[Contribution from the Rollin H. Stevens Memorial Laboratory of the Detroit Institute of Cancer Research]

THE SYNTHESIS, STRUCTURE PROOF AND AROMATIZATION OF 2-KETO-3-CARBOXY-10-METHYL-$\Delta^{1:9,\,3:4}$-HEXAHYDRONAPHTHALENE[1, 2]

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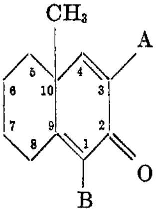
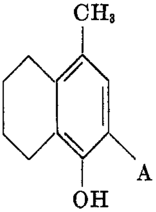
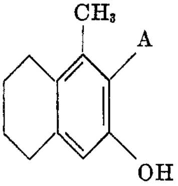
The aromatization of 2-keto-10-methyl-$\Delta^{1:9,\,3:4}$-hexahydronaphthalene (I) depends on the nature of the reaction medium: In acetic anhydride the ring methylene group (carbon-5) migrated to position-1 to give 4-methyl-ar-1-tetralol (IV) (1), while aqueous mineral acids led primarily to 4-methyl-ar-2-tetralol (VI) by the shift of the angular methyl group to carbon-4 (2, 3). Some information is also available on the effect of substituents: A methyl group migration occurred in an acetic anhydride medium when an additional double bond or aromatic ring was present in the 7:8-position (4) or in the case of santonin (VIII) (5), which has substituents at the 1-, 7-, and 8-positions[3] of the basic bicyclic



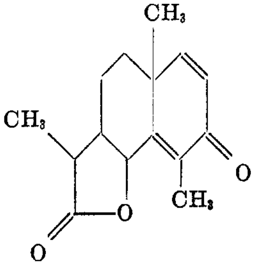
I, A = B = H
II, A = COOH, B = H
III, A = H, B = COOH



IV, A = H
V, A = COOH



VI, A = H
VII, A = COOH



VIII

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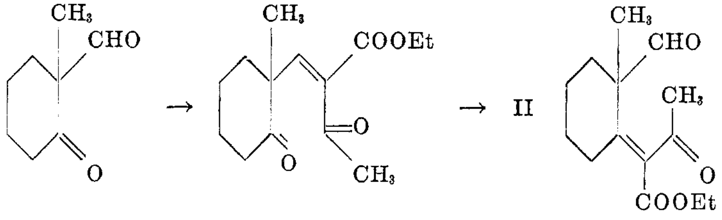
[1] Presented at the W. E. Bachmann Memorial Session, Organic Chemistry Division, American Chemical Society, Chicago Meeting, September 8, 1953.

[2] This work was supported in part by a research and development contract between the Detroit Institute of Cancer Research and the United States Atomic Energy Commission. Additional support was provided by institutional grants from the American Cancer Society, the Michigan Cancer Foundation, and The Kresge Foundation.

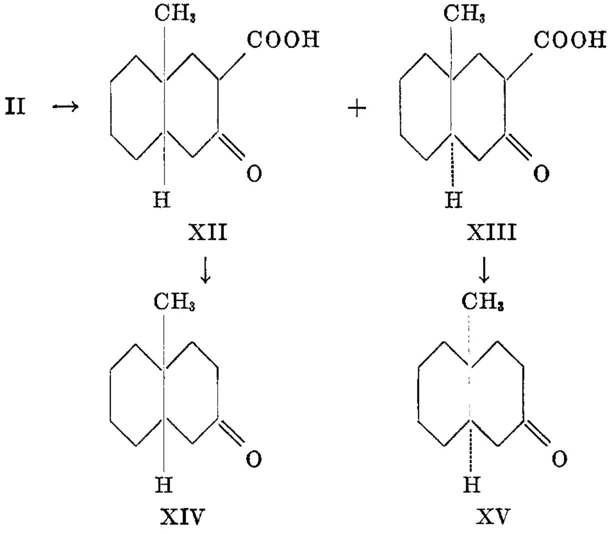
[3] The numbering system used in the present discussion for santonin and the steroids is that indicated in formula I which differs from that conventionally used for these natural products.

dienone system. Alkyl groups at the 5- and 6-positions,[3] such as in the steroids (1, 3, 6), did not alter the effects observed with I. An additional bromine atom at carbon-3 did not affect the nature of the acetic anhydride rearrangement of a steroidal dienone (7),[3] both cases being accompanied by a migration of carbon-5 to position-1.[4]

It was of interest to investigate the effect of an α-carboxyl group on the aromatization of I. A dienone acid (m.p. 134°, $\lambda_{\max}^{\text{alc}}$ 251 mμ) was obtained in 19% yield by the condensation of 2-methyl-2-formylcyclohexanone (IX) with acetoacetic ester, followed by cyclization and saponification. If the condensation took place first with the aldehyde carbonyl the intermediate would be X and the dienone acid would have structure II. While this reaction path appeared more likely than the alternative one, leading *via* XI to III, it was nevertheless desirable to obtain additional evidence for the position of the carboxyl group. Structure II was confirmed by the catalytic hydrogenation which yielded two saturated β-keto acids, m.p. 115° and 130° in a 6:1 ratio, separable by fractional crystallization.



IX X XI



XII XIII

XIV XV

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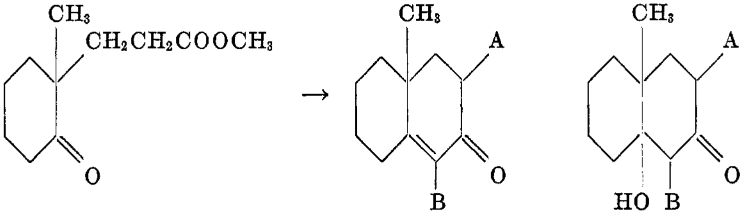
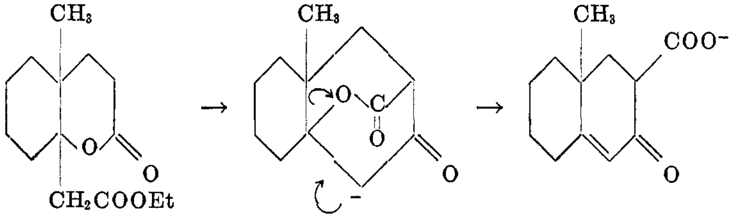
[4] In reference 7, the product of the rearrangement of 2-bromo-1,4-androstadiene-3-one-17-ol-17-hexahydrobenzoate was said to yield 1-methyl-2-bromo-estradiol. However, since it was also obtained by the bromination of the so-called 1-methylestradiol, which is now known to be 1-hydroxy-4-methyl-3-desoxyestradiol, its structure is established as 1-hydroxy-2-bromo-4-methyl-3-desoxyestradiol.

An alternative synthesis showed these β-keto acids to be the *cis* and *trans* forms of 3-carboxy-10-methyl-2-decalone (XII and XIII): The base-soluble product (21% yield) from a Reformatsky reaction in benzene with methyl β-(1-methyl-2-ketocyclohexyl)propionate (XVI) and ethyl bromacetate consisted of a β-keto acid which, on brief heating at 100°, was converted to the known 2-keto-10-methyl-$\Delta^{1:9}$-octahydronaphthalene (XVII) (8). The β-keto acid analyzed correctly for $C_{12}H_{18}O_4$ which could apply to either of the two structures (XX), the possible result of a Reformatsky reaction with XVI followed by a Dieckmann type cyclization and hydrolysis. However, its ultraviolet absorption spectrum (λ_{max}^{alc} 239 mμ, ϵ 14,280) and its facile catalytic hydrogenation indicated that it was instead a conjugated unsaturated β-keto acid containing one molecule of water of crystallization.

The result of the decarboxylation indicated that this acid could have either structure XVIII or XIX, but the former structure (XVIII) was assigned on the basis of the following evidence: (a) The acid gave a strong blue color with alcoholic ferric chloride. (b) Turner (9) had observed the same type of cyclization during the Reformatsky reaction with a δ-keto ester (related to XVI) derived from cholestenone. On the basis of his results with radioactive methyl bromacetate Turner concluded that the intermediate was related to XVIII and not to XIX.[5] (c) The fact that an unsaturated β-keto acid (and not an ester) was isolated, adds support to the reaction course, proposed by Turner, which leads



XVI XVII, A = B = H
XVIII, A = COOH, B = H
XIX, A = H, B = COOH
XX, A or B = COOH



XXI XXII XXIII

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[5] Turner used carboxyl-labelled methyl bromacetate and isolated, after a sodium hydride and a hydrochloric acid-acetic acid treatment, a 32% yield of cholestenone, which had retained almost all of the radioactivity of the methyl bromacetate. In another experiment without radioactivity, where the sodium hydride treatment was omitted, the yield of cholestenone was 21%. A comparison of the yields permits the conclusion that in the latter experiment, too, the intermediate was largely related to XVIII and not XIX.

to XVIII. The trans-annular ring closure product from the intermediate lactone ester (XXI) would be expected to lose one of the hydrogens *alpha* to the keto group (but not the bridge head hydrogen) to give the anion XXII, which can stabilize itself as XXIII.[6]

The product of the hydrogenation of XVIII was a 5:1 mixture of the *cis* and *trans* isomers of 3-carboxy-10-methyl-2-decalone (XII and XIII), m.p. 115° and 130°. The identity of these acids with the hydrogenation products from the dienone acid (II) was established by mixture melting points and by comparisons of the infrared absorption spectra. The fact that these acids indeed differed from each other in the configuration at the ring juncture was shown by decarboxylation, which transformed the 115° isomer into *cis*-10-methyl-2-decalone (XIV) (1, 8, 10, 12) and the 130° isomer into *trans*-10-methyl-2-decalone (XV) (10).[7]

Further evidence on the position of the carboxyl group in the two saturated β-keto acids was sought from the nitric acid oxidation. It was hoped that the presence of the 3-carboxyl group would direct the oxidation between carbons-2 and -3 to give the two stereoisomeric 1-methylcyclohexane-1,2-diacetic acids. The *cis* β-keto acid (XII) actually did yield a diacid, $C_{11}H_{18}O_4$, the melting point of which (190–191°) corresponded closely to that reported (189–190°) for *cis*-1-methylcyclohexane-1,2-diacetic acid (XXIV) (11, 12). The isomeric diacid obtained from XIII, however, melted at 198–199° and thus was clearly different from the sample (m.p. 163–165°) which had been reported to be *trans*-1-methylcyclohexane-1,2-diacetic acid (XXV) (11). There is the possibility that the oxidations of XII and XIII were preceded by a decarboxylation and that the intermediate ketones (XIV and XV) were cleaved at the 2,3- and the 1,2-bonds respectively. This is in accord with the observation (11) that nitric acid oxidation of XIV gives XXIV, while the corresponding reaction of the *trans* isomer (XV) has not been investigated. Thus the 198–199° diacid may be *trans*-β-(1-methyl-2-carboxycyclohexyl)propionic acid (XXVII) or perhaps, by a subsequent isomerization, the *cis* isomer (XXVI). This possibility, however, is not easily reconciled with the observations (13) that coprostanone (A/B = *cis*) is cleaved by oxidation at the 1,2-positions[3] and cholestanone (A/B = *trans*) between carbons-2 and -3.[3] At present, a decision between these possible structures for the 198–199° diacid cannot be made.

It is of interest to compare the major maximum in the ultraviolet absorption spectrum of the dienone acid (II, $\lambda_{\text{max}}^{\text{alc}}$ 251 mμ, ϵ 10,900, $\lambda_{\text{min}}^{\text{alc}}$ 229 mμ, ϵ 7,250)

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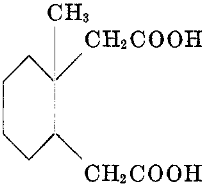
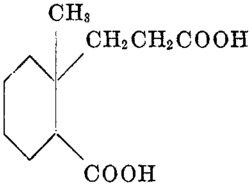
[6] In addition to Turner's example, there are at least three cases in the literature where a Dieckmann type cyclization occurred during Reformatsky reactions with δ-keto esters. See Mukherji, *Science and Culture (India)*, **11**, 574 (1946); Dutt and Banerjee, *Science and Culture (India)*, **12**, 507 (1947); Adamson, McQuillin, Robinson, and Simonsen, *J. Chem. Soc.*, 1576 (1937). The same Reformatsky reaction as described in this paper was also reported by Ruzicka and Pieth, *Helv. Chim. Acta*, **14**, 1151 (1931), who used the ethyl ester corresponding to XVI and isolated only the dehydrated Reformatsky ester in low yield.

[7] We are grateful to Professor R. B. Woodward for informing us of the properties of his synthetic 10-methyl-2-decalones prior to publication and for supplying us with a comparison sample of the 2,4-dinitrophenylhydrazone of *cis*-10-methyl-2-decalone.

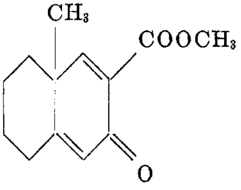
with that of the corresponding ester (XXVIII, $\lambda_{\max}^{\text{alc}}$ 242 mμ, ϵ 10,980, $\lambda_{\min}^{\text{alc}}$ 219 mμ, ϵ 6,500) and that of the simple dienone (I, $\lambda_{\max}^{\text{alc}}$ 241 mμ, ϵ 14,970). The dienone (I) and the dienone ester (XXVIII) show the typical absorption maximum of the α,β-unsaturated ketone system, which is unaffected by the additional double bond in I and by the additional α,β-unsaturated ester system in XXVIII, presumably because they are in cross-conjugation with it. In the dienone acid, however, the major absorption maximum is shifted by about 10 mμ to the red. This may be explainable by assuming a hydrogen bond between the carboxyl and the keto group, as shown in structure XXIX. In this way the carboxyl group can participate in the conjugation of the entire system.[8] The chelated structure XXIX is supported by the observation that the dienone acid did not react with diazomethane in an ether-methanol mixture. The dienone ester (XXVIII) had to be prepared by adding silver oxide to a solution of the acid (II) in methyl iodide.



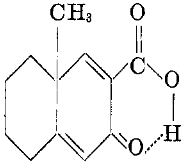
XXIV, *cis* form
XXV, *trans* form



XXVI, *cis* form
XXVII, *trans* form



XXVIII



XXIX

The dienone acid (II) was readily soluble in concentrated hydrochloric acid and the solution rapidly deposited a quantitative yield of a phenolic acid, m.p. 161–163°, $\lambda_{\max}^{\text{alc}}$ 247.5 and 309 mμ. If the aromatization had taken place with a concomitant 1,3-shift of the ring methylene carbon, it would have resulted in 2-carboxy-4-methyl-ar-1-tetralol (V), while a migration of the angular methyl group would have given rise to 3-carboxy-4-methyl-ar-2-tetralol (VII). That the latter was the case was shown by the mild bromination of the phenolic acid, which yielded a monobromo derivative and thus indicated the presence of a free position *ortho* (or *para*) to the phenolic hydroxyl group, and by its decarboxylation to the known 4-methyl-ar-2-tetralol (VI). Thus the course of the aromatization of the dienone acid (II) with hydrochloric acid was not essentially different

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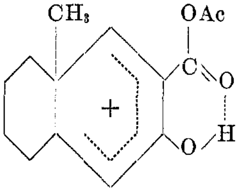
[8] This effect may be similar to the conjugated chelation effect mentioned by Rasmussen, Tunnicliff, and Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

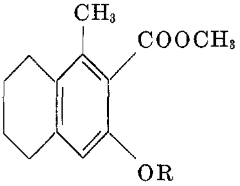
from that of the dienone (I) without the carboxyl group (2, 3), a migration of the angular methyl group predominating in both cases.

The effect of the carboxyl group became evident in the acetic anhydride-sulfuric acid aromatization. While the dienone (I) suffered exclusively ring methylene group migration under these conditions (1), the shift of the methyl group predominated in the rearrangement of the dienone acid (II) by a factor of almost four. This was determined by saponifying the crude rearrangement product to a mixture consisting of 3-carboxy-4-methyl-ar-2-tetralol (VII) and 2-carboxy-4-methyl-ar-1-tetralol (V) which was analyzed by taking advantage of the fact that VII readily lost carbon dioxide in a hot hydrochloric-acetic acid mixture while V was entirely unaffected. In this way the mixture was separated into a 52% yield of 4-methyl-ar-2-tetralol (VI) and a 14% yield of 2-carboxy-4-methyl-ar-1-tetralol (V). The structure of V was confirmed by its decarboxylation at 250° to the known 4-methyl-ar-1-tetralol (IV) (1). Incidentally, the isolation of V in this reaction confirms the conclusion mentioned above that the dienone acid has the carboxyl group at carbon-3.

To test the possibility that the hydrogen bond in II (XXIX) may be responsible for this effect of the carboxyl group, perhaps through an intermediate such as XXX, the dienone ester (XXVIII) was also subjected to the acetic anhydride-sulfuric acid rearrangement. In this case, the methyl group migration still overshadowed the shift of the ring methylene group by a factor of three. The products, obtained after a combination of direct crystallization, saponification, and acid-catalyzed decarboxylation, were a 41% yield of the acetate of 3-carbomethoxy-4-methyl-ar-2-tetralol (XXXII), 18% of 4-methyl-ar-2-tetralol (VI), and 20% of 2-carboxy-4-methyl-ar-1-tetralol (V). A mild saponification converted XXXII to a mixture of 3-carbomethoxy-4-methyl-ar-2-tetralol (XXXI) and the corresponding acid (VII). XXXI and XXXII were resynthesized from VII by conventional procedures. The isolation of the methyl esters XXXI and XXXII from the rearrangement is evidence that the methyl iodide-silver oxide treatment had indeed esterified the dienone acid.



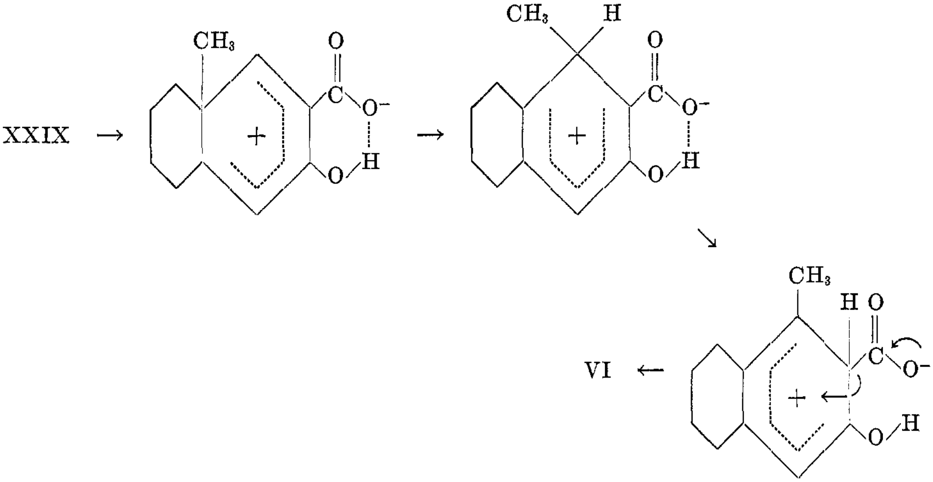
XXX



XXXI, R = H
XXXII, R = OAc

These results do not completely exclude XXX as an intermediate but they do indicate that the hydrogen bond cannot be the sole cause for the predominance of the methyl group migration in the acetic anhydride treatment of the dienone acid. It may be concluded that the carboxyl- and the carbomethoxyl-group at the 3-position exert a similar effect which favors methyl group migration, perhaps by increasing the electropositive nature of carbon-4 in the intermediate and thus favoring migration in that direction, which can be followed only by the methyl group.

Finally an attempt was made to decarboxylate the dienone acid (II) by heat. It is remarkable that no reaction took place in the clear melt below 220°. According to the cyclic decarboxylation mechanism (14) the intermediate in the decarboxylation of II would be a $\Delta^{2:3}$-enol. The resistance of II towards decarboxylation may be explainable by the reluctance of the keto group to enolize in the direction of a conjugated double bond which is unmovable, except by a rearrangement of the carbon skeleton. Such a rearrangement indeed took place when the decarboxylation was accomplished by heating II above 220°, the product being a 72% yield of 4-methyl-ar-2-tetralol (VI). Since the simple dienone (I) was recovered unchanged after the same thermal treatment, it must be concluded that the decarboxylation of II took place either along with, or subsequent to, the aromatization. This "decarboxylative aromatization" may be considered an auto-acid catalyzed reaction which proceeds through a cyclic transition state.[9]



EXPERIMENTAL[10]

2-Keto-3-carboxy-10-methyl-$\Delta^{1:9,\ 3:4}$-hexahydronaphthalene (II). To a solution of 11.2 g. (0.08 mole) of 2-methyl-2-formylcyclohexanone (IX) (15) and 4.8 g. of acetic acid in 100 cc. of ethyl acetoacetate was added dropwise, with swirling and cooling under the tap, 6.8 g. of piperidine. The precipitate which formed soon dissolved to give a colorless solution which

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[9] In a similar decarboxylative aromatization with a dienone acid derived from lanosterol, Barnes, Barton, Fawcett, and Thomas, *J. Chem. Soc.*, 2339 (1952), concluded that the migration of the angular methyl group had taken place. While the carboxyl group, which in that case was at carbon-4,[3] could not participate in a cyclic transition state, there was another carboxyl group in a position to interact with the dienone oxygen.

[10] The melting points are not corrected. The analyses are by Micro-Tech Laboratories in Skokie, Illinois. We are grateful to Dr. J. M. Vandenbelt and Mr. Bruce Scott of Parke, Davis and Co. for the measurement and a discussion of several of the ultraviolet and infrared absorption spectra.

turned yellow on standing in a closed vessel for 17 hours at room temperature. The solution was incubated at 55° for 80 hours, diluted with ether, and washed with 500 cc. of water, 25 cc. of sodium bicarbonate, and an excess of saturated sodium chloride solution. The ether and ethyl acetoacetate were removed at reduced pressure, leaving an oil which was treated with a solution of sodium ethoxide, made from 4 g. of sodium hydride and 200 cc. of ethanol, at room temperature overnight. After heating for one-half hour to reflux, 25 cc. of water was added, and the alcohol was distilled at atmospheric pressure for one hour and then at reduced pressure. Addition of water to the residue, ether extraction, and acidification with cold dilute acid gave an oil, which was taken up in chloroform and ether. The residue from the evaporation of the solvents was treated with ether to give 3.13 g. (19% yield) of *2-keto-3-carboxy-10-methyl-*$\Delta^{1:9,\ 3:4}$*-hexahydronaphthalene* (II) as a light tan solid, m.p. 128–132°. Recrystallization from ether raised the melting point to 133–134.5° (at 220° a gas was evolved, but below that temperature the light yellow melt showed no signs of decomposition); neutral equivalent 202 (calc'd 206); $\lambda_{\text{max}}^{\text{alc}}$ 251 mμ (ϵ 10,900), $\lambda_{\text{min}}^{\text{alc}}$ 229 mμ (ϵ 7,250); $\lambda_{\text{max}}^{\text{mineral oil}}$ 3.78 (w), 5.73 (s), 6.07 (s), 6.33 (s), 7.15 (m), 7.90 (w), 8.35 (w), 8.51 (w), 8.88 (w), 9.55 (w), 10.33 (w), 11.13 (w), 11.42 (s) μ (the infrared absorption spectrum in chloroform is almost identical).

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84.
Found: C, 69.85; H, 7.22.

The dienone acid (II) did not decolorize a solution of bromine in chloroform and did not react with an ethereal solution of diazomethane even after the addition of methanol. It was soluble in aqueous sodium bicarbonate.

The *2,4-dinitrophenylhydrazone* of what appears to be the methyl ester of the dienone acid (XXVIII) resulted when a methanolic solution of the dienone acid (II) was treated with an excess of a solution of 2,4-dinitrophenylhydrazine in 50% sulfuric acid. Recrystallization from methanol gave dark red needles, m.p. 179–180°. This sample was insoluble in sodium bicarbonate solution.

Anal. Calc'd for $C_{19}H_{20}N_4O_6$: C, 56.99; H, 5.03; N, 13.98.
Found: C, 56.52; H, 5.43; N, 13.95.

Rearrangement of 2-keto-3-carboxy-10-methyl-$\Delta^{1:9,\ 3:4}$*-hexahydronaphthalene* (II). (*a*) *By cold concentrated hydrochloric acid.* The clear, almost colorless solution, which resulted from the addition of 0.2 g. of dienone acid (II) to 3 cc. of concentrated hydrochloric acid, became turbid on standing at room temperature for a few minutes and set to a solid mass after two hours. Dilution with water and filtration gave 0.19 g. (95%) of *3-carboxy-4-methyl-ar-2-tetralol* (VII), m.p. 159–160°. An analytical sample was obtained from ether-petroleum ether as colorless needles, m.p. 161–163° (a gas was evolved at 170°); $\lambda_{\text{max}}^{\text{alc}}$ 247.5 and 309 mμ (ϵ 8,480 and 3,740), $\lambda_{\text{min}}^{\text{alc}}$ 242 and 274 mμ (ϵ 7,310 and 1,440); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 6.09 (s), 6.24 (m), 6.40 (w), 6.90 (s), 7.65 (m), 7.90 (m–s), 8.03–8.25 (s), 8.60 (w), 9.20 (m), 9.61–9.80 (w), 11.05 (w), 11.60 (w) μ.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84.
Found: C, 69.68; H, 6.92.

(*b*) *By acetic anhydride and sulfuric acid.* To a clear solution of 0.3 g. of the dienone acid (II) in 5 cc. of acetic anhydride was added a solution of 0.115 g. of concentrated sulfuric acid in 2 cc. of acetic anhydride. The pale yellow solution was allowed to stand at room temperature for 24 hours, poured cautiously into 100 cc. of 15% aqueous potassium hydroxide, and heated at reflux for one hour. Acidification precipitated 0.275 g. (91%) of a mixture of VII and V, m.p. 145–148°. Recrystallization from cyclohexane gave a sample of 3-carboxy-4-methyl-ar-2-tetralol, m.p. 159–160° undepressed on admixture with the sample obtained in the preceding experiment. The infrared absorption spectrum of this sample was superimposable on that of the above mentioned sample.

In another experiment, 125 mg. of II was treated in the same way, but the crude mixture of acids (VII and V) was heated in a refluxing mixture of 4 cc. of acetic acid and 2 cc. of hydrochloric acid for two hours. After diluting with excess water, the products were extracted with ether. Acidification of the sodium bicarbonate extract of the ethereal solution precipitated 18 mg. (14%) of 2-carboxy-4-methyl-ar-1-tetralol (V), m.p. 225–228° d. Recrystallization from ether-petroleum ether raised the m.p. 230–232° d. undepressed on admixture with the sample of V obtained from the rearrangement of the dienone ester. Concentration of the ethereal solution and crystallization of the residue from petroleum ether yielded 52 mg. (53%) of 4-methyl-ar-2-tetralol (VI), m.p. 102–104° [reported (1) 104–105°].

1-Bromo-3-carboxy-4-methyl-ar-2-tetralol. A 5% solution of bromine in carbon tetrachloride was added to a solution of 0.11 g. of 3-carboxy-4-methyl-ar-2-tetralol (VII) in 5 cc. of chloroform until the bromine color persisted. The solution was heated to boiling for two minutes and the solvent was removed in a stream of dry air. The residual solid was recrystallized from aqueous methanol to give 0.15 g. (98% of *1-bromo-3-carboxy-4-methyl-ar-2-tetralol*, m.p. 200–205°. Recrystallization from dilute methanol as slightly yellow prisms raised the m.p. to 212–213° (softening at 209°); $\lambda_{\max}^{\text{alc}}$ 313 mμ (ϵ 4,160), $\lambda_{\text{infl}}^{\text{alc}}$ 251 mμ (ϵ 7,120), $\lambda_{\min}^{\text{alc}}$ 278 mμ (ϵ 1,400).

Anal. Calc'd for $C_{12}H_{13}BrO_3$: C, 50.54; H, 4.60; Br, 28.03.
Found: C, 50.72; H, 4.82; Br, 27.74, 27.90.

Rearrangement of 2-keto-3-carbomethoxy-10-methyl-$\Delta^{1:9,\ 3:4}$-hexahydronaphthalene (XXVIII) *by acetic anhydride and sulfuric acid.* A clear solution of 476 mg. of the dienone acid (II) in 10 cc. of methyl iodide was treated with 1 g. of silver oxide in small portions and the mixture was stirred for one hour at room temperature. The solids were removed by filtration through Celite and the filtrate, after dilution with ether, was washed with saturated sodium bicarbonate, dried and concentrated. The residual oily *2-keto-3-carbomethoxy-10-methyl-$\Delta^{1:9,\ 3:4}$-hexahydronaphthalene* (XXVIII) weighed 540 mg. (theoretical yield, 508 mg.) and showed the following spectra: $\lambda_{\max}^{\text{alc}}$ 242 mμ (ϵ 10,980), $\lambda_{\min}^{\text{alc}}$ 219 mμ (ϵ 6,500); $\lambda_{\max}^{\text{CHCl}_3}$ 5.72 (s), 6.00 (s), 6.09 (m), 6.91 (m), 7.19 (m), 7.80 (s), 8.00 (m), 8.15–8.25 (m), 8.50 (w), 8.81 (m), 9.09 (w), 9.45 (s), 10.22 (m), 10.91 (w), 11.12 (w), 11.33 (s), 11.71 (w) μ.

The above crude dienone ester was allowed to stand at room temperature for 16 hours in a solution of 13 cc. of acetic anhydride and 117 mg. of concentrated sulfuric acid, when only a pale yellow color developed. After decomposing the acetic anhydride with cold water, 547 mg. (90%) of a mixture of acetate-esters was filtered off, m.p. 80–95°. Recrystallization from petroleum ether (b.p. 30–60°) afforded an almost pure sample of the *acetate of 3-carbomethoxy-4-methyl-ar-2-tetralol* (XXXII), m.p. 99–101°, yield 250 mg. (41%, based on II). The material in the mother liquor consisted of 260 mg. of solid, m.p. 82–90°, which could not be purified by further recrystallization and thus was treated as will be described further below. An analytical sample of XXXII was obtained as clusters of thick colorless prisms by a recrystallization from petroleum ether, m.p. 103–104°, $\lambda_{\max}^{\text{CHCl}_3}$ 3.29 (m), 3.40 (m), 5.66 (s), 5.78 (s), 6.20 (w), 6.92 (m), 7.29 (m), 7.85 (s), 8.19 (m), 8.38 (s), 8.63 (m), 9.36 (m), 9.55 (w), 9.70 (w), 10.28 (w), 10.52 (w), 10.79 (w), 10.99 (w), 11.19 (w), 11.29 (w), 11.70 (w) μ.

Anal. Calc'd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92.
Found: C, 68.83; H, 7.15.

When 145 mg. of the acetate of 3-carbomethoxy-4-methyl-ar-2-tetralol (XXXII), m.p. 99–101°, was saponified in a refluxing solution in 5% methanolic-aqueous sodium hydroxide for 15 minutes, and the solution was concentrated and acidified, there resulted 106 mg. of a crude mixture, m.p. 120–133°. This was triturated with aqueous sodium bicarbonate, leaving 46 mg. (38% yield) of *3-carbomethoxy-4-methyl-ar-2-tetralol* (XXXI) undissolved, m.p. 55–57°. One recrystallization from aqueous methanol as colorless plates raised the m.p. to 56–57°, $\lambda_{\max}^{\text{CHCl}_3}$ 3.29 (m), 3.39 (m), 5.79 (w), 6.00 (s), 6.19 (m), 6.35 (m), 6.91 (s), 7.39 (m), 7.60 (m), 7.71 (m), 7.85 (m), 8.10–8.32 (s), 8.63 (s), 9.16 (m), 9.58 (w), 10.29 (w), 10.59 (w), 11.02 (w), 11.59 (m) μ.

Anal. Calc'd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.31.
Found: C, 70.68; H, 7.49.

Acidification of the sodium bicarbonate filtrate afforded 52 mg. (38% yield) of 3-carboxy-4-methyl-ar-2-tetralol (VII), m.p. 156–159°. Recrystallization raised the m.p. to 160–162°‘ which was not depressed on admixture with a sample of VII obtained from the hydrochloric acid rearrangement of II. Both XXXI and VII gave a green color with alcoholic ferric chloride.

The esterification of 103 mg. of 3-carboxy-4-methyl-ar-2-tetralol (VII, m.p. 161–163°, from the hydrochloric acid aromatization of II) with ethereal diazomethane gave 110 mg. (100%) of 3-carbomethoxy-4-methyl-ar-2-tetralol (XXXI), m.p. 55–56°, which was recrystallized from aqueous methanol, m.p. 56–57°, undepressed on admixture with the above described sample. The acetylation of 50 mg. of this sample of XXXI in 3 cc. of acetic anhydride and 0.2 cc. of a 5% solution of zinc chloride in acetic acid for 60 hours at room temperature gave 55 mg. of XXXII, m.p. 103–104°. When mixed with the sample of XXXII from XXVIII, the m.p. was not depressed.

The mother liquor material from the crystallization of XXXII, mentioned above (260 mg., m.p. 82–90°) was saponified by heating in 10 cc. of 5% aqueous-methanolic sodium hydroxide. Acidification gave a solid which was purified by solution in aqueous sodium bicarbonate, filtration, and reacidification to give 185 mg. of a mixture of phenolic acids, m.p. 142–150°. Two recrystallizations from cyclohexane produced 70 mg. (15% yield based on II) of almost pure *2-carboxy-4-methyl-ar-1-tetralol* (V), m.p. 226–229°. Recrystallization from ether-petroleum ether as flat colorless needles raised the m.p. to 232–233°d.; $\lambda_{\max}^{\text{alc}}$ 250 and 315 mμ (ϵ 10,500 and 4,430), $\lambda_{\min}^{\text{alc}}$(231 and 272 m$\mu$ (ϵ 5,220 and 430).

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84.

Found: C, 69.89; H, 7.02.

The phenolic acid (V) (20 mg.) was recovered unchanged after being heated in a refluxing mixture of 4 cc. of acetic acid and 2 cc. of hydrochloric acid for two hours. When 15 mg. of V was heated under an atmosphere of nitrogen at 240–250° for five minutes, there condensed on the walls of the test tube 10 mg. of a solid, m.p. 74–79°. Recrystallization from petroleum ether afforded colorless needles of 4-methyl-ar-1-tetralol (IV), m.p. 86–88°. This m.p. was not depressed when the sample was mixed with authentic IV, m.p. 86–88° [reported (1) 87.5–88.5°].

The mother liquors of the various crystallizations of V contained 110 mg. of a solid mixture. This was heated for two hours in 2 cc. of hydrochloric and 2 cc. of acetic acid. After concentration and dilution with water, the solids were filtered and triturated with aqueous sodium bicarbonate. The undissolved material was crystallized from petroleum ether to give 68 mg. (18% yield based on II) of 4-methyl-ar-2-tetralol (VI), m.p. 101–103°. Acidification of the solution yielded 22 mg. (5% yield based on II) of 2-carboxy-4-methyl-ar-1-tetralol (V), m.p. 228–230° d.

Thus the total yield of V in the acetic anhydride-sulfuric acid aromatization of the dienone ester (XXVIII) was at least 20%, while the combined yield of XXXII and VI was at least 59%. This indicates that the ratio of methyl-migration to ring-methylene-migration in this reaction is approximately 3:1.

In another experiment, 115 mg. of XXVIII was rearranged in the same manner, but the acetic anhydride solution was poured directly into aqueous sodium hydroxide and the product was saponified and partially decarboxylated as described above for the second acetic anhydride rearrangement of the dienone acid (II). In this way 46 mg. (54%) of 4-methyl-ar-2-tetralol (VI), m.p. 100–103°, and 19 mg. (17%) of 2-carboxy-4-methyl-ar-1-tetralol (V), m.p. 224–227°, were obtained.

Rearrangement and decarboxylation of 2-keto-3-carboxy-10-methyl-$\Delta^{1:9,\,3:4}$*-hexahydronaphthalene* (II). (*a*) *By hot hydrochloric acid.* A solution of 0.5 g. of the dienone acid (II) in 20 cc. of concentrated hydrochloric acid was allowed to stand at room temperature for 15 minutes, diluted with 15 cc. of acetic acid, and refluxed for 5 hours. The solution was cooled, diluted with water, and extracted with ether. The ethereal extract was washed with sodium bicarbonate, dried, and evaporated to give, on trituration with petroleum ether, 0.353 g. (90%) of 4-methyl-ar-2-tetralol (VI), m.p. 100–103°. Recrystallization raised the m.p. to 105–107° [reported, (1) 104–105°]. When mixed with an authentic sample of VI, the m.p. was not depressed. The *p*-nitrobenzoate melted at 115–116° [reported (16) 116–118°] alone and when mixed with this derivative of an authentic sample of VI.

(*b*) *By heating at 250°.* When 0.5 g. of the dienone acid (II) was heated at 250° in an atmosphere of nitrogen a vigorous evolution of a gas took place. The bubbling ceased after

10 minutes and the cooled pale yellow melt was evaporatively distilled at 120–140° and 10 mm. as a colorless oil which solidified with petroleum ether to give 0.302 g. (72%) of 4-methyl-ar-2-tetralol (VI), m.p. 104–106°. There was no depression of m.p. on admixture of an authentic sample of VI.

In order to see whether the simple dienone (I) was aromatized under these conditions, 152 mg. of pure I [m.p. 14–15°, $\lambda_{\max}^{\text{alc}}$ 241 mμ (ϵ 14,970)] (1) was heated at 250° in an atmosphere of nitrogen for ten minutes. The ultraviolet absorption spectrum of the product, which had darkened only slightly, was: $\lambda_{\max}^{\text{alc}}$ 241 mμ (ϵ 14,900). This indicated that the dienone (I) was not affected by this thermal treatment.

2-Keto-3-carboxy-10-methyl-$\Delta^{1:9}$-octahydronaphthalene (XVIII). A mixture of 50 g. (0.25 mole) of methyl β-(1-methyl-2-ketocyclohexyl)propionate (XVI) [prepared in 85% yield from the corresponding acid, m.p. 48–49° (17) with methanol and sulfuric acid, b.p. 107–110° at 0.6 mm., n_{D}^{29} 1.4680], 50 g. (0.3 mole) of ethyl bromoacetate, and 32 g. (0.5 mole) of granulated zinc in 400 cc. of anhydrous benzene was heated to reflux with stirring until a vigorous reaction started (5–10 minutes). The reaction maintained itself for about 20 minutes without external heating. An additional 10 g. (0.15 mole) of zinc and 25 g. (0.15 mole) of ethyl bromoacetate was added and the mixture was refluxed for 1½ hours. After cooling, the complex was decomposed with cold dilute acetic acid and the ethereal solution was extracted with five 200 cc.-portions of 2% ammonium hydroxide at 0°. The basic extracts were acidified in the cold to precipitate 11 g. (21%) of *2-keto-3-carboxy-10-methyl-$\Delta^{1:9}$-octahydronaphthalene* (XVIII) as a pale yellow sticky solid, which on trituration with isopropyl ether yielded 8.5 g. of colorless solid, m.p. 86–87° d.; $\lambda_{\max}^{\text{alc}}$ 239 mμ (ϵ 14,280). The keto acid (XVIII) was soluble in aqueous sodium bicarbonate and gave a strong blue color with alcoholic ferric chloride. The solid acid, which crystallized from ether as the hydrate, m.p. 84–86° d., turned into an oil on standing at room temperature for 12 hours; it remained stable when stored in a closed bottle at −20° for two months.

Anal. Calc'd for $C_{12}H_{16}O_3 + H_2O$: C, 63.70; H, 8.02.
Found: C, 63.97; H, 7.98.

The ethereal solution remaining from the ammonium hydroxide extraction was concentrated and the residue distilled to give 32 g. (63%) of recovered methyl β-(1-methyl-2-ketocyclohexyl)propionate, b.p. 93–95° (0.3 mm.), n_{D}^{29} 1.4710, and 9.8 g. of a higher-boiling fraction, b.p. 100–155° (0.07 mm.), which may be the normal Reformatsky ester, methyl β-(1-methyl-2-hydroxy-2-carbethoxymethylcyclohexyl)propionate; $\lambda_{\max}^{\text{CHCl}_3}$ 2.81 and 5.81 μ.

2-Keto-10-methyl-$\Delta^{1:9}$-octahydronaphthalene (XVII). The unsaturated keto acid (XVIII) (1 g.) was decarboxylated by brief heating at 100° and the residual ketone was evaporatively distilled at 160–170° and 30 mm. to give 0.71 g. (90%) of 2-keto-$\Delta^{1:9}$-octahydronaphthalene (XVII) as a colorless oil, $\lambda_{\max}^{\text{alc}}$ 240 mμ (ϵ 15,680). The *2,4-dinitrophenylhydrazone* crystallized from methanol-chloroform as dark red needles, m.p. 172–174° [reported (10) 173–174°].

cis- and trans-3-Carboxy-10-methyl-2-decalone (XII and XIII). (*a*) *From the dienone acid* (II). A solution of 0.37 g. of the dienone acid (II) in 10 cc. of methanol was shaken under an atmosphere of hydrogen in the presence of 57 mg. of 5% palladium on charcoal until the gas absorption was complete. After 8 minutes, 92 cc. of hydrogen had been consumed, corresponding to two double bonds. After filtration of the catalyst and distillation of the methanol at reduced pressure and low temperature, the residual oil was treated with water to give 0.345 g. (93%) of a pink solid, m.p. 101–102° dec. Recrystallization from ether-petroleum ether yielded an insoluble and a more soluble crop. The insoluble crop consisted of 0.040 g. (11%) of *trans-3-carboxy-10-methyl-2-decalone* (XIII), m.p. 123–124° dec. Recrystallization from ether-petroleum ether as colorless plates raised the m.p. to 129–130° dec., $\lambda_{\max}^{\text{CHCl}_3}$ 6.0 (s), 6.2 (s), 6.9 (s), 7.2 (w), 7.5 (m), 7.6 (m), 7.8 (s), 8.0 (m-s), 8.3 (m), 8.6 (m-w), 8.7 (w), 8.9 (w), 9.1 (w), 9.7 (w), 10.4 (w) μ. The keto acid gave a strong green-blue color with alcoholic ferric chloride.

Anal. Calc'd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63.
Found: C, 68.70; H, 8.92.

The more-soluble crop crystallized on concentration of the mother liquor and consisted of 0.23 g. (61%) of *cis-3-carboxy-10-methyl-2-decalone* (XII), m.p. 109–110° dec. Recrystallization from ether-petroleum ether afforded an analytical sample as colorless plates, m.p. 114–115° dec; $\lambda_{\mathrm{ma}}^{\mathrm{CHCl_3}}$ 6.0 (s), 6.2 (s) 6.9 (s), 7.2 (w), 7.5 (m), 7.7 (s), 8.1–8.3 (m), 8.6 (m–w), 8.9 (w), 9.1 (w), 9.4 (w), 9.9 (w), 10.5 (w) μ. The acid gave a positive ferric chloride test.

Anal. Calc'd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63.

Found: C, 69.25; H, 8.85.

(*b*) *From the unsaturated keto acid* (XVIII). The hydrogenation of 1 g. of 2-keto-3-carboxy-10-methyl-$\Delta^{1:9}$-octahydronaphthalene (XVIII) by the method described in the preceding experiment gave 650 mg. of the crude solid mixture of isomeric keto acids, m.p. 98–100°. Fractional crystallization afforded 70 mg. (7%) of *trans*-3-carboxy-10-methyl-2-decalone (XIII), m.p. 128–129° dec., and 350 mg. (35%) of *cis*-3-carboxy-10-methyl-2-decalone (XII), m.p. 113–114° dec. The melting points of these samples were not depressed on admixture with the respective samples from the preceding experiment and the infrared spectra of the corresponding samples were superimposable.

cis-1-Methylcyclohexane-1,2-diacetic acid (XXIV). A solution of 0.211 g. of *cis*-3-carboxy-10-methyl-2-decalone (XII, m.p. 114–115°) in 6 cc. of concentrated nitric acid was heated to reflux for 15 minutes. Then 10 cc. of water was added and the solution was boiled down to 3 cc. On dilution with 5 cc. of water and ice, 0.11 g. (51%) of *cis-1-methylcyclohexane-1,2-diacetic acid* (*XXIV*) precipitated as a colorless solid, m.p. 185–189°. Two recrystallizations from water produced colorless nodules, m.p. 190–191° [reported (11, 12) 189–190°].

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47.

Found: C, 61.63; H, 8.63.

trans-1-Methylcyclohexane-1,2-diacetic acid (XXV) *or cis- or trans-β-(1-methyl-2-carboxycyclohexane)propionic acid* (XXVI or XXVII). By using the procedure described in the previous experiment 0.077 g. of *trans*-3-carboxy-10-methyl-2-decalone (XIII, m.p. 129°) was transformed into 0.063 g. (80%) of a colorless diacid, m.p. 195–196°. The analytical sample was obtained by crystallizing from water as colorless needles, m.p. 198–199°. When this sample was mixed with *cis*-1-methylcyclohexane-1,2-diacetic acid (XXIV, m.p. 189–190°), obtained from the preceding experiment, the melting point was 171–179°.

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47.

Found: C, 61.73; H, 8.65.

This oxidation product could be either *trans*-1-methylcyclohexane-1,2-diacetic acid (XXV), [reported (11) m.p. 163–165°], *trans-β*-(1-methyl-2-carboxycyclohexane)propionic acid (XXVII), or *cis-β*-(1-methyl-2-carboxycyclohexane)propionic acid (XXVI).

cis-10-Methyl-2-decalone (XIV). The decarboxylation of 0.145 g. of *cis*-3-carboxy-10-methyl-2-decalone (XII, m.p. 114–115°) proceeded smoothly at 120° for five minutes to give a camphoraceous oil, which solidified on standing, m.p. 45–47° [reported (10) 46–48°]. It was converted to an orange *2,4-dinitrophenylhydrazone*, yield 0.24 g. (100%), m.p. 116–119°. Two recrystallizations from methanol afforded light orange needles, m.p. 132–133°.

Anal. Calc'd for $C_{17}H_{22}N_4O_4$: C, 58.92; H, 6.40; N, 16.18.

Found: C, 59.12; H, 6.48; N, 16.25.

This 2,4-dinitrophenylhydrazone of XIV had been reported to melt at 152–152.5° (8, 18) and at 125.5–127° (1). When the interesting experience, which Woodward and his co-workers (10) had with the melting point of this derivative, became known to us[7] we recrystallized our analytical sample from ether-petroleum ether, which raised the m.p. to 169–171°. Recrystallization from methanol-ethyl acetate gave orange needles, m.p. 175–177°. This m.p. was not raised further on recrystallization from ethyl acetate [reported (10) m.p. 175–176°] and was not depressed on admixture with a sample kindly furnished by Prof. Woodward.[7]

trans-10-Methyl-2-decalone (XV). The reactions described in the preceding experiment, when applied to 0.063 g. of *trans*-3-carboxy-10-methyl-2-decalone (XIII, m.p. 128–129°), gave 0.07 g. (67%) of an orange *2,4-dinitrophenylhydrazone*, m.p. 150–152°. The analytical sample was obtained as yellow-orange plates from methanol-ethyl acetate, m.p. 173–175° [reported, (10) 178–179°]. When this sample was mixed with the derivative of *cis*-10-methyl-2-decalone (XIV, m.p. 175–177°) the m.p. was depressed to 145–165°.

Anal. Calc'd for $C_{17}H_{22}N_4O_4$: C, 58.92; H, 6.40; N, 16.18.
Found: C, 59.03; H, 6.57; N, 16.37.

SUMMARY

1. 2-Keto-3-carboxy-$\Delta^{1:9,\ 3:4}$-hexahydronaphthalene (II) was synthesized. Its hydrogenation products, *cis*- and *trans*-3-carboxy-10-methyl-2-decalone (XII and XIII) were also obtained by reduction of 2-keto-3-carboxy-10-methyl-$\Delta^{1:9}$-octahydronaphthalene (XVIII), the direct base-soluble product from a Reformatsky reaction with methyl β-(1-methyl-2-ketocyclohexyl) propionate (XVI).

2. The ultraviolet absorption spectrum of the dienone acid (II) was found to have a maximum at 251 mμ while that of its ester (XXVIII) and that of 2-keto-10-methyl-$\Delta^{1:9,\ 3:4}$-hexahydronaphthalene (I) exhibited peaks near 241 mμ.

3. The aromatization of II was conducted in three ways:

(a) With concentrated hydrochloric acid the exclusive migration of the angular methyl group resulted in 3-carboxy-4-methyl-ar-2-tetralol (VII).

(b) With acetic anhydride and sulfuric acid, the predominant shift of the methyl group was accompanied by some ring methylene group migration. The product was a mixture consisting mostly of 3-carboxy-4-methyl-ar-2-tetralol (VII) and also some 2-carboxy-4-methyl-ar-1-tetralol (V). The aromatization of the dienone ester (XXVIII) under these conditions gave the same result.

(c) By brief heating at 250° a "decarboxylative aromatization" took place which resulted in 4-methyl-ar-2-tetralol (VI).

4. 3-Carboxy-4-methyl-ar-2-tetralol (VII) was readily decarboxylated in a hot mixture of acetic acid and hydrochloric acid, while 2-carboxy-4-methyl-ar-1-tetralol (V) was unaffected.

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