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

Santonin and Related Compounds. XXII.[1] Some Dienone-Phenol Rearrangements[2]

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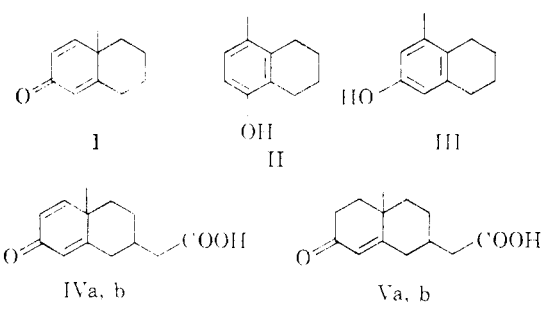
The rearrangement of the *trans*-dienoneacetic acid (IVa) in acetic anhydride-sulfuric acid furnished predominantly the *p*-cresol (IX), whereas with 50% sulfuric acid the unexpected *m*-cresol (XI) was obtained as a chief product, together with minor amounts of the normal *m*-cresol (X). On the other hand, the *cis*-dienoneacetic acid (IVb) with acetic anhydride–sulfuric acid mainly rearranged to the normal *m*-cresol (X), accompanied with IX. Also with 50% sulfuric acid, the *cis*-isomer (IVb) predominantly afforded X. The structures of these rearranged products were confirmed by unequivocal syntheses. Both *trans*- and *cis*-isomers of the 4-methyl homologues (XXXIIIa and XXXIIIb. R^1 = COOH and R^2 = H, respectively) of IV reacted with 50% sulfuric acid giving exclusively the identical xylenol (XXXV). Plausible routes for the formation of the unusual *m*-cresol (XI) from IVa were tentatively proposed.

It has been stated[3,4] that the dienone-phenol rearrangements of a number of naphthalenic dienones proceeded through two different courses principally depending on the media used. For a typical example, 9-methyl-3-keto-$\Delta^{1,4}$-hexahydronaphthalene (I) has been reported to rearrange in acetic anhydride, *via*, the spiran, to the acetate of the *p*-cresol, 4-methyl-*ar*-1-tetralol (II). On the other hand, treatment of I with aqueous mineral acid mostly led, *via* a simple 1,2-methyl shift, to the *m*-cresol 4-methyl-*ar*-2-tetralol (III). Similar relationships between the reaction processes and media used have



I II III

IVa, b Va, b

been reported in many cases of the aromatizations of the steroidal $\Delta^{1,4}$-3-dienones.[4,5]

To test this generality the same reactions were applied to the aromatization of the $\Delta^{1,4}$-3-dienone system possessing the acetic acid side chain at the 6-position. This would serve to examine the conformational effects of the relatively bulky substituent on the course of the rearrangement.

The starting materials, *trans*- and *cis*-9-methyl-3-keto-$\Delta^{1,4}$-hexahydronaphthyl-6-acetic acids (IVa and IVb, respectively), were prepared by selenium dioxide oxidation of the corresponding stereomers of the 3-octalone-6-acetic acid (Va and Vb), in which the configurations have been established.[6] Rearrangement of the *trans*-dienoneacetic acid (IVa) was effected in acetic anhydride–sulfuric acid under standard conditions[3] and resuted in a mixture of the acetates. On recrystallization of this mixture, one acetate, m.p. 137.5–138.5°, was isolated in a 76% yield, which was hydrolyzed with alkali to a phenol A, m.p. 143–144°. Hydrolysis of the mother liquors of this acetate gave minute amounts of two other phenols B and C, which will be described below. The *trans*-dienone (IVa) was treated with 50% sulfuric acid leading to a mixture of the phenols. This mixture was subjected to chromatography on silica gel and eluted with chloroform-benzene. The first eluted fractions furnished in a 40% yield a phenol B, m.p. 158–158.8°, and traces of the phenol A. In addition, a phenol C, m.p. 160–161°, was isolated, in a 24% yield, from the last eluted fractions. The existence of the three different phenols were confirmed by the mixture melting point determinations and infrared spectra.

The aromatization of the *cis*-dienoneacetic acid (IVb) took place in a somewhat different way from that of the *trans*-isomer (IVa). With acetic anhydride–sulfuric acid, the *cis*-dienoneacetic acid rearranged to give predominantly the acetate of the phenol C, the yield of which was much better (50%) than that from IVa under the same conditions. Nevertheless the phenol A was obtained only in a relatively lower yield (20%) after hydrolysis of the mother liquors. Dilute sulfuric acid treatment of IVb, like that of IVa, resulted in a mixture, which separated predominantly the phenol C (70%) on fractional crystallizations. In addition, the mother liquors afforded traces of the phenol A.

These three products exhibited the same ultra-

(1) Paper XXI, H. Ogura, *J. Org. Chem.*, **25**, 679 (1960).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

(3) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950).

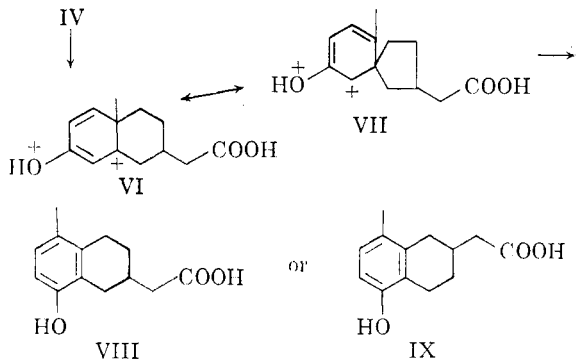
(4) A. S. Dreiding, W. J. Pummer, and A. J. Tomasewski, *J. Am. Chem. Soc.*, **75**, 3159 (1953).

(5) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and St. Kaufmann, *J. Am. Chem. Soc.*, **72**, 4540 (1950); R. B. Woodward, H. H. Inhoffen, H. O. Larson, and H. K. Menzel, *Chem. Ber.*, **86**, 594 (1953); A. S. Dreiding and W. J. Pummer, *J. Am. Chem. Soc.*, **75**, 3162 (1953); A. S. Dreiding and A. Voltman, *J. Am. Chem. Soc.*, **76**, 537 (1954).

(6) M. Yanagita, S. Inayama, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 690 (1958).

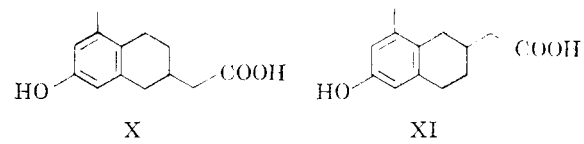
violet absorption maximum, $\lambda_{max}^{C_2H_5OH}$ 280 mμ (ε 2,050 ~ 2,200), typical of a phenol.[7] In the infrared spectrum the phenol A showed λ_{max}^{Nujol} 800 cm.$^{-1}$, attributable to two adjacent hydrogens on a benzene ring.[4,8] It indicates that it is a compound of the *p*-cresol type analogous to II. Contrary to phenol A, the phenols B and C had almost the same bands, respectively, ν_{max}^{Nujol} 868 and 864 cm.$^{-1}$, because of isolated hydrogens on a benzene ring.[8] From this, these latter two may be reasonably assigned the structures of the *m*-cresol type such as III.

Based on the mechanisms of the dienone-phenol rearrangements suggested previously,[3,4,9] the formation of a type of the *p*-cresol compound from IV may be anticipated to pass through the spiran intermediate (VII) *via* the cation (VI). The cleavage of the spiran ring would occur in either of two possible ways, leading to 4-methyl-*ar*-1-tetralol-7- or -6-acetic acid (VIII or IX, respectively). A choice between these two structures for the rearranged phenol A was made by synthetic study.



First, the former acid (VIII) was prepared by the standard method involving the reactions sequence (XVII → XXI), details of which will be described below. The desired tetralol-acetic acid (VIII), so obtained, had the m.p. 121–122°, and was obviously differentiated from the above phenol A, m.p. 143° (the mixture melting point examination and the infrared spectra). Evidently it follows that the phenol A must be represented by the alternative structure (IX), which was rigidly proved by the unequivocal syntheses (XXVII → XXX) described below.

For the two other phenols B and C, either of the two possible structures, 4-methyl-*ar*-2-tetralol-7- (X) or -6-acetic acid (XI) must be taken into consideration. Of these two, the former (X) seems more preferable, as it may reasonably result from the usual 1,2-shift of the angular methyl group in the dienone (IV), whereas the latter is much less probable. To clarify the problem, syntheses of these structures were undertaken. The 2-tetralol-7-acetic acid (X) was prepared by the conventional method starting with the tetralone (XXXI, R = H), which



was submitted to the reactions sequence similar to that described for IX from XXVII. The resulting product (X) m.p. 160–161°, was identified in every respect with the second phenol C. Parallel sequence starting with XXXII (R = H), in place of XXXI (R = H), led to the 2-tetralol-6-acetic acid (XI), m.p. 158–158.5°, completely indentical to the third phenol B. More detailed syntheses of these *m*-cresols will be stated later.

The rearranged products, described above, are summarized in Table I.

TABLE I

Compound	Medium	Major Products (Cresols)	Yield (%)
trans-Dienone (IVa)	$Ac_2O + H^+$	*p*-Type (Phenol A, IX)	76[a]
trans-Dienone (IVa)	50% H_2SO_4	*m*-Type (Phenol C, X)	24
		m-Type (Phenol B, XI)	40
cis-Dienone (IVb)	$Ac_2O + H^+$	*p*-Type (Phenol A, IX)	25[a]
		m-Type (Phenol C, X)	50
cis-Dienone (IVb)	50% H_2SO_4	*m*-Type (Phenol X)	77

[a] Including its acetate.

From this Table, it can be seen that the course of the rearrangements of the present dienones (IV) does not always conform to the above cited generalization[3,4] about the influences of the reaction media on the rearrangement processes. It is easily noted that, in agreement with this generality, the reaction of the *trans*-dienoneacetic acid (IVa) in anhydrous medium and of the *cis*-isomer (IVb) in aqueous acid afforded chiefly the normal *p*- and *m*-cresols, respectively. On the other hand, the predominant formation of the *m*-cresol (X), over the *p*-isomer, from the *cis*-dienone (IVb) in anhydrous medium was unexpected. Also it is somewhat surprising that the *trans*-dienone (IVa) with mineral acid furnished the anomalous compound *m*-cresol (XI), as the major product.

On the basis of the previous postulation for the dienone-phenol rearrangements, two possible mechanisms for the formation of the anomalous product (XI) from IVa are tentatively proposed as follows.

(7) A. Sondoval, L. Miramontes, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 990 (1951).

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co., Ltd., London, 1954, p. 67.

(9) R. B. Woodward, *Perspectives in Organic Chemistry*, Interscience, New York, 1956, p. 178; S. M. Bloom, *J. Am. Chem. Soc.*, 80, 6280 (1958).

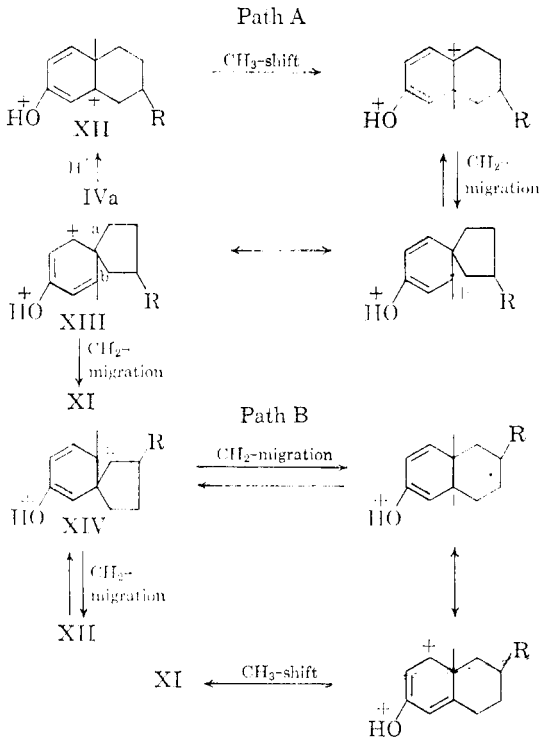
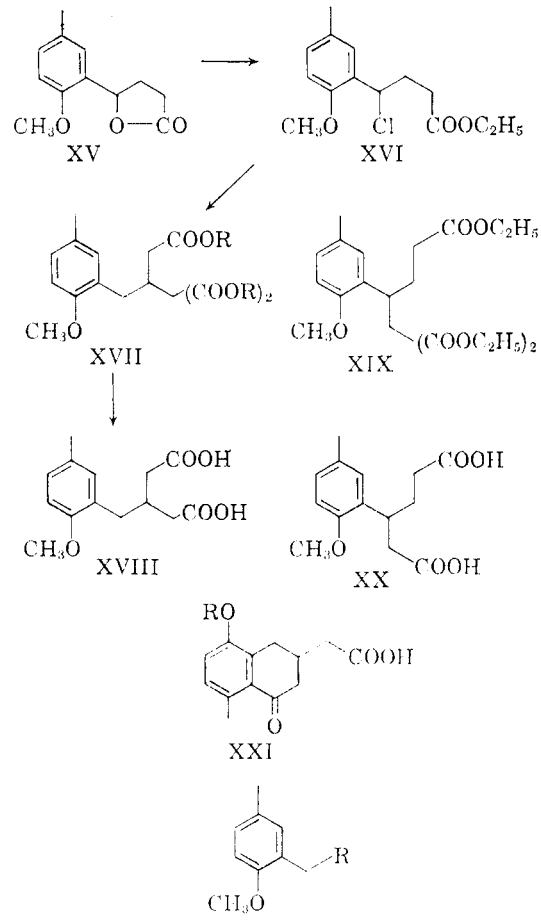


Figure 1

Two pathways (Fig. 1) involve different modes of triple Wagner-Meerwein rearrangements. Path A, starting with the cation XII, would in three steps form the spiran (XIII), in which, if the bond a is cleaved, XI would result. Alternatively the rupture of the bond b would lead to X, the normal product, the formation of the latter being differently explained as stated above. In Path B,[10] the cation (XII) would directly yield the spiran (XIV) relating to XI.

The foregoing results may demonstrate that on dienone-phenol rearrangement, the *trans*-dienone (IVa) carrying the acetic acid side chain axial shows stronger tendency to undergo the ring methylene group migration, whereas the *cis*-isomer (IVb) with the same residue at the equatorial position is inclined to suffer the shift of the angular methyl group. Such striking differences in the behavior of these two stereomers may be clearly ascribed to the differences in the conformational features, but a complete rationale of the available data is not yet apparent.

Now we should like to state the detailed syntheses of the above four phenols (VIII, IX, X, and XI). As simply described above, 4-methyl-*ar*-1-tetralol-7-acetic acid (VIII) was prepared through the sequence of reactions (XV → XVIII → XXI). By application of the procedures reported previously,[11] γ - hydroxy - γ - (2 - methoxy - 5 - methylphenyl)-butyric acid lactone (XV)[12] was treated with thionyl chloride and then with dry hydrogen chloride–ethanol. There was obtained in a satisfactory yield an oily chloroester (XVI), which was not completely purified. Moller[13] has published that condensation of ethyl α-bromoisobutyrate with sodiomethylmalonate produced, under a 1,2-shift, ethyl γ,γ - dicarbethoxy - α - methylvalerate. Under the similar conditions, the above crude chloroester was heated to reflux with diethyl sodiomalonate in ethanol. The crystalline adduct, obtained in a 66% yield, may be favorably assigned the rearranged structure (XVII R = C_2H_5) rather than the normal one (XIX), in view of the Moller's observation. This formulation was further supported by the fact that the triester (XVII, R = C_2H_5) was hydrolyzed and decarboxylated to give a dibasic acid (XVIII). The latter is different from the known adipinic acid (XX),[14] which would be derived from XIX under the same conditions. To



XXII. R = Cl
XXIII. R = $CH(COOC_2H_5)_2$
XXIV. R = $CH(CH_2OH)_2$
XXV. R = $CH(CH_2OSO_2CH_3)_2$
XXVI. R = $CH(CH_2CN)_2$

(10) This route was suggested by a referee.

(11) J. Cason, C. E. Adams, and L. L. Bennet, *J. Am. Chem. Soc.*, **66**, 1764 (1944).

(12) K. W. Rosenmund and D. Shopira, *Arch. Pharm.*, **313**, 272 (1934).

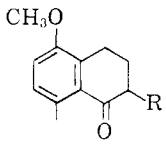
(13) E. Moller, *Ber.*, **43**, 3250 (1910).

(14) A. S. Dreiding and A. J. Tomasewski, *J. Org. Chem.*, **76**, 540 (1954).

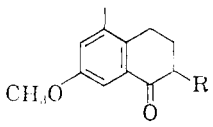
definitely prove the structure, XVIII was made by the standard method.[15] The alkylation of diethyl sodiomalonate with 2-methoxy-5-methylbenzyl chloride (XXII)[16] gave the benzylmalonate (XXIII), which was reduced with lithium aluminum hydride to the 1,3-diol (XXIV). The bismethanesulfonate (XXV) of this diol was converted to the dinitrile (XXVI) and, hence, to the corresponding benzylglutaric acid, identical to XVIII.

Cyclization of the chloride of the above benzylglutaric acid (XVIII) to the tetralone-acetic acid (XXI, R = CH_3) was readily effected with stannic chloride. On demethylation and subsequent Clemmensen reduction, the latter was converted to the desired tetralol-acetic acid (VIII), m.p. 121–122°.

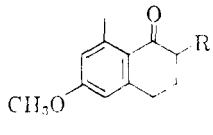
The structure (IX) for the phenol A was synthesized by the conventional method as follows: Condensation of 5-methoxy-8-methyl-1-tetralone (XXVII)[17] with ethyl oxalate gave the glyoxalate (XXVIII), which was decarbonylated to the β-keto ester (XXIX). The latter was condensed with ethyl



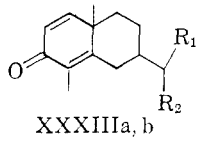
XXVII. R = H
XXVIII. R = $COCOOC_2H_5$
XXIX. R = $COOC_2H_5$
XXX. R = CH_2COOH



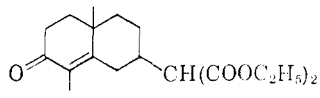
XXXI



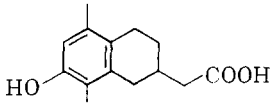
XXXII



XXXIIIa, b



XXXIVa, b



XXXV

bromoacetate, and then treated with alkali to give the acetic acid compound (XXX), which was demethylated and reduced by the Clemmensen method. The end product (IX) showed the m.p. 143°.

The starting point for X was 7-methoxy-5-methyl-1-tetralone (XXXI. R = H), which has been reported previously.[18] As described above, the conversion of this tetralone into the acetic acid compound (X) was carried out, through the glyoxalate (XXXI. R = $COCOOC_2H_5$) in five-steps, paralleling that cited above for XXVII → IX. The resulting 7-acetic acid (X) showed the m.p. 160–161°. By similar sequence, 6-methoxy-8-methyl-1-tetralone (XXXII. R = H), prepared as reported earlier,[18] was transformed into the 6-acetic acid isomer (XI), m.p. 158–158.5°.

In view of the above anomaly in the rearrangements of the dienones (IV), it seems worthwhile to study the rearrangement of the 4-methyl homologue of IV, 4,9-dimethyl-3-keto-$\Delta^{1,4}$-hexahydronaphthyl-6-acetic acid (XXXIII. R^1 = COOH and R^2 = H). It is well known that the 4,9-dimethyldienone moiety in the santonin series readily rearranges with acid to the *p*-xylenol derivatives. A small possibility, however, must be considered that, as in IV, the differences in the cofigurational features of the side chains would exert important influences on the rearrangement course in the same moiety in XXXIII (R^1 = COOH and R^2 = H).

Miki[19] has claimed that the *cis*-isomer of the above dimethyldienone, m.p. 194°, was prepared using the Δ^4-3-octalonemalonate (XXXIV) as the starting material. The reported sequence, involving five steps, was lengthy and the over-all yield was considerably low. Furthermore, the starting malonate, used by this worker, was supposedly assigned *cis*, but later corrected to *trans*.[6] Therefore, it is desirable to synthesize the dimethyldienones of the correct configurations. In the present work, the two stereomers of XXXIII (R^1 = COOH and R^2 = H) were prepared, in three steps, starting from the octalonemalonates (XXXIV) of the well established configurations. On usual selenium dioxide oxidation, the octalones (XXXIV) furnished, in satisfactory yields, the corresponding isomers of the dienonemalonates (XXXIII. R^1 = R^2 = $COOC_2H_5$). Upon hydrolysis and decarboxylation, the *trans*-malonate gave, in an over-all yield of 32%, the *trans*-dienoneacetic acid (XXXIIIa. R^1 = COOH and R^2 = H), m.p. 194–195°, identified with a sample of the Miki's "*cis*"-isomer.[20] Similarly, the *cis*-malonate (XXXIIIb. R^1 = R^2 = $COOC_2H_5$) afforded in better over-all yield (68%) the *cis*-dienone acetic acid (XXXIIIb. R^1 = R^2 = COOH), m.p. 151–153°. Rearrangements of both stereomers of the above dimethyldienone were effected with dilute sulfuric acid under the standard conditions.[3] There resulted in reasonable yields the identical xylenol 1,4-dimethyl-*ar*-2-tetralol-7-acetic acid (XXXV), as the only product detectable. This structure is based on the elementary analyses and the analogous migration of santonin. It was further supported by its ultraviolet spectrum (λ_{max} 285 mμ, log ϵ 3.29), similar to that

(15) J. H. Boothe, A. S. Kende, T. L. Fields, and R. G. Wilkinson, *J. Am. Chem. Soc.*, **81**, 1006 (1959).
(16) R. Quelet, *Compt. rend.*, **198**, 102 (1934).
(17) J. Herran, Q. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 899 (1951).
(18) A. S. Dreiding and W. J. Pummer, *J. Am. Chem. Soc.*, **75**, 3162 (1953).
(19) T. Miki, *J. Pharm. Soc. Japan*, **75**, 410 (1955).
(20) We wish to thank Dr. Miki, Research Laboratory, Takeda Pharmaceutical Industries, Osaka, Japan, for generous supply of this sample.

of 1,4-dimethylestradiol (λ_{max} 288 mμ, log ε 3.23).[21]

From these results, it is clear that 4,9-dimethyl-$\Delta^{1,4}$-dienones with mineral acid rearrange exclusively to the *p*-xylenol compound (XXXV), irrespective of the configurations of the acetic acid residue. These straightforward processes of the rearrangements of the dimethyldienones are in sharp contrast to the complicated courses described above for IV.

EXPERIMENTAL[22]

All temperatures were uncorrected. Infrared absorption spectra were measured with a Perkin-Elmer model 21 double beam spectrophotometer.

trans-9-Methyl-3-keto-$\Delta^{1,4}$-hexahydronaphthyl-6-acetic acid (IVa). Under the same conditions as described previously for the oxidation of 4,9-dimethyl-Δ^4-3-octalone,[6] *trans*-9-methyl-Δ^4-3-octalone-6-acetic acid[6] (Va, 4.02 g.) was heated to reflux with selenium dioxide (2.0 g.) in *tert*-butyl alcohol (280 cc.) for 48 hr., without addition of acetic acid as the solvent. The brown viscous product was dissolved in ethyl acetate, and on addition with benzene, the *trans*-9-methyldienoneacetic acid (IVa) separated as the crude crystals (1.36 g., 34%), m.p. 142–147°. Recrystallization from benzene-ethyl acetate formed pale yellow prisms, m.p. 150–151°; $\lambda_{max(m\mu)}^{C_6H_5OH}$ 241 (ε 15.800).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, C, 70.58; H, 7.26.

On chromatography, the mother liquors gave an additional 0.52 g. (total 47%).

cis-9-Methyl-3-keto-$\Delta^{1,4}$-hexahydronaphthyl-6-acetic acid (IVb). As described above for IVa, *cis*-9-methyl-Δ^4-3-octalone-6-acetic acid[6] (Vb, 2.05 g.) was oxidized with selenium dioxide. The brown viscous product was chromatographed on silica gel (30 g.) and the chloroform elution afforded the *cis*-dienoneacetic acid (IVb, 0.76 g. 38%), which was recrystallized from ethyl acetate-petroleum ether to form fine prisms, m.p. 95–96°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 240 (ε 14.400).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.22; H, 7.52.

Rearrangment of the trans-9-methyldienoneacetic acid (IVa) *in acetic anhydride.* This reaction was carried out principally by the procedure described for 9-methyl-3-keto-$\Delta^{1,4}$-hexahydronaphthalene.[3] IVa (0.56 g.) was dissolved in acetic anhydride (10 cc.) containing a trace of concentrated sulfuric acid, and allowed to stand for 20 hr. To decompose the anhydride, the pale yellow reaction was poured into cold water, and, on standing in a refrigerator, the acetate of the phenol A, 4-methyl-*ar*-1-tetralol-6-acetic acid (IX), deposited as crude crystals (0.44 g.), m.p. 131–135°. The mother liquors gave an additional 0.06 g. (total 76%). Recrystallization from benzene–petroleum ether formed colorless plates, m.p. 137.5–138.5°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 264 (ε 310); $\nu_{max(cm.^{-1})}^{Nujol}$ 1764 (CO of $OCOCH_3$), 1706 (CO of COOH), and 813 (adjacent hydrogens on a benzene ring).[4,8]

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.72 H, 7.17.

The above acetate (0.05 g.) was hydrolyzed in 10% potassium hydroxide at room temperature for 5 hr. to give the phenol A (IX, 0.035 g.), m.p. 142–143°. Recrystallization from benzene formed prisms, m.p. 143–144°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 280 (ε 2.140); $\nu_{max(cm.^{-1})}^{Nujol}$ 3190 (OH), 1688 (CO of COOH) and 800 (adjacent hydrogens on a benzene ring).[4,8] Its melting point was not depressed on admixture with IX, but obviously depressed with VIII, both of which were synthesized as described below.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.54; H, 7.03.

The mother liquor materials of the crystallizations of the acetate was hydrolyzed and the resulting phenolic mixture was chromatographed on silica gel. The elution with chloroform-ethyl acetate gave, in order, the phenols A (0.05 g.), B (0.02 g.), and C (0.02 g.), the latter two being described in the following paragraph and all identified by the mixture melting point examinations.

Rearrangement of the trans-9-methyldienoneacetic acid (IVa) *with 50% sulfuric acid.* This rearrangement was carried out by a slight modification of the procedure reported for the steroidal $\Delta^{1,4}$-3-dienones.[4] IVa (0.50 g.) was dissolved in 38 cc. of 50% sulfuric acid and heated at 55–60° for 20 hr. Soon a brown oil separated out from the solution, and after cooling, the mixture was diluted with water and extracted with ethyl acetate. The bicarbonate washing of the acetate extract was acidified and shaken with ethyl acetate. A viscous residue from evaporation of the acetate solution was chromatographed on silica gel (15 g.). The first elution with chloroform–ethyl acetate (19:1) afforded 0.20 g. (40%) of a mixture, chiefly consisting of the phenol B, 4-methyl-*ar*-2-tetralol-6-acetic acid (XI). Recrystallization from ethyl acetate–or benzene–petroleum ether gave fine prims, m.p. 158–158.5°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 280 (ε 2.200); $\nu_{max(cm.^{-1})}^{Nujol}$ 3360 (OH), 1712 (CO of COOH) and 864 (isolated hydrogens on a benzene ring).[4,8] This showed no depression of the melting point on admixture with an authentic sample of XI synthesized as described below.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.69: H, 7.11.

The mother liquors of the phenol B gave minute amounts of the phenol A, m.p. and mixed m.p. 143–144°.

From the later elution of the above chromatography, the crude phenol C (0.12 g., 24%), 4-methyl-*ar*-2-tetralol-7-acetic acid (X), m.p. 155–158°, was isolated. Recrystallization from ethyl acetate–petroleum ether formed prisms, m.p. 160–161°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 280 (ε 2.050); $\nu_{max(cm.^{-1})}^{Nujol}$ 3190 (OH), 1705 (CO of COOH) and 868 (isolated hydrogens on a benzene ring).[4,8] This melting point was not depressed on admixture with an authentic sample of X synthesized as described below.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found C, 70.71; H, 7.34.

Rearrangement of the cis-9-methyldienoneacetic acid (IVb) *in acetic anhydride.* Under the same conditions as described above for IVa, the *cis*-dienoneacetic acid (IVb, 0.48 g.) was allowed to react with acetic anhydride-sulfuric acid. After decomposition of the anhydride, the aqueous solution, separating no solid, was extracted with ethyl acetate. Evaporation of the acetate left a viscous oil, which crystallized from benzene–petroleum ether to give the above acetate (0.12 g., 21%), m.p. and mixed m.p. 137.5–138.5°, of the phenol A.

The combined mother liquors of the acetate afforded a viscous oil (0.38 g.), which was hydrolyzed with alkali to give a crystalline mixture of the phenols. On recrystallization from benzene, the phenol C (X), m.p. and mixed m.p. 160–161°, separated out in a 50% yield (0.25 g.). From its mother liquors, minute amounts of the additional phenol A (IX, 0.02 g., 4%) were detected after chromatography on silica gel.

Rearrangement of the cis-9-methyldienoneacetic acid (IVb) *with 50% sulfuric acid.* Similarly as described for IVa, IVb (0.30 g.) was treated with 50% sulfuric acid (25 cc.) resulting in a viscous oil. Crystallization from ethyl acetate–petroleum ether afforded the phenol C (X, 0.21 g.), m.p. and mixed m.p. 160–161°. On chromatographic separation of the mother liquors on silica gel, the elution with chloroform furnished traces of IX and the following elution with chloroform–ethyl acetate gave an additional X (0.02 g., total 77%).

(21) F. Sondheimer and Y. Mazur, *J. Am. Chem. Soc.*, **79**, 2906 (1957).

(22) Microanalyses were carried out by Mrs. Ch. Inayama and the ultraviolet measurements by Miss M. Suzuki, both of Keio University.

Ethyl γ-chloro-γ-(2-methoxy-5-methylphenyl)butyrate (XVI) By application of the procedure of Cason and Adams,[11] 14.2 g. of thionyl chloride was added to a solution of 8.16 g. of γ-hydroxy-γ-(2-methoxy-5-methylphenyl)butyric acid lactone (XV)[12] in 10 cc. of dry benzene. and heated to reflux for 3 hr. To the cooled brown solution, 28 cc. of ethanol saturated with dry hydrogen chloride was added in a period of 10 min., and allowed to stand at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residual oil was fractionated to afford 8.16 g. (77%) of the crude chlorobutyrate (XVI) as almost colorless oil, b.p. 160–165° at 7 mm. It distilled with slight decomposition even under reduced pressure, and was used for the following step without further purification.

Diethyl α-carbethoxy-α-(2-methoxy-5-methylphenyl)glutarate (XVII. R = C_2H_5). This was prepared by the general procedure[13] for preparing the malonate adducts. To a solution of diethyl sodiomalonate (1.56 g. of metallic sodium in 25 cc. of absolute ethanol and 11.0 g. of diethyl malonate) was added a solution of 9.16 g. of the above crude chloroester (XVI) in 10 cc. of absolute ethanol. The mixture was heated to reflux on a water bath for 50 min. After cooling, the reaction was acidified with acetic acid and concentrated under reduced pressure. The residual oil was mixed with water, extracted with ether, and the ether extract was washed with aqueous bicarbonate. Evaporation of the ether and three distillations of the residue furnished 8.85 g. of almost colorless viscose, b.p. 205–210° at 5 mm., which solidified after standing in a refrigerator; m.p. 61–63°. Recrystallization from petroleum ether afforded 7.86 g. of the triester (XVII. R = C_2H_5), m.p. 64–65°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 222.5 (ε 6.550) and 280 (ε 2.330).

Anal. Calcd. for $C_{21}H_{30}O$: C, 63.74; H, 7.66. Found: C, 63.95; H, 7.56.

The mother liquors gave an additional 0.52 g. (total 74%).

Hydrolysis of the triester (5.0 g.) was conducted by refluxing with alkaline solution (9 g. of potassium hydroxide in 12 cc. of water and 60 cc. of methanol) for 5 hr. The product crystallized out from ethyl acetate by addition of petroleum ether to afford 3.6 g. (93%) of the tribasic acid (XVII. R = H) as colorless prisms, m.p. 167–168° (dec.); $\lambda_{max(m\mu)}^{C_2H_5OH}$280 (ε 2.400).

Anal. Calcd. for $C_{15}H_{18}O$: C, 58.06; H, 5.85. Found: C, 57.94; H, 5.87.

β-(2-Methoxy-5-methylbenzyl)glutaric acid (XVIII). The above tribasic acid (XVII. R = H, 4.10 g.) was pyrolyzed at 200–210° for 15 min. The melt crystallized from ethyl acetate by addition of petroleum ether to give the glutaric acid (XVIII, 2.84 g., 81%) as fine needles, m.p. 130–131°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 280 (ε 2.140).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.13; H, 6 81. Found: C, 63.31; H, 6.89.

For rigid proof of the structure, this material was prepared by another route described below.

5-Methoxy-8-methyl-1-tetralone-3-acetic acid (XXI. R = CH_3). To a suspension of 2.20 g. of the above glutaric acid (XVIII) in 12 cc. of dry benzene was added 4.60 g. of phosphorus pentachloride in portions. The reaction started somewhat exothermically and, after standing for 2 hr. at room temperature, the mixture was gently warmed to make a clear solution. To the cooled solution was added 7.30 g. of stannic chloride in 8 cc. of dry benzene and kept in an ice bath for 20 min. The mixture was poured into iced dilute hydrochloric acid and extracted with ether. The residual oil of the ether extract, which in some runs contained a substantial amount of a neutral fraction, was hydrolyzed by reflux in 5% aqueous methanolic sodium carbonate for 2 hr. On concentration and acidification, the reaction furnished 1.79 g. (87%) of the 5-methoxytetralone (XXI. R = CH_3), m.p. 146–151°. Recrystallization from ethyl acetate-petroleum ether formed colorless prisms, m.p. 154–155°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 226 (ε 24.000), 256 (ε 9.700), and 325 (ε 3.800).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.85; H, 6.58.

5-Hydroxy-8-methyl-1-tetralone-3-acetic acid (XXI. R = H). The above methoxytetralone (XXI. R = CH_3, 0.45 g.) was heated to reflux in 8 cc. of 48% hydrobromic acid for 2 hr. On cooling, a small amount of crystals separated out from the reaction, and after dilution with water, 0.37 g. (81%) of XXI (R = H), m.p. 209–211°, was collected. Recrystallization from ethanol- or acetone-benzene formed colorless needles, m.p. 216–217°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 228 (ε 17.000), 258 (ε 9.050), and 329 (ε 3.470).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.68; H, 5.89.

4-Methyl-ar-1-tetralol-7-acetic acid (VIII). The above 5-hydroxytetralone (XXI. R = H, 0.15 g.) was added to a suspension of 1.7 g. of zinc amalgam in a mixture of 1 cc. of water, 4 cc. of concd. hydrochloric acid and 0.5 cc. of toluene, and heated to reflux for 16 hr. The cooled reaction was decanted from the undissolved metals and shaken with ethyl acetate, and the organic layer was washed with water. Drying and concentration of the solvent left a yellowish solid (VIII) (0.08 g., 53%), which was recrystallized from ethyl acetate by addition of petroleum ether to give prisms, m.p. 121–122°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 280 (ε 1.860); $\nu_{max(cm.^{-1})}^{Nujol}$ 3310 (OH), 1700 (CO of COOH), and 818 (adjacent hydrogens on a benzene ring).[8]

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.46; H, 7.43.

2-(2-Methoxy-5-methylbenzyl)-1,3-propanediol (XXIV). Essentially as described above for the glutarate (XIX. R = C_2H_5), the sodiomalonate (from 18.0 g. of diethyl malonate and 2.37 g. of metallic sodium) was alkylated with 17.2 g. of 2-methoxy-5-methylbenzyl chloride (XXII), prepared as reported previously.[16] There was obtained 24.9 g. (80%) of diethyl 2-methoxy-5-methylbenzylmalonate (XXIII) as an almost colorless liquid, b.p. 169–171° at 5 mm., which was used for the next step without further purification.

The lithium aluminum hydride reduction of the above benzylmalonate (XXIII) was carried out by the standard procedure. To an ice-cooled solution of 10.0 g. of XXIII in 10 cc. of absolute ether was added, with stirring, a solution of 1.6 g. of lithium aluminum hydride in 80 cc. of absolute ether over a period of 30 min. After the stirring was continued at room temperature for additional 15 min., the mixture was heated to reflux for 10 min. The reaction was worked up as usual to afford a crystalline solid, which was recrystallized from petroleum ether to give 5.3 g. (76%) of the 1,3-propanediol (XXIV) as colorless plates, m.p. 76–78°. Further recrystallization from benzene-petroleum ether raised the melting point to 80–81°; $\lambda_{max(m\mu)}^{C_2H_4OH}$ 221 (ε 6.360) and 279 (ε 2.050).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 68.54; H, 8.63. Found: C, 68.38; H, 8.38.

2-(2-Methoxy-5-methylbenzyl)-1,3-propanediolbis(methanesulfonate) (XXV). According to the general procedure reported previously,[23] the above 1,3-propanediol (XXIV, 0.33 g.) in pyridine (2 cc.) reacted with methanesulfonyl chloride (0.5 cc.). The reaction was poured into dilute hydrochloric acid, and an oil, separated, was taken up in ether. Drying and evaporation of the ether solution gave quantitatively the bismethanesulfonate (XXV) as crystals. Recrystallization from benzene by addition of petroleum ether formed needles, m.p. 67–68°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 225 (ε 8.080) and 280 (ε 2.820).

Anal. Calcd. for $C_{14}H_{22}O_7S_2$: C, 45.63; H, 6.05; S, 17.49. Found: C, 45.88; H, 6.25; S, 16.97.

β-(2-Methoxy-5-methylbenzyl)glutaric acid (XVIII). This was prepared from the above bismethanesulfonate (XXV) *via* the dinitrile (XXVI) by similar procedures as described previously.[23] To a solution of 0.37 g. of XXV in

(23) M. S. Newman and R. M. Wise, *J. Am. Chem. Soc.*, 78, 450 (1956).

2 cc. of dimethylformamide was added a solution of 0.2 g. of potassium cyanide in 0.5 cc. of water. After heating at 90–100° for 3 hr., the mixture was poured into ice water and extracted with benzene. Drying and evaporation of the benzene extract afforded 0.19 g. of the crude dinitrile (XXVI) as a light-brown oil.

To the above dinitrile, dissolved in 3 cc. of ethanol, was added a solution of 0.15 g. of potassium hydroxide in 0.5 cc. of water, and heated to reflux on a water bath for 5 hr. Worked up as usual, there was obtained 0.18 g. (68%) of the benzylglutaric acid (XVIII), from benzene-petroleum ether. This melting point was not depressed on admixture with a sample, alternatively prepared as above.

Ethyl 5-methoxy-8-methyl-1-tetralone-2-glyoxalate (XXVIII). By the general method described by Bachman *et al.*,[24] 0.96 g. of 5-methoxy-8-methyl-1-tetralone (XXVII), prepared as described previously,[17] was condensed with 1.5 g. of diethyl oxalate in dry benzene in the presence of sodium ethoxide (from 0.23 g. of metallic sodium). After working up as usual, the reaction product was completely dissolved in 2% iced alkali, and acidification of the alkaline solution separated immediately 1.45 g. (quantitative) of the glyoxalate (XXVIII) as yellow crystals, m.p. 63–67°. Purification by passing through silica gel in benzene and recrystallization from petroleum ether formed yellow needles, m.p. 68–69°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 253 (ϵ 7.800) and 332.5 (ϵ 16.400). This showed a wine-red coloration with ethanolic ferric chloride.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.29; H, 6.27.

Ethyl 5-methoxy-8-methyl-1-tetralone-2-carboxylate (XXIX). The above glyoxalate (XXVIII, 1.00 g.) was pyrolyzed over powdered glass (0.7 g.) at 170–175° for 30 min. The reaction mass, removed from the glass, was fractionated to 0.72 g. (80%) of a pale yellow oil (XXIX), b.p. 165–170° at 3 mm., which soon solidified; m.p. 74–76°. Recrystallization from petroleum ether formed colorless needles, m.p. 77–78°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 228 (ϵ 22.050), 257 (ϵ 9.800), and 322 (ϵ 4.750). This, in spite of a β-keto ester, showed no coloration with ethanolic ferric chloride.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.61; H 6.74.

5-Methoxy-8-methyl-1-tetralone-2-acetic acid (XXX). To a *tert*-butoxide solution (0.15 g. of metallic potassium in 5 cc. of *tert*-butyl alcohol) was added, with stirring, a solution of 0.26 g. of the above carboxylate (XXIX) in 0.5 cc. of dry benzene, followed by 0.65 g. of ethyl bromoacetate. The stirring was further continued at room temperature for 30 min., and then the mixture was heated on a water bath for additional 30 min. The light brown solution was concentrated under reduced pressure and extracted with ether. After washing with aqueous bicarbonate and water, the ether was evaporated to leave a brown oil (0.4 g.), which could not be crystallized. This oil, as described above for XVII (R = H), was hydrolyzed by refluxing in alkaline solution to give 0.20 g. (81.5%) of the acetic acid (XXX), m.p. 118–121°. Recrystallization from ethyl acetate by addition of petroleum ether formed needles, m.p. 122–123°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 226 (ϵ 19.800), 254 (ϵ 8.450), and 320 (ϵ 3.210).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6 50. Found: C, 67.55: H, 6.35.

5-Hydroxy-8-methyl-1-tetralone-2-acetic acid (XXX. OH instead of OCH_3). The above 5-methoxyacetic acid (XXX, 0.10 g.) was heated with 48% hydrobromic acid as described above for XXI (R = H). There was obtained 0.08 g. (85% of the crude 5-hydroxy compound, m.p. 214–220°. Recrystallization from ethyl acetate formed prisms, m.p. 220–221°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 226 (ϵ 19.000), 257 (ϵ 9.300), and 324 (ϵ 3.500).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.52; H, 5.93.

4-Methyl-ar-1-tetralol-6-acetic acid (IX). The above 5-hydroxyacetic acid (XXX, OH instead of OCH_3) (0.06 g.) was reduced by the Clemmensen method as described above for VIII. The product (IX, 0.04 g., 70%) was recrystallized from ethyl acetate by addition of petroleum ether to form fine prisms, m.p. 143–144°.

Ethyl 7-methoxy-5-methyl-1-tetralone-2-glyoxalate (XXXI. R = $COCOOC_2H_5$). Under similar conditions as described above for XXVIII, 7-methoxy-5-methyl-1-tetralone (XXXI. R = H) (1.90 g.), prepared as described previously,[18] was condensed with diethyl oxalate (2.92 g.) in the presence of sodium ethoxide. Acidification of the alkaline extract from the reaction afforded the glyoxalate (XXXI. R = $COCOOC_2H_5$) as crystals (2.62 g., 91%), m.p. 92–98°. Recrystallization from benzene by addition of petroleum ether furnished yellow plates, m.p. 101–102°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 325 (ϵ 10.160) and 370 (ϵ 9.420). This showed a brown-green coloration with ethanolic ferric chloride.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 65 96; H, 6.57.

Ethyl 7-methoxy-5-methyl-1-tetralone-2-carboxylate (XXXI. R = $COOC_2H_5$). As described for XXIX, the above 7-methoxyglyoxalate (XXXI. R = $COCOOC_2H_5$) (2.42 g.) was pyrolyzed over powdered glass (1.7 g.). The product was fractionated to a light yellow oil (1.73 g., 79%), b.p. 195–201° at 2 mm., which soon solidified. Two recrystallizations from benzene by addition of petroleum ether formed pale yellow prisms, m.p. 91–91.5°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 225 (ϵ 20.800), 265.5 (ϵ 6.650), 295 (ϵ 11.800), 307.5 (ϵ 11.700), and 335 (ϵ 9.800). This, in spite of a β-keto ester, showed no coloration with ethanolic ferric chloride.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68 73; H, 6.93.

It formed quantitatively a 2,4-dinitrophenylhydrazone, m.p. 206–207°, from benzene–petroleum ether.

Anal. Calcd. for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 501; N, 12.66. Found: C, 57.28; H, 5.04; N, 12.92.

7-Methoxy-5-methyl-1-tetralone-2-acetic acid (XXXI. R = CH_2COOH). The above 7-methoxy-carboxylate (XXXI. R = $COOC_2H_5$) (1.10 g.), as described for XXX, was alkylated with ethyl bromoacetate (1.94 g.) and then hydrolyzed with alkali. The acetic acid compound was obtained as crude crystals (0.96 g., 93%), melting in the range 143–150°. Recrystallization from benzene formed fine prisms, m.p. 151–152°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 220 (ϵ 19.100), 275.5 (ϵ 8.250), and 320 (ϵ 3.030).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: 67.80; H, 6.84.

7-Hydroxy-5-methyl-1-tetralone-2-acetic acid (XXXI R = CH_2COOH, OH instead of OCH_3). As described for XXI (R = H), the above 7-methoxyacetic acid (0 30 g.) was treated with hydrobromic acid to give the 7-hydroxy compound (0.265 g., 94%), m.p. 182–187°. Recrystallization from ethyl acetate or dilute methanol formed needles, m.p. 193–194°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 214 (ϵ 20.600), 258 (ϵ 9.800) and 326 (ϵ 3.360).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.93; H, 6.20.

4-Methyl-ar-2-tetralol-7-acetic acid (X). As described above for VIII, the above 7-hydroxyacetic acid (0.50 g.) was reduced by the Clemmensen method. The product (X, 0.30 g., 64%), m.p. 155–160°, was recrystallized from ethyl acetate by addition of petroleum ether to give prisms, m.p. 160–161°.

Transformation of XXXII (R = H → $COCOOC_2H_5$ → CH_2COOH) *into* XI This reaction sequence was conducted parallel to that described above for IX from XXVII. Reaction of diethyl oxalate (1.35 g.) with 6-methoxy-8-methyl-1-tetralone (XXXII. R = H, 0 90 g.), prepared as described previously,[18] furnished the glyoxalate (XXXII. R = $COCOOC_2H_5$) (1.22 g., 90%), m.p. 57–60°. Recrystallization from petroleum ether formed yellow prisms, m.p. 61–62°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 247 (ϵ 5.020) and 345 (ϵ 15.400). This material showed a brown-green coloration with ethanolic ferric chloride.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25; Found: C, 65.78; H, 6.11.

(24) W. E. Bachman, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

Pyrolysis of the glyoxalate (1.15 g.) afforded the carboxylate (XXXII. R = $COOC_2H_5$) (0.85 g., 82%) as a pale yellow oil, b.p. 167–176° at 1.5 mm.; $\lambda_{max(M\mu)}^{C_2H_5OH}$ 226 (ϵ 11.200) and 277 (ϵ 14.350). Alkylation of this ester (0.90 g.) with ethyl bromoacetate (1.20 g.) gave the diethyl ester (XXXII. R = $COOC_2H_5$ and $CH_2COOC_2H_5$) (0.77 g., 64%) as crystals, m.p. 68–72°. Recrystallization from benzene-petroleum ether formed fine colorless prisms, m.p. 74–75°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 227 (ϵ 13.150) and 277 (ϵ 16.200).

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.76; H, 6.93.

Alkaline hydrolysis of the diester (0.60 g.) furnished quantitatively the ketoacetic acid (XXXII. R = CH_2COOH) which was recrystallized from benzene to give prisms, m.p. 155–156°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 225 (ϵ 13.300) and 273 (ϵ 14.800).

Anal. Calcd. for $C_{14}H_{16}O_4$; C, 67.73; H, 6.50. Found: C, 67.52; H, 6.37.

Clemmensen reduction of the above ketoacetic acid (0.08 g.) gave the methoxyacetic acid (XI. OCH_3 instead of OH) (0.05 g.), which was recrystallized from dilute methanol to give prisms, m.p. 127–128°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 215 (ϵ 7.400) and 283 (ϵ 1.900).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.87; H, 7.48.

Acid treatment of the above methoxyacetic acid (0.05 g.) afforded 4-methyl-*ar*-2-tetralol-6-acetic acid (XI) as crude crystals (0.02 g.), m.p. 153–155°. Purification by passing through silica gel in chloroform–ethyl acetate (1:1) and recrystallization from ethyl acetate–petroleum ether formed fine prisms, m.p. 158–158.5°.

Diethyl trans- and cis-4,9-dimethyl-3-keto-$\Delta^{1,4}$-hexahydronaphthyl-6-malonates (XXXIII. $R^1 = R^2 = COOC_2H_5$). By the general method described above for IV, *trans*-4,9-dimethyl-Δ^4-3-octalone-6-malonate (XXXIVa, 3.2 g.), prepared as reported previously,[6] was treated with selenium dioxide (1.15 g.). There resulted a red-brown oil, which was fractionated to give the *trans*-dimethyldienone (XXXIIIa. $R^1 = R^2 = COOC_2H_5$) as a light brown oil (2.33 g., 73%), b.p. 171–172° at 0.015 mm. This fraction could not be induced to crystallization.

It formed quantitatively a 2,4-dinitrophenylhydrazone as brown-red scales, m.p. 167–169°, from ethanol-ethyl acetate; $\lambda_{max(m\mu)}^{CHCl_3}$ 257.5 (ϵ 19.155), 311 (ϵ 7.122), and 403 (ϵ 38.100).

Anal. Calcd. for $C_{25}H_{30}N_4O_8$: C, 58.36; H, 5.58; N, 10.89. Found: C, 58.81; H, 5.59; N, 10.75.

The distillation residue of the above fraction was dissolved in ether and the ether solution was passed through an alumina column. On evaporation of the ether, the selenium compound[25] (0.02 g.) was obtained as white crystals, m.p. 168–171°. Two recrystallizations from ethyl acetate raised the melting point to 177–179°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 242 (ϵ 9.661) and 264 (ϵ 10 589).

Anal. Calcd. for $C_{19}H_{26}O_5$ Se: C, 55.18; H, 6.34. Found: C, 55.08; H, 6.07.

Similarly, the *cis*-octalonemalonate (XXXIVb, 1.1 g.), prepared as reported previously,[6] was dehydrogenated to give the *cis*-dimethyldienone (XXXIIIb. $R^1 = R^2 = COOC_2H_5$) as a pale yellow oil (0.83 g., 76%), b.p. 171–172° at 0.015 mm.; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 242 (ϵ 10.602) and 265 (ϵ 7.121) (inf.). This fraction could not be induced to crystallization. Contrary to the *trans*-series, the distillation residue in this case did not reveal the presence of the selenium compound.

The *cis*-ketone formed quantitatively a 2,4-dinitrophenylhydrazone as deep-red scales, m.p. 164–166°, from ethyl acetate-ethanol; $\lambda_{max(m\mu)}^{CHCl_3}$ 257 (ϵ 15.500), 311 (ϵ 5.609), and 405 (ϵ 29.520).

Anal. Calcd. for $C_{25}H_{30}N_4O_8$: C, 58.36; H, 5.58; N, 10.89. Found: C, 58.49; H, 5.62; N, 10.71.

Respective transformations of the dimethyldienonemalonates (XXXIII. $R^1 = R^2 = COOC_2H_5$) *into the acetic acid compounds* (XXXIII. R^1 = H and R^2 = COOH) *via the malonic acids* (XXXIII. $R^1 = R^2$ = COOH). These sequences were conducted under similar conditions as described earlier for the analogous dienone malonates.[6]

Alkaline hydrolysis of the *trans*-dienonemalonate (XXXIIIa. $R^1 = R^2 = COOC_2H_5$) (0.80 g.) gave in 60% crude yield the *trans*-malonic acid XXXIIIa. $R^1 = R^2$ = COOH) (0.40 g.), which on crystallization from ethyl acetate formed colorless prisms, m.p. 125–126° dec.; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 241 (ϵ 20.805) and 263 (ϵ 15.203) (inf.).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.49; H, 6.68.

Pyrolysis of the above malonic acid (0.37 g.) afforded the *trans*-dienoneacetic acid (XXXIIIa. R^1 = H and R^2 = COOH) (0.23 g., 74%), which was recrystallized from ethyl acetate to give colorless prisms, m.p. 194–195°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 241 (ϵ 11.320) and 265 (ϵ 8.002) (inf.). This showed no depression of the melting point on admixture with a sample of the Miki's "*cis*"-dienoneacetic acid.[19,20]

Similarly, the *cis*-dienonemalonate (XXXIIIb. $R^1 = R^2 = COOC_2H_5$) furnished in a 96% yield the *cis*-malonic acid (XXXIIIb. $R^1 = R^2$ = COOH), which on crystallization from ethyl acetate formed colorless prisms, m.p. 176–178° (dec.); $\lambda_{max(m\mu)}^{C_2H_5OH}$ 241 (ϵ 20.550) and 262 (ϵ 15.185) (inf.).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.28; H, 6.73.

Decarboxylation of the *cis*-malonic acid led to a 95% yield of the *cis*-acetic acid (XXXIIIb. R^1 = H and R^2 = COOH), which on crystallization from ethyl acetate formed colorless prisms, m.p. 152–154°; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 240 (ϵ 10.824) and 265 (ϵ 7.799) (inf.).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.52; H, 7.35.

It formed quantitatively a 2,4-dinitrophenylhydrazone as deep-red prisms, m.p. 197–202°, from ethyl acetate; $\lambda_{max(m\mu)}^{CHCl_3}$ 258 (ϵ 17.343), 311 (ϵ 6.402) and 404.5 (ϵ 33.214).

Anal. Calcd for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.88; H, 5.68; N, 13.09.

Rearrangements of the dimethyldienoneacetic acids (XXXIII. R^1 = H and R^2 = COOH). Under the same conditions as described above for IVa, the *trans*-acetic acid (XXXIIIa. R^1 = H and R^2 = COOH, 0.50 g.) was warmed with 50% sulfuric acid (30 cc.). Soon the clear solution turned cloudy and the brown semisolid separated out in 6 hr. After increase of the separation had not been observed, the reaction was diluted with ice water and the crude crystals (0.45 g.), melting in the range 120–153°, were collected and chromatographed on silica gel (10 × 1.5 cm.) in chloroform. All fractions, after crystallization from ethyl acetate-petroleum ether, had the same melting point (mixed), 153–160°, indicating the homogeneity of the rearranged product. Further recrystallizations from the same mixture afforded 0.30 g. (60%) of the xylenol (XXXV) as white prisms, m.p. 164–166°[26]; $\lambda_{max(m\mu)}^{C_2H_5OH}$ 213 (ϵ 8.258) and 285 (ϵ 1.968).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.30; H, 7.76.

It formed quantitatively an acetate, colorless prisms, m.p. 108–110° (from benzene–petroleum ether).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.32; H, 7.28.

The combined mother liquors furnished an additional 0.04 g., but any other traceable materials could not be isolated.

(25) Similar selenium adducts have been reported to be isolated from selenium dioxide oxidations of the Δ^4-3-monoenone systems; K. Florey and A. R. Restivo, *J. Org. Chem.*, **22**, 406 (1957) and related references cited there.

(26) T. Miki [*J. Pharm. Soc. Japan.*, **75**, 399 (1955)] gave the m.p. 111° for the *d*-form of XXXV

The action of sulfuric acid on the *cis*-isomer (XXXIIIb. R^1 = H and R^2 = COOH) proceeded similarly giving the comparable yield (86%) of the identical xylenol (XXXV), m.p. 160–162°. Recrystallization from ethyl acetate–hexane formed white prisms, m.p. and mixed m.p. 164–166°. Any other traceable materials could not be obtained from the mother liquors.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF HAWAII]

Hawaiian Plant Studies. VI. The Structure of Holeinine[1]

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A new colorless alkaloid, *holeinine*, was isolated from *Ochrosia sandwicensis* A. Gray. It was shown to be N_b-methylisoreserpilinium chloride.

In the course of our research on the constituents of Hawaiian plants it seemed attractive to investigate the alkaloids of *Ochrosia sandwicensis* A. Gray. *Ochrosia* is one of some 300 genera in the plant family APOCYNACEAE and its *ca.* thirty-six species[3] are distributed from Madagascar through Malaya and tropical Australia into Polynesia.[4] *O. sandwicensis* is the only endemic Hawaiian representative of the genus. It is reported[4] to be botanically related to *O. elliptica* and *O. oppositifolia*. The Hawaiian name of the tree, which is rather scarce now, is *holei*. A yellow *tapa* dye used to be extracted from the wood and the roots[4]; the bark and leaves were extracted with boiling water and the steaming extract was used in sweat bath treatments.[5]

When the present study was initiated, the chemical literature of the genus *Ochrosia* consisted of one paper by Greshoff[6] in which he reported the presence of alkaloids in four *Ochrosia* species. He surmised the presence of three separate bases by virtue of color and solubility. While this work was in progress Buzas *et al.*[7] isolated and characterized a yellow base from *O. oppositifolia;* Goodwin and co-workers[8] isolated four alkaloids from *O. elliptica*, of which they identified the known isoreserpiline and characterized three new compounds, ellipticine, methoxyellipticine and elliptinine; from a small collection of *O. sandwicensis*[9] Goodwin[8] isolated ellipticine, methoxyellipticine, and a new colorless alkaloid; the synthesis of ellipticine, which represents the first example of a novel ring system was reported by Woodward, Hochstein, and Iacobucci[10]; and, most recently, Moore[11] reported the isolation of five new alkaloids in addition to isoreserpiline from *O. poweri*.

During the early stages of this work we, too, isolated ellipticine and methoxyellipticine, but we discontinued our efforts in that direction when Goodwin informed us of her work prior to publication. This paper deals with the structure determination of a new colorless alkaloid from *O. sandwicensis*, which we have called holeinine after the Hawaiian name of the *Ochrosia* tree.

The plant material was collected on the island of Maui in the Auahi lava fields, about eight miles from Ulupalakua at an elevation of *ca.* 3000 feet.[12] The dried and milled root and trunk bark was extracted by conventional procedures (see experimental). The crude alkaloids were obtained as a brown solid, which was repeatedly treated with benzene. This treatment removed a mixture of yellow bases, ellipticine, methoxyellipticine and, after chromatography on acid-washed alumina a third yellow base, m.p. 289–296° dec., whose spectral characteristics were similar to, but not identical with, those of ellipticine. It was obtained in 0.04% yield and has not been investigated further. The benzene-insoluble residues were extracted with water. Removal of the water, treatment of the solid residue with methanol and chro-

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(9) Goodwin *et al.* name their plant material *O. sandwicensis* A. DC. According to Rock[4] this name is synonymous with *Rauwolfia sandwicensis* A. DC. and the authority for *O. sandwicensis* is A. Gray.

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(12) The assistance of Mr. Henry C. Inciong is gratefully acknowledged.