper XIII, M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958).

(2) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

(3) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

(4) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(5) V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948).

(6) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 190.

(7) M. Yanagita, K. Yamakawa, A. Tahara, and H. Ogura, *J. Org. Chem.*, **20**, 1767 (1955).

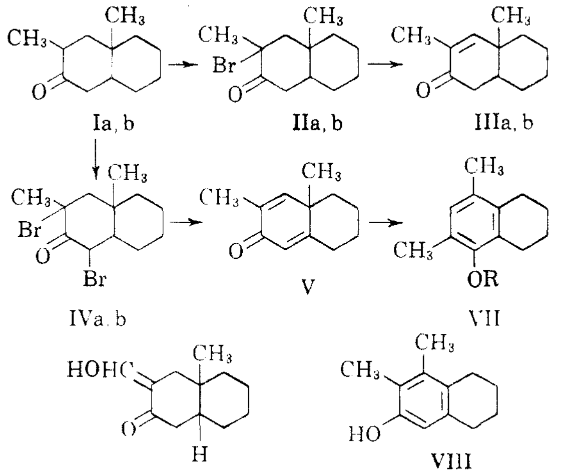
(8) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(9) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4226 (1952).

been recorded, was effected by conversion to the hydroxymethylene derivatives, and the above *trans*-derivative (VI) was isolated in 10% yield.

Monobromination of the *trans*-ketone (Ib) with bromine proceeded less readily than that of the *cis*-isomer (Ia). It has been reported from our laboratory[2] that in isomeric pairs of 9-methyl-3-decalone systems bearing no substituents at the 2-position, the *trans*-locked isomer is always more readily attacked by electrophilic reagents at the position α to the keto group than the *cis*-isomer. It is noteworthy that the relative reactivity of the isomers of 2,9-dimethyl-3-decalone toward bromine is opposite to this generalization. The *trans*-monobromide (IIb) was always dehydrobrominated to the *trans*-Δ^1-ketone (IIIb), the structure of which was proved on the same grounds as described for IIIa. This indicated that monobromination in the *trans*-ketone (Ib) also occurred at the 2-position. The 2-bromination of both isomers of 2,9-dimethyldecalone can be rationalized by the assumption that in conformations of these ketones (Ia and Ib), the Δ^2-enol structures are more favored than the Δ^3-enol structure by the electronic factor (hyperconjugation effect), as discussed earlier with the simple 3-decalone rings.[1,10]

A 2,4-dibromo derivative (IVb) of the *trans*-ketone was normally eliminated with γ-collidine or 2,4-dinitrophenylhydrazine to give the dienone (V) or its hydrazone. The use of anhydrous sodium acetate in place of these bases gave a mixture of the dienone (V) and the monoenone (IIIb), which were separated only with difficulty as the 2,4-dinitrophenylhydrazone. Elevation of the reaction temperature seems to favor the formation of the dienone.



Catalytic hydrogenation of the dienone (V) over palladium-charcoal resulted in a possible mixture of the isomeric ketones, from which only the predominant *cis*-ketone (Ia), as its 2,4-dinitrophenylhydrazone, was isolated after persistent recrystallization. It had been shown[4] that 4,9-dimethyl-Δ^4-3-decalone was catalytically hydrogenated to the *trans*-locked decalone as the chief product. The difference in behavior between these two types of Δ^4-3-octalones systems on hydrogenation is in accord with the previous argument[4] that the steric course in such hydrogenation is governed by the catalyst hindrance due to the combined effect of the substituents at the 4- and 9-positions in the 3-octalone ring.

The dienone-phenol rearrangement of V was readily carried out with acetic anhydride and concentrated sulfuric acid in the usual manner. Of the two possible structures (VII and VIII) for the rearranged product, the former seems preferable since the product has a different melting point from the compound (VIII) reported previously.[11] The structure of the phenol (VII) was unequivocally proved by the independent synthesis, as follows.

A route to the tetralol methyl ether (XII) from 2,4-xylenol methyl ether through IX, X, and XI was announced by Cocker and Lipman.[12] The yield in each step of this sequence was reported to be relatively low or unspecified. On repeating this reaction, it was found that their results are in some respects incompatible with the present observation. Correction of the melting point of certain intermediates as well as improvement in all steps were made, details of which will be described in the Experimental section. It is worthwhile, however, to mention here that, when an intermediate, the methoxybutyric acid (X), of high purity was heated with 48% hydrobromic acid in acetic acid, demethylation of the methoxyl group was accompanied by ring closure to form a tetralone (XIII) in 70% yield. No sizable amount of acidic product could be isolated from the reaction mixture. A similar result was obtained by substitution of hydrobromic acid with hydriodic acid. It was reported[12] that on reaction with hydriodic acid alone, the methoxybutyric acid (X) was converted to the normal hydroxy acid (XIV).[12] Since this reaction process was described only briefly, it could not be repeated exactly by the reported procedure, but the use of 57% hydriodic acid alone gave only the tetralone (XIII) in 90% yield. When the methoxybutyric acid of relatively low purity was employed in this reaction, the above hydroxy acid (XIV) was obtained together with XIII. Also it was found that the hydroxy acid (XIV) was converted, though in a low yield, to the tetralone (XIII) on similar treatment with hydrobromic acid. This tetralone, which was also obtained from XI by hydrobromic acid, was readily reduced by the Clemmensen procedure to the end product (VII, R=H), which was identified with the rearranged phenol from the dienone (V).

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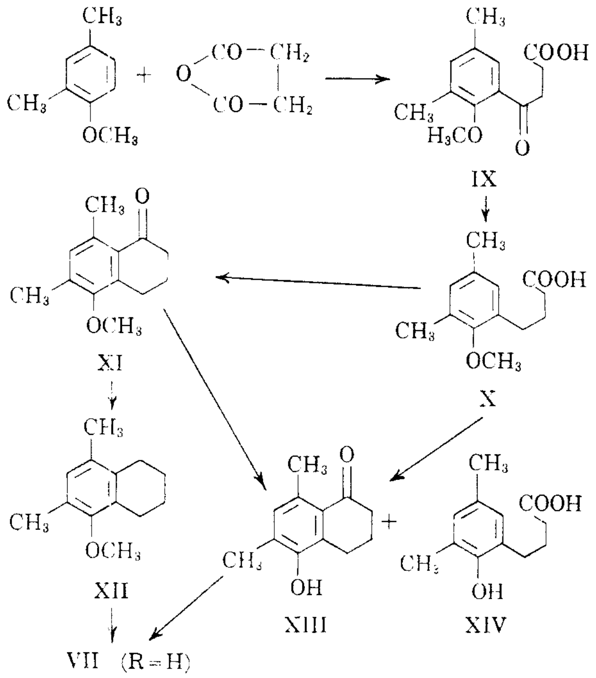
(10) A. S. Dreiding, *Chemistry & Industry*, 1419 (1954).

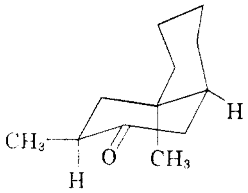
(11) W. Cocker, *J. Chem. Soc.*, 36 (1946).

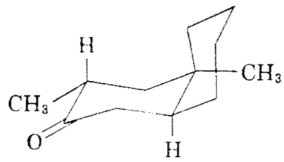
(12) W. Cocker and C. Lipman, *J. Chem. Soc.*, 533 (1947).

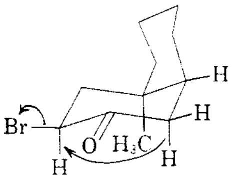


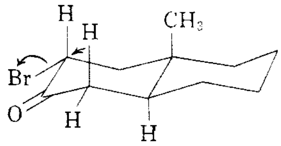
The methyl group at the 2-position in *cis*- and *trans*-2,9-dimethyl-3-decalones (Ia and Ib) is most likely to possess the equatorial orientation. The *cis*-ketone (Ia) can be represented by two conformations (XV and XVI), in which the former is assumed to be more favored by steric effects.[10] It was demonstrated[13] that in α-bromocyclohexanone rings with gem-dimethyl (or methylene) groups at the 4-position, the bromine preferably assumes an equatorial position. When the methyl group is present at the brominated 2-position, these cyclic ketones are shown to possess the methyl group equatorial and bromine axial, in a stable form.[14] Following these conclusions, the 2-bromo compounds of *cis*-[2] and *trans*-9-methyl-3-decalones[3] may possibly be assigned, respectively, the stereoformulas XVII[15] and XVIII, both carrying the bromine in an equatorial position. On the other hand, the 2-bromo derivatives (IIa and IIb) of *cis*- and *trans*-2,9-dimethyl-3-decalones are assumed to possess preferably an axial bromine, as shown in XIX and XX, respectively.

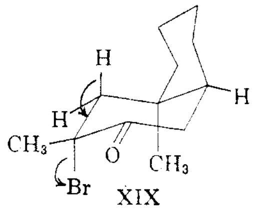
For explanation of the rearrangement during dehydrobromination of cyclic α-bromo ketones, a possible mechanism was offered involving an intermediate formation of cyclopropane ring.[16] A similar mechanism may possibly be applied to the conversion of the 2-bromo compounds of *cis*- and *trans*-9-methyl-3-decalones into the identical Δ^4-3-ketone (XXII).[2,3] It may be assumed that in

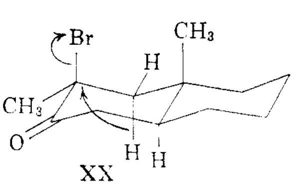

XV


XVI

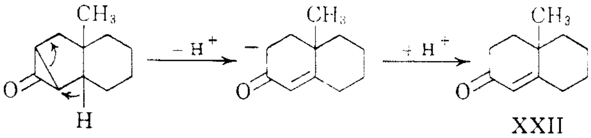

XVII


XVIII


XIX


XX

XVII and XVIII, extraction of axial hydrogen at the 4-position by a base and simultaneous separation of equatorial bromine would result in the formation of a 2,4-cyclopropane ring (XXI), involving a *trans*-steric course. Such transannular γ-elimination finds analogy in a plausible mechanism suggested by Shoppee and Summers[17] for explanation of 3,5-cyclosteroid rearrangements.[18] Ready elimination of hydrogen bromide from the 2-bromo compound (IIa and IIb) of 2,9-dimethyl-3-decalones to form the corresponding Δ^1-ketones is in accord with the stereoformulas (XIX and XX, respectively), both of which possess the most favorable geometry for ionic β-elimination.



EXPERIMENTAL[19]

All temperatures are uncorrected. Infrared absorption spectra were determined with a Perkin-Elmer Model 21 double-beam spectrophotometer.

Separation of cis- and trans-9-methyl-3-decalones from hydrogenation mixture of 9-methyl-Δ^4-3-octalone (XXII). The octalone (XXII, 5.7 g.) was catalytically hydrogenated over palladium-charcoal as reported previously.[2] The oily product was distilled with steam and the crystalline *cis*-isomer (2.61 g., 47%), m.p. 47°, was isolated. The remaining oil was distilled to give a colorless oil (3.00 g.), b.p. 95–97°

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(13) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953).

(14) S. Inayama, *Pharm. Bull. Japan*, **4**, 198 (1956).

(15) Of two possible conformations, only XVII, considered more stable, is used here.

(16) M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954); M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955); *cf.* M. Gates and G. M. K. Hughes, *Chemistry & Industry*, 1506 (1956).

(17) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(18) During the preparation of this manuscript, a similar mechanism for explanation of the Favorskii rearrangement of 3-ketosteroids was proposed by D. E. Evans, A. C. de Paulet, C. W. Shoppee, and F. Winternitz [*J. Chem. Soc.*, 1451 (1957)].

(19) Microanalyses were by Miss Ch. Shibuya; ultraviolet measurement by Miss M. Suzuki, both of this school.

at 3 mm., which formed a mixture of 2,4-dinitrophenylhydrazones, melting in the range 90–97°. Repeated recrystallization from ethanol separated only the hydrazone of the *cis*-isomer, m.p. 173–175°,[2] probably indicating that the oil consists mainly of the *cis*-ketone. This fraction was formylated by the procedure reported previously for *trans*-3-keto-9-methyl-$\Delta^{1,6}$-hexahydronaphthalene.[9]

Reaction of this fraction (2.68 g.) with ethyl formate (5.8 g.) in the presence of dried sodium methoxide (from 0.95 g. of sodium) in benzene (11 cc.) gave 2.95 g. of an alkali-soluble oil, which was kept in a refrigerator for 2 days. The 2-hydroxymethylene derivative (VI) of the *trans*-ketone (0.85 g., 10% from XXII) was obtained as yellow crystals, m.p. 68–70°. Recrystallization from petroleum ether raised the melting point to 75–75.5°, undepressed on admixture with an authentic sample described below.

A brown-red oil (1.84 g.), separated from the crystals, was heated in 20 cc. of 10% sodium hydroxide on a boiling water bath for 5 hr. The separated oil was taken up in ether, the ether solution was dried, and evaporated. The residual oil (1.30 g.) was distilled with steam, and the distillate was kept in a refrigerator, an additional 0.42 g. (6%) of the *cis*-ketone, m.p. 47–48° separating.

Attempt was made to effect separation of the above hydrogenation mixture with ethyl oxalate as described earlier for the separation of isomeric mixture of 4,9-dimethyl-3-decalones,[4] but it failed.

cis-2,9-Dimethyl-3-decalone (Ia) was prepared from *cis*-9-methyl-3-decalone by formylation and subsequent hydrogenation as reported previously.[4] The crude hydroxymethylene derivative was obtained in 93% yield. Distillation afforded a pure sample as a light yellow oil, b.p. 85–87° at 0.012 mm.; n_D^{20} 1.5300. Hydrogenation of the crude hydroxymethylene compound afforded a 88% yield of the 2,9-dimethyl ketone (Ia), which was distilled to give a colorless oil, b.p. 95–98° at 3 mm.; n_D^{19} 1.4893. This ketone formed the *2,4-dinitrophenylhydrazone* in four modifications, of which the one of yellowish brown crystals, m.p. 164–165°, was reported previously.[4] Two crystallizations from ethanol-chloroform (10:1) gave yellowish brown plates, m.p. 175–177°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.98; H, 6.97; N, 15.71.

Recrystallization from ethanol furnished a mixture of two forms, yellow needles, m.p. 183–184°, and orange-red prisms, m.p. 178°, which were separated mechanically.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found (sample of m.p. 183–184°): N, 15.87. Found (sample of m.p. 178°): C, 60.11; H, 6.78; N, 15.59.

This ketone gave, in quantitative yield, a semicarbazone, melting in the range 180–187°, which was recrystallized from ethanol to give cubes, m.p. 203–205° (sublim.).

Anal. Calcd. for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.77; N, 17.71. Found: C, 65.42; H, 9.43; N, 17.89.

With acid, it generated the parent ketone (Ia), b.p. 85–90° at 3 mm.; n_D^{20} 1.4870; λ_{max}^{EtOH} 235 mμ (log ε 1.51) and 284 mμ (log ε 1.28); $\nu_{C=O}$ 1709 cm.$^{-1}$ (liquid film).

trans-2-Hydroxymethylene-9-methyl-3-decalone (VI). *trans*-9-Methyl-3-decalone (4.24 g.), prepared from the above octalone (XXII) with lithium and liquid ammonia as reported previously,[7,20] was treated with ethyl formate (9.1 g.) in the presence of sodium methoxide (from 1.47 g. of sodium) by the procedure described above. The alkali-soluble fraction, which mostly solidified, was washed with a small amount of cold ethanol to give 3.45 g. (70%) of light yellow crystals, m.p. 70–72°. Two crystallizations from petroleum ether afforded white prisms, m.p. 75–75.5°. It gave violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.88; H, 9.53.

The crystals slowly decomposed at room temperature.

trans-2,9-Dimethyl-3-decalone (Ib). The above 2-hydroxymethylene compound (VI, 3.45 g.), m.p. 70–72°, was hydrogenated over palladium-charcoal (prepared from 8 cc. of 1% palladium chloride solution and 0.4 g. of charcoal). About 2 moles (825 cc., 104%) of hydrogen was absorbed in 1.5 hr. Removal of the catalyst and evaporation of the solvent left a pale yellow oil, which was fractionated to a colorless oil (2.90 g., 91%) b.p. 92–94° at 2 mm.; n_D^{20} 1.4888. This oil showed a negative test with alcoholic ferric chloride. It formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 142–144°, which was twice recrystallized from ethanol to brownish yellow needles, m.p. 149–150°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.90; H, 6.38; N, 15.97.

This ketone formed almost quantitatively a *semicarbazone*, melting in the range of 155–165°, which was recrystallized from dilute ethanol to colorless prisms, m.p. 187–190° (sublim.).

Anal. Calcd. for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.77; N, 17.71. Found: C, 65.81; H, 9.43; N, 17.90.

This derivative with acid regenerated the parent ketone, b.p. 85–90° at 3 mm.; n_D^{20} 1.4888; λ_{max}^{EtOH} 240 mμ (log ε 1.29) and 284 mμ (log ε 1.37); $\nu_{C=O}$ 1710 cm.$^{-1}$ (liquid film).

Monobromination and dehydrobromination of cis-2,9-dimethyl-3-decalone (Ia). This reaction sequence was carried out essentially as described previously for 4,9-dimethyl-3-decalone[4] and others.[2] The *cis*-ketone (Ia, 0.30 g.) was treated with 1 equivalent of bromine in chloroform. Bromine uptake took place smoothly to give the crude monobromide (IIa, 0.44 g.) in quantitative yield.

Dehydrobromination of the monobromide (IIa, 0.44 g.) with hot collidine (1.5 cc.) in a stream of nitrogen yielded 0.24 g. (63% as 1 equivalent) of the collidine salt. The monoenone (IIIa) was obtained as a pale yellow oil (0.15 g., 50%), b.p. 87–90° at 3 mm.; λ_{max}^{EtOH} 239 mμ (log ε 3.78). It formed in 90% yield a *2,4-dinitrophenylhydrazone* as red crystals, m.p. 120–124°, which was recrystallized from ethanol to red plates, m.p. 139°.

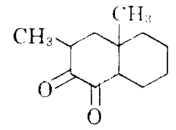
Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 59.92; H, 5.81; N, 15.46.

The monoenone (0.12 g.) was dissolved in a solution of semicarbazide hydrochloride (0.08 g.) and sodium acetate crystals (0.09 g.) in dilute methanol, and a little water was added until the appearance of turbidity. The separated oil began to solidify in a few days. After standing for three weeks, a solid (0.08 g.) was obtained. Recrystallization from dilute ethanol gave a *semicarbazone*, as prisms, m.p. 188–193°.

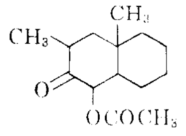
Anal. Calcd. for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.37; H, 8.59; N, 17.47.

Catalytic hydrogenation of the *cis*-monoenone over palladium-charcoal in methanol gave back the parent ketone (Ia), identified as its 2,4-dinitrophenylhydrazone, yellow-brown plates, m.p. 173–175° (mixed m.p.), after recrystallization from ethanol.

The monobromide (IIa, 0.44 g.) was treated with sodium acetate (0.30 g.) in glacial acetic acid (3 cc.). As the alkali-soluble product there was obtained a minute amount of a brown viscous oil, showing dark violet color with alcoholic ferric chloride. Presumably it indicated that this oil contained the α-diketone (XXIII), and hence, the neutral fraction was contaminated with the ketol acetate (XXIV).



XXIII



XXIV

After treatment with alkali to remove XXIV, the neutral oil was fractionated to 0.11 g. (37%) of a colorless oil, b.p. 93–98° at 4 mm., consisting mainly of the monoenone (IIIa). It formed in about 80% yield a red-brown 2,4-di-

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(20) *Cf.* ref. (4), footnote (22).

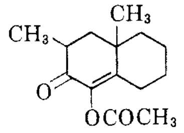
nitrophenylhydrazone, melting in the range of 150–230°. Two recrystallizations from ethanol gave the hydrazone of IIIa as red plates, m.p. 137–138° (mixed m.p.). The mother liquor of the first recrystallization of the above hydrazone furnished a small amount of red-brown plates, m.p. 280–281°, which was not further investigated.

Reaction of the monobromide (IIa, 0.15 g.) with 2,4-dinitrophenylhydrazone (0.15 g.) in hot glacial acetic acid (3 cc.) for 5 min. gave a red sirup (0.15 g.), which was chromatographed on neutral alumina. Elution with carbon tetrachloride furnished the hydrazone of the *cis*-monoenone (IIIa) as red plates (0.08 g.), m.p. 139° (mixed m.p.), after recrystallization from ethanol.

Dibromination and dehydrobromination of cis-2,9-dimethyl-3-decalone (Ia). This reaction sequence was carried out essentially as described previously for 4,9-dimethyl-3-decalone.[4] The yield of the crude dibromide (IVa) was quantitative. The dibromide (0.95 g.) was gently refluxed with γ-collidine (5 cc.) for 30 min., yielding the collidine salt (1.1 g., 95% as 2 equivalents). The product, a dark red viscous oil (0.41 g.), was fractionated to give 0.18 g. (36%) of the dienone (V) as a pale yellow oil, b.p. 105–106° at 6 mm., which on refractionation had b.p. 105–106° at 6 mm.; $\lambda_{\max}^{\mathrm{EtOH}}$ 244 mμ (log ϵ 3.98).

It formed in 82% yield a 2,4-dinitrophenylhydrazone, m.p. 157–162°, which was recrystallized from ethanol to deep red plates, m.p. 170°. It showed no depression of the melting point on admixture with a sample obtained from the *trans*-dibromide (IVb), which will be described below.

Treatment of IVa (0.95 g.) with sodium acetate (1.5 g.) in glacial acetic acid (5 cc.) gave a brown oil (0.52 g.) as the neutral product and a dark brown oil (20 mg.) as the alkali-soluble fraction. The latter showed dark green color with alcoholic ferric chloride, probably indicating the presence of the above α-diketone (XXIII) in it. It seems that the neutral fraction was contaminated with the enol acetate (XXV) of the α-diketone. On treatment with alkali to remove XXV, a pale yellow oil (0.17 g.) was obtained which was fractionated to 0.08 g. of the dienone (V), a colorless oil, b.p. 95–97° at 3 mm. It formed in 70% yield the 2,4-dinitrophenylhydrazone, m.p. 132–140°, which was recrystallized from ethanol to deep red plates, m.p. 170° (mixed m.p.).



XXV

Monobromination and dehydrobromination of trans-2,9-dimethyl-3-decalone (Ib). Employing the conditions described above for the *cis*-ketone (Ia), the *trans*-ketone (Ib) was brominated with bromine and then treated with bases. The monobromination started smoothly, but when about one third of bromine had been added, the bromine uptake became slow. After completion of the addition, the stirring was further continued for 1 hr. A yellow-brown solution gave in a quantitative yield the crude monobromide (IIb) as a brown oil. Treatment of IIb (0.30 g.) with γ-collidine gave, with the collidine salt (60% as 1 equivalent), the *trans*-monoenone (IIIb, 0.18 g., 60%), a pale yellow oil, b.p. 93–95° at 4 mm.; $\lambda_{\max}^{\mathrm{EtOH}}$ 239 mμ (log ϵ 4.0). It formed in 90% yield a *2,4-dinitrophenylhydrazone*, melting in the range of 132–144°, which was recrystallized from ethanol to red plates, m.p. 160–161°.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.33; H, 5.89; N, 15.45.

On standing with the semicarbazide in dilute acetic acid overnight, the monoenone (0.16 g.) much more readily formed a *semicarbazone* (0.15 g., 71%) than the *cis*-isomer (IIIb). It was recrystallized from dilute ethanol to white cubes (0.11 g., 50%), m.p. 215–217°.

Anal. Calcd. for $C_{13}H_{21}N_3O_4$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.56; H, 8.59; N, 17.68.

The semicarbazone with acid regenerated the parent ketone (IIIb), b.p. 130° at 4 mm. (bath temperature); $\lambda_{\max}^{\mathrm{EtOH}}$ 238 mμ (log ϵ 4.08).

Hydrogenation of the monoenone (IIIb) over palladium-charcoal gave only the *trans*-ketone (Ib), which was identified as the 2,4-dinitrophenylhydrazone, m.p. 148–150° (mixed m.p.), after two crystallizations from ethanol.

On reaction with sodium acetate and subsequent treatment with alkali, the monobromide (IIb, 0.30 g.) gave the *trans*-monoenone (IIIb, 0.03 g.), forming in about 80% yield the 2,4-dinitrophenylhydrazone, melting in the range of 68–102°. Five recrystallizations from ethanol gave red plates, m.p. 160–161° (mixed m.p.).

Dibromination and dehydrobromination of trans-2,9-dimethyl-3-decalone (Ib) was carried out essentially by the procedure described above for the *cis*-ketone (Ia). Dibromination of Ib (0.5 g.) was effected by slow addition of bromine for 70 min. The crude dibromide (IVb, 0.91 g., 95%) was obtained as a light brown oil which was used without delay for dehydrobromination with bases.

Collidine treatment of IVb afforded the dienone as a pale yellow oil, b.p. 100–107° at 4 mm.; $\lambda_{\max}^{\mathrm{EtOH}}$ 243 mμ (log ϵ 3.9). On standing with Brady's reagent overnight, it formed quantitatively a *2,4-dinitrophenylhydrazone* as red plates m.p. 162–167°. Three recrystallizations from ethanol raised the m.p. to 171°. It showed an obvious depression (about 15°) of the melting point on admixture with the same derivative of the *trans*-monoenone (IIIb), m.p. 160–161°.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.40; H, 5.90; N, 15.91.

When the reflux time with collidine was shortened to 20 min., the reaction was incomplete.

An oily product from acetolysis of the dibromide (IVb) formed a mixture of 2,4-dinitrophenylhydrazones, from which a minute amount of derivatives of the *trans*-monoenone (IIIb) and the dienone (V) was separated only after tedious procedure. Therefore, the elimination reaction was conducted under more drastic conditions.

The *trans*-dibromide (IVa, 1.00 g.), prepared from 0.52 g. of the ketone (Ib), was heated to reflux with 1.50 g. of anhydrous sodium acetate in 5 cc. of glacial acetic acid for 3 hr. The dark red mixture was worked up as described above for the *cis*-dibromide (IVa). There was obtained, with the acidic product (0.015 g., positive ferric chloride test), a neutral dark oil (0.29 g.), which was fractionated to a yellow oil (0.16 g.), b.p. 100–115° at 3 mm. Alkali treatment of this distillate afforded a neutral brown oil, which was refractionated to a pale yellow oil (0.07 g., 14%), b.p. 95–102° at 3 mm.

It formed the 2,4-dinitrophenylhydrazone, m.p. 161–164°, of the dienone (V). Two recrystallizations from ethanol afforded red plates, m.p. 169–170° (mixed m.p.).

The mother liquor of the crystallization of the above hydrazone furnished a red solid (0.04 g.), from which a minute amount of the hydrazone of the *trans*-monoenone (IIIb) was isolated after chromatography on alumina (elution with carbon tetrachloride).

Hydrogenation of 3-keto-2,9-dimethyl-$\Delta^{1,4}$*-hexahydronaphthalene* (V). The dienone (V, 0.09 g.) was hydrogenated over palladium-charcoal (prepared from 1 cc. of 1% palladium chloride solution and 0.05 g. of charcoal) in 3 cc. of methanol. Hydrogen absorption (20.8 cc., 84% as 2 moles) almost ceased in about 10 min. After removal of the catalyst, the solution was distilled to a small bulk and Brady's reagent was added. On standing overnight, the 2,4-dinitrophenylhydrazone (0.15 g., 83%) was obtained as a brown crystalline powder, melting in the range of 98–107°. Persistent fractional recrystallization from ethanol-chloroform (5:1) afforded the hydrazone (0.075 g., 42% from V), m.p. 170–173°, of the *cis*-ketone (Ia). Further recrystallization from the same solvent mixture raised the m.p. to 175–177° (mixed m.p.).

From the mother liquor of the above hydrazone, the derivative of the *trans*-ketone (Ib) could not be isolated in a pure state.

Dienone-phenol rearrangement of 3-keto-2,9-dimethyl-$\Delta^{1,4}$-*hexahydronaphthalene* (V). To a solution of 0.05 g. of the dienone (V) in 3 cc. of acetic anhydride was added 1 cc. of a mixture of 10 cc. of acetic anhydride and 0.18 cc. of concentrated sulfuric acid, and the mixture was allowed to stand for 2 days. The reaction solution was mixed with water and colorless elongated needles soon separated. After standing in a refrigerator overnight, the crystals (0.05 g., 83%), m.p. 62–63°, were collected. Recrystallization from dilute methanol did not raise the melting point. It showed no depression of the melting point on admixture with the acetate (VII, R = $COCH_3$) of 1,3-dimethyl-*ar*-4-tetralol described below.

The acetate (0.03 g.) was heated with concentrated hydrochloric acid in ethanol as usual.[4] Evaporation of the solvent at reduced pressure left yellowish needles, which were dissolved in 20% sodium hydroxide and washed with ether. Acidification of the alkali solution deposited the tetralol (VII, R = H) as white elongated needles (0.02 g.), m.p. 76–77°. Recrystallization from dilute methanol raised the m.p. to 77–78°, undepressed on admixture with 1,3-dimethyl-*ar*-4-tetralol described below.

Methyl 2,4-xylenol ether. 2,4-Xylenol (5 g.) was methylated with dimethyl sulfate (10 g.) in 15% sodium hydroxide and the methyl ether was obtained as a colorless liquid (4.9 g., 88%), b.p. 73–75° at 13 mm. (reported, b.p. 188–191°[12]).

β-(3,5-Dimethyl-6-methoxybenzoyl) propionic acid (IX) was prepared by an effective variation of the method reported by Cocker and Lipman.[12] To a stirred solution of 8.8 g. of the above xylenol methyl ether and 7.0 g. of succinic anhydride in 50 cc. of nitrobenzene was added, in small portions, 22 g. of powdered aluminum chloride, and the temperature of the mixture was controlled within the range 35–40° by external cooling. After the addition was completed, the stirring was maintained for an additional 2 hr. at this temperature. The dark red mixture was poured into dilute hydrochloric acid and shaken with ether. The ether extract was washed with water and the solvent was removed by distillation with steam. The residual brown crystals were dissolved in 10% sodium carbonate and filtered. Acidification of the filtrate deposited crystals which were collected after standing in a refrigerator overnight. There was obtained 11.9 g. (65%) of the keto acid (IX), m.p. 121–124°, which was of sufficient purity to be used for the following step. A pure sample was prepared by recrystallization from dilute acetic acid as elongated white needles, m.p. 129–130° (reported m.p. 129–130°[12]).

γ-(3,5-Dimethyl-6-methoxyphenyl)butyric acid (X) was prepared by an effective variation of the method reported by Cocker and Lipman.[12] The above crude keto acid (IX, 3.0 g.), m.p. 121–124°, in 3 cc. of toluene was heated to reflux with 9 g. of zinc amalgam (prepared from 9 g. of granular zinc and a solution of 0.5 g. of mercuric chloride in 10 cc. of water containing 0.5 cc. of hydrochloric acid), 3 cc. of water, and 7 cc. of concentrated hydrochloric acid. After heating for 6 hr., a further 1 cc. of concentrated hydrochloric acid was added and the refluxing was continued for an additional 12 hr. On cooling, white crystals separated, which, after addition of the same volume of water, were taken up in ether. The separated organic layer was shaken with 10% sodium carbonate and the carbonate solution was filtered. Acidification of the filtrate deposited 2.5 g. (89%) of the butyric acid (X), m.p. 114–119°. Recrystallization from benzene-petroleum ether gave white plates, m.p. 120–121°. Cocker and Lipman[12] reported m.p. 92–93°. Their sample may be impure since no pure compounds of such low melting point were encountered in the present work.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.95; H, 7.65.

Cocker and Lipman[12] reported the isolation of the hydroxy acid (XIV), m.p. 116–117°, as a by-product during the Clemmensen reduction of the keto acid (IX) with relatively concentrated hydrochloric acid in the absence of toluene. This hydroxy acid, the preparation of which is described below, was not isolated in the present experiment.

1-Keto-6,8-dimethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (XI). The above crude methoxy acid (X, 1.5 g.), m.p. 114–119°, was treated with concentrated sulfuric acid (9 cc.) as described earlier for the preparation of 1-keto-5,8-dimethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene.[4] There was obtained the tetralone (XI), (1.02 g., 74%) as brown needles, m.p. 36–39°. Fractionation gave an oil (1.02 g., 74%), b.p. 145–147° at 6 mm., which immediately solidified, m.p. 38–40°. Recrystallization from petroleum ether furnished white prisms, m.p. 41°. Cocker and Lipman[12] reported m.p. 61.5–62° for the tetralone (XI) prepared from the above "methoxy acid (X)," m.p. 92–93°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 75.84; H, 7.85.

5,7-Dimethyl-8-methoxy-1,2,3,4-tetrahydronaphthalene (*methyl 1,3-dimethyl-ar-4-tetralol ether*) (XII). The above methoxy ketone (XI, 0.9 g.), m.p. 38–40°, was reduced by the Clemmensen procedure as described above for the butyric acid (X). The product (0.85 g.), a yellowish brown liquid, was distilled to give a pale yellow oil (0.57 g., 68%), b.p. 114–116° at 4 mm. Refractionation afforded a colorless oil, b.p. 108–110° at 3 mm.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.29; H, 9.65.

Cocker and Lipman[12] claimed that the Clemmensen reduction of the "tetralone (XI)," m.p. 61.5–62°, yielded this tetralol methyl ether, b.p. 128° at 3 mm., which solidified to colorless needles (the melting point was not given).

1,2-Dimethyl-ar-4-tetralol (VII, R = H). This was prepared from the above tetralol methyl ether (XII, 0.20 g.) by refluxing with a mixture of glacial acetic acid (1 cc.) and 48% hydrobromic acid (2 cc.) for 3 hr. On standing overnight, the dark red solution deposited the tetralol (VII, R = H) as elongated needles, m.p. 75–76°. Additional crystals (total 0.14 g., 97%) were obtained from the mother liquor on addition of water. Recrystallization from dilute methanol and then from petroleum ether gave colorless needles, m.p. 78°.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.33.

The tetralol (0.1 g.) was added to a mixture of 1 cc. of acetic anhydride and a drop of concentrated sulfuric acid, and warmed at 40–50° for 10 min. Water was added to the reaction and soon the *acetate* (VII, R = $COCH_3$) separated as brown needles (0.12 g., 99%), m.p. 60–63°. Recrystallization from dilute methanol gave colorless needles, m.p. 64–65°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 67.18; H, 7.25. Found: C, 67.39; H, 7.27.

Reaction of γ-(3,5-dimethyl-6-methoxyphenyl)butyric acid (X) with hydrobromic acid. The pure methoxybutyric acid (X, 0.20 g.), m.p. 120–121°, was treated with hydrobromic acid exactly as described for XII. The dark red solution was poured into water, extracted with ether, and the ether layer was washed with bicarbonate solution and then with water. Evaporation of the dried ether solution left 0.13 g. (76%) of 1-keto-6,8-dimethyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene (XIII) as yellowish crystals, m.p. 58–60°. Recrystallization from dilute ethanol afforded white needles, m.p. 60–61°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.78; H, 7.50.

Similar treatment of the methoxytetralone (XI, 0.20 g.) with hydrobromic acid gave the same hydroxy tetralone (XIII) (0.18 g., 97%), m.p. 58–60°, which was recrystallized from dilute methanol to needles, m.p. 61°. (mixed m.p.). It formed a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethanol to red silk-like needles, m.p. 273°.

Anal. Calcd. for $C_{18}H_{18}N_4O_5$: N, 15.13. Found: N, 15.40.

Clemmensen reduction of the hydroxytetralone (XIII, 0.20 g.) led to a quantitative yield of the tetralol (VII, R = H) as brown crystals, m.p. 71–75°. Recrystallization from dilute methanol afforded colorless needles, m.p. 78° (mixed m.p.).

When the relatively impure specimen of the methoxy acid (X) was used in the above reaction, a different result was obtained. X (0.70 g.), m.p. 114–115°, was treated with 48% hydrobromic acid (7 cc.) in glacial acetic acid (3.5 cc.), as described above. Along with the tetralone (XIII, 0.11 g., 20%), an acid (XIV, 0.13 g., 19%) was obtained as brown needles, m.p. 110–113°. Recrystallization from water gave colorless elongated needles, m.p. 116–117°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.27; H, 7.80.

Shortening (1 hour) of the reflux time in this reaction increased the yield of the two products, XIII (23%) and XIV (50%).

Based on the identity of the melting points, this hydroxy acid (XIV) is assumed to be identical with the sample of Cocker and Lipman,[12] which was obtained either by Clemmensen reduction of the keto acid (IX) or by reaction of "the methoxy acid (X)," m.p. 92–93°, with hydriodic acid.

Reaction of γ-(3,5-dimethyl-6-methoxyphenyl)butyric acid (X) with hydriodic acid. By the procedure described in the preceding paragraph, the pure methoxy acid (X, 0.2 g.) was treated with 57% hydriodic acid-glacial acetic acid, except that the refluxing time was shortened to 2 hours. The tetralone (XIII, 0.11 g.) m.p. 56–58° (mixed m.p.) was obtained in 64% yield. Also, the use of hydriodic acid alone raised the yield of the tetralone (XIII) to 91%.

Reaction of γ-(3,5-dimethyl-6-hydroxyphenyl)butyric acid (XIV) with hydrobromic acid. The hydroxy acid (XIV, 0.2 g.) was treated with 48% hydrobromic acid-glacial acetic acid, exactly as described above for the methoxy acid (X). From the alkali-soluble fraction, the starting acid (0.12 g., 60%) was recovered. The neutral fraction gave the hydroxy-tetralone (XIII, 0.04 g., 23%), m.p. 59–60° (mixed m.p.), after recrystallization from dilute ethanol.

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Reaction of 2,4-Dibromomenthone with Zinc and Ethanol. Investigation of the Thujone of Guha and Nath

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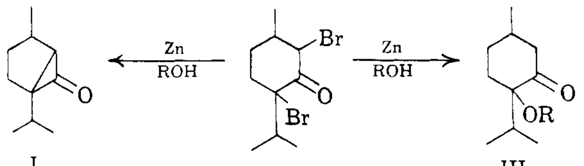
It was reported by Guha and Nath that a cyclopropanone, thujone, was formed in the reaction of 2,4-dibromomenthone with zinc and ethanol. It has been found that the product actually is an ethoxymenthone, most likely the 4-substituted derivative.

The formation of a transient cyclopropanone in the reaction of an α-haloketone with base has been postulated by Loftfield[1] on the basis of results obtained in his study of the Favorski rearrangement. Although such an intermediate could well be expected to show the reactions postulated,[2] little is known about such small ring ketones. The preparation of cyclopropanones has been claimed many times but in most cases the proof of structure was not definitive.[3-8] One case of special interest is that of a thujone (I)[5] in view of its similarity to the postulated intermediate of Loftfield. Guha and Nath[5] reported that when 2,4-dibromomenthone (II) was allowed to react with zinc and ethanol, the thujone (I) was obtained. The proof of structure was based upon elementary analysis, carbonyl derivatives, reduction to thujane with zinc and hydrochloric acid, and reduction to menthol with sodium and ethanol. If, indeed, the material was a cyclopropanone, it possessed a chemical reactivity entirely different from that expected on the basis of the work of Loftfield. In order to establish the structure of the compound of Guha and Nath, the reaction of 2,4-dibromomenthone has been reexamined.



I II III

When 2,4-dibromomenthone was allowed to react with zinc and ethanol, a 50% yield of a material possessing the physical properties reported by Guha and Nath[5] was obtained. Care had to be taken in the distillation of the material since it was found that upon prolonged distillation through an efficient column, the elements of ethanol were lost and an unsaturated product slowly formed. The elemental analysis of the product, however, differed from that expected for a thujone (I). A Zeisel ether determination established the presence of one

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