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.

[Contribution from the Department of Chemistry, University of California, Berkeley]

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

I   II   III
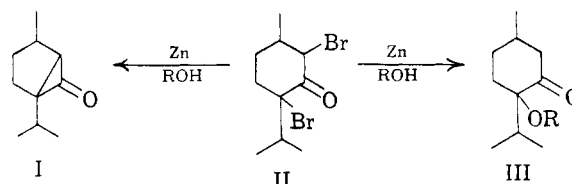
thujone (I) was obtained. The proof of structure was based upon elementary analysis, carbonyl derivatives, reduction to thujane with zinc and hydrochloric acid, and reduction to menthol with sodium and ethanol. If, indeed, the material was a cyclopropanone, it possessed a chemical reactivity entirely 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.

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

(1) R. B. Loftfield, *J. Am. Chem. Soc.*, **72**, 632 (1950); R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951); R. B. Loftfield and L. Schaad, *J. Am. Chem. Soc.*, **76**, 35 (1954).

(2) For an alternate explanation of the results, see J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).

(3) C. K. Ingold, *J. Chem. Soc.*, **119**, 305 (1921); C. K. Ingold, S. Sako, and J. F. Thorpe, *J. Chem. Soc.*, **121**, 1177 (1922).

(4) P. Lipp, J. Buchkremer, and H. Seeles, *Ann.*, **499**, 1 (1932).

(5) P. C. Guha and B. Nath, *Ber.*, **70**, 931 (1937).

(6) N. Ya. Demyanov and V. V. Feofilaktov, *J. Gen. Chem.*, (U.S.S.R.), **9**, 340 (1939).

(7) J. F. Cogdell and O. R. Quayle, 118th Meeting of the American Chemical Society, Chicago, 1950, p-6N.

(8) M. Mousseron, R. Jacquier, and R. Fraisse, *Compt. rend.*, **243**, 1880 (1956).

ethoxyl grouping and all data fit a formula best represented as an ethoxymenthone (III). The ultraviolet spectrum showed the presence of a normal isolated carbonyl grouping (λ_{max} 302 mμ, log ϵ 1.5) and the infrared spectrum showed absorption at 5.83μ which also is characteristic of the same grouping. In addition, bands at 8.91 and 8.98μ, characteristic of ethereal linkages, were present. The compound did not react with Tollen's reagent, sodium nitroprusside or bromine but did form a semicarbazone which melts in the range reported by Guha and Nath.[5] The analytical data for this derivative also fit a structure related to an ethoxymenthone. In order to establish the generality of the reaction of the dibromide, methanol also was employed as the solvent and in this case a methoxymenthone was obtained. On the basis of the present work, it must be concluded that the material obtained by Guha and Nath[5] was not the cyclopropanone derivative postulated.

In an attempt to locate the alkoxyl grouping, the material was allowed to react with p-nitrobenzaldehyde and a mono-p-nitrobenzal derivative of the ethoxymenthone was obtained. This result suggested the presence of a methylene grouping adjacent to the carbonyl function and eliminated C_2 as a possible location for the ethoxyl grouping.

When ethoxymenthone was treated with hydrochloric acid, Δ^4-menthenone was obtained. This product was characterized as the 2,6-dibenzal derivative and possessed an ultraviolet spectrum identical with authentic material. The isolation of this degradation product indicated that the alkoxyl group was present either on C_4 or C_5 of the ring or on C_8 of the isopropyl sidechain, $i.e.$, α or β to the carbonyl grouping.

The reaction of ethoxymenthone with 2,4-dinitrophenylhydrazine in hot alcoholic hydrochloric acid indicated that the ethoxyl group was located on the ring. It was found that the 2,4-dinitrophenylhydrazone formed had lost the elements of ethanol and possessed a λ_{max} at 379 mμ (ϵ 26,000). When this derivative (m.p. 141.0–143.3°), was admixed with the 2,4-dinitrophenylhydrazone of Δ^4-menthenone (m.p. 143.9–144.2°), no depression in melting point was observed. That the derivative of menthenone was the original product formed and not a rearrangement product of pulegone was shown by the preparation of the 2,4-dinitrophenylhydrazone of the latter compound (m.p. 147.5–148.5°) under the same acidic conditions. The pulegone derivative depressed the melting point (to 130–132°) of the derivative obtained from ethoxymenthone or Δ^4-menthenone upon mixing.

To differentiate between the C_4 and C_5 positions on the ring, the stability of the ethoxymenthone toward base was studied since an alkoxyl group at C_6 being β to the ketone should be lost with great facility. As it is known that such a reaction is re-

versible,[9] the stability of Δ^4-menthenone and pulegone towards alcoholic potassium hydroxide was studied. It was found that neither compound showed any tendency to add the elements of ethanol during the course of 7 days. When ethoxymenthone was subjected to similar reaction conditions, no band characteristic of either unsaturated ketone developed. These experiments support an assignment of the ethoxyl grouping at C_4 on the ring.

EXPERIMENTAL[10]

Ethoxymenthone. A mixture of 110 g. (0.35 mole) of 2,4-dibromomenthone (m.p. 76–77°)[11] and 71.5 g. of zinc (1.1 moles) in 275 ml. of absolute ethanol was stirred at room temperature for 24 hr. and then refluxed on a steam bath for 24 hr. The reaction mixture was filtered and acidified with aqueous 5% sulfuric acid. The insoluble layer was removed, diluted with ether, and the ethereal solution dried. After removal of the solvent, the product was distilled from a Claisen flask, b.p. 95–102° (10 mm.), $[\alpha]_D^{21}$ + 26.7° (CHCl$_3$), n_D^{20} 1.4526, yield 33.2 g. (51%) [lit.[5] b.p. 110–112° (14 mm.), $[\alpha]_D^{26}$ + 25.1° n 1.4505.] The ultraviolet spectrum showed a maximum at 302 mμ (ϵ 30), characteristic of an isolated ketone, and a maximum at 236 mμ (ϵ 160), indicating 1–2% of a conjugated unsaturated ketone (Δ^4-menthenone).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; OEt, 22.72. Found: C, 72.60; H, 11.29; OEt, 22.32.

The semicarbazone was prepared using semicarbazide hydrochloride and sodium acetate in ethanol and allowing the reaction mixture to reflux for 5 hr. The crude product was recrystallized from aqueous ethanol, m.p. 182.5–184.5°.

Anal. Calcd. for $C_{13}H_{25}O_2N_3$: C, 61.14; H, 9.87; N, 15.46. Found, C, 61.58; H, 9.89; N, 16.10.

The 2,4-dinitrophenylhydrazone was prepared by heating the ethoxymenthone with an ethanolic hydrochloric acid solution of 2,4-dinitrophenylhydrazine. The crude product was recrystallized twice from ethanol, m.p. 141.0–143.2°, λ_{max} 379 mμ (ϵ 26,000).

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: C, 57.82; H, 6.07. Found: C, 57.62; H, 6.01.

The p-nitrobenzal derivative was prepared by allowing the ether to react with p-nitrobenzaldehyde and sodium ethoxide in absolute ethanol solution. The product was recrystallized from benzene-ethanol, m.p. 135.0–136.0°.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.08; H, 7.65; N, 4.17.

Methoxymenthone. This material was prepared as described above except that absolute methanol was used as the solvent. Starting with 62 g. (0.2 mole) of the dibromide there was obtained 14 g. (41%) of product, b.p. 85–88° (10 mm.), n_D^{20} 1.4452.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; OMe, 16.84. Found: C, 71.94; H, 11.04; OMe, 16.52.

Cleavage of ethoxymenthone with hydrochloric acid. A mixture of 10 g. (0.055 mole) of ethoxymenthone and 130 ml. of 6N hydrochloric acid was refluxed for 6 hr. During the course of this period, 6 ml. of concentrated hydrochloric acid was added each hour. At the end of this time, the mixture was steam distilled, the distillate saturated with sodium chloride, and extracted with ether. The ethereal solution was dried, the solvent removed and the product distilled, b.p. 106–109° (20 mm.), n_D^{23} 1.4730, λ_{max} 236 mμ (log ϵ 3.96),

(9) D. K. Fukashima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).

(10) Analyses were performed by the Microanalytical Laboratory of the Department of Chemistry, University of California, Berkeley.

(11) O. Wallach, *Ann.*, **414**, 296, 333 (1918).

yield 5.3 g. (65%). Authentic Δ^4-menthenone prepared from Δ^3-menthene nitrosochloride[12] has the following properties: n_D^{23} 1.4710, λ_{max} 236 mμ (log ϵ 3.97).

The dibenzal derivative was prepared by allowing the cleavage product to react with benzaldehyde in absolute ethanol in the presence of sodium ethoxide. The product

(12) J. Reid and G. J. Robertson, J. Chem. Soc., 2209 (1926).

was recrystallized from ethanol and sublimed, m.p. 138–139°, λ_{max} 275 mμ (log ϵ 4.35) [lit.[13] 140–141°].

Anal. Calcd. for $C_{24}H_{24}O$: C, 87.76; H, 7.36. Found: C, 87.86; H, 7.31.

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(13) O. Wallach, Ann., 397, 214 (1913).

Contribution to the Study of Marine Products. XLVI. 24- and 25-Dehydrocholesterol

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24- and 25-dehydrocholesterol have been prepared from 25-ketonorcholesterol. The identity of desmosterol and 24-dehydrocholesterol has been substantiated.

Desmosterol is one of the two new sterols which Stokes, Fish, and Hickey[1] have recently isolated from chick embryos. It shows some superficial resemblance to 25-dehydrocholesterol[2,3] (IIa) but the absence in its infrared spectrum of a strong band at 11.3μ indicated a lack of terminal unsaturation and consequently a difference in the two compounds. On the basis of other chemical evidence, and on good biogenetic grounds, the authors drew the significant conclusion that desmosterol is 24-dehydrocholesterol (IVa), a compound assumed to be one of the final steps in the biosynthesis of cholesterol.

Since it is to be expected that desmosterol will be encountered in many other natural sterol mixtures, its preparation and that of its 25-dehydro-isomer have been included in the program of synthesis of natural sterol now in progress in this laboratory.[4] The 25-dehydrocholesterol (IIa) may readily be prepared from 25-ketonorcholesterol by means of the Wittig reaction. This very useful method was first applied to sterols by Barton, Campos-Neves, and Cookson[5] in their preparation of 3-methylsterols, and more extensively also by Sondheimer and Mechoulian.[6] More recently the method has been used in the synthesis of 24-methylenecholesterol by the present authors[7] and

Idler and Fagerlund.[8] The latter authors largely anticipated our own observations on the Wittig-type synthesis of 25-dehydrocholesterol (IIa). In the present approach 25-ketonorcholesterol (Ia) was first converted by a transpyranylation reaction into the ether (Ic) which afforded the corresponding 25-dehydrocholesterol derivative (IIc) when treated with the required Wittig reagent. To prove its structure, the sterol (IIa) was converted to cholestanol and to 25-ketonorcholesterol (Ia). In the latter conversion the double bond of the sidechain was first selectively hydroxylated with osmium tetroxide, and the resulting glycol cleaved with periodic acid according to procedures previously described.[7] The properties of 25-dehydrocholesterol are in close agreement with those reported by Idler and Fagerlund.[8]

Compounds assigned the structure of 25-dehydrocholesterol had first been prepared by the direct or indirect dehydration of 25-hydroxycholesterol (IIIa).[2,3] The presence in these preparations of terminal unsaturation was well substantiated through spectrographic evidence by the original authors and subsequently by Stokes.[1] Idler and Fagerlund,[8] however, did not observe the characteristic infrared band at 11.3 μ, and concluded that such preparations contained little if any of 25-dehydrocholesterol (IIa), and consisted essentially of the 24-dehydroisomer (IVa). We have reinvestigated the dehydration of the tertiary alcohol (III) in the hope of finding a method leading mainly if not exclusively to the 24-isomer, i.e., desmosterol (IVa). An analogous elimination has recently been used in the synthesis of lanosterol.[9] When the monoacetate of the tertiary al-

(1) W. M. Stokes, W. A. Fish, and F. C. Hickey, J. Biol. Chem., 220, 415 (1956).

(2) A. I. Ryer, W. H. Gebert, and N. M. Murrill, J. Am. Chem. Soc., 72, 4247 (1950).

(3) W. G. Dauben and H. Leon Bradlow, J. Am. Chem. Soc., 72, 4248 (1950).

(4) The authors are greatly indebted to Dr. W. M. Stokes for his cooperation.

(5) D. H. R. Barton, A. S. Campos-Neves, and R. C. Cookson, J. Chem. Soc., 3500 (1956).

(6) F. Sondheimer and R. Mechoulian, Abstracts 131st Meeting American Chemical Society, Miami, Fla., 35–O (1957).

(7) W. Bergmann and J. P. Dusza, Ann., 603, 36 (1957).

(8) D. R. Idler and U. H. M. Fagerlund, J. Am. Chem. Soc., 79, 1988 (1957).

(9) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, J. Chem. Soc., 1131 (1957).