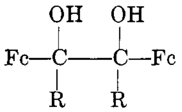
TABLE I

DIFERROCENYLDIOLS



$$Fc-\underset{R}{\overset{OH}{C}}-\underset{R}{\overset{OH}{C}}-Fc$$

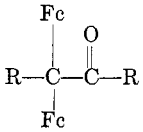
Fc = ferrocenyl

R	Yield, %	M.p., °C.[a]	Calcd., %			Found, %		
			C	H	Fe	C	H	Fe
C_2H_5–	31	113–115	61.93	6.40	22.15	61.86	6.43	22.30
n-C_3H_7–	55[b]	126–128	65.39	6.66	21.72	65.27	6.69	21.93
n-C_4H_9–	60[b]	94–97	66.44	7.06	20.60	66.25	7.11	20.85

[a] Recrystallized product. [b] Crude yield.

TABLE II

DIFERROCENYL KETONES



$$R-\underset{Fc}{\overset{Fc}{C}}-\overset{O}{\overset{\|}{C}}-R$$

Fc = ferrocenyl

R	Yield, %	M.p., °C.	Calcd., %			Found, %		
			C	H	Fe	C	H	Fe
C_2H_5–	47	110–111.5	66.70	6.03	23.86	66.67	6.25	23.80
n-C_3H_7–	60	108.5–109.5	67.76	6.50	22.51	67.65	6.65	22.55
n-C_4H_9–	42	62–64	68.72	6.92	21.31	68.69	7.11	21.33

petroleum ether (60–90°). The infrared spectrum of the diol (tetrachloroethane solution) showed strong hydroxyl absorption at 3400 cm.$^{-1}$. After several days' storage at room temperature, a sample of the solid slowly turned to a reddish brown oil which which was identified through its infrared spectrum as n-butyrylferrocene.

Preparation of Diferrocenyl Ketones.—The rearranged ketones prepared through the dehydration of the diols are listed in Table II. Preparation of 5,5-diferrocenyl-4-octanone (R = n-C_3H_7, Table II) illustrates the general procedure. A solution of 4,5-diferrocenyl-4,5-octanediol (10.3 g., 0.02 mole) in 50 ml. of chlorobenzene was added to a solution of 20 ml. of concentrated sulfuric acid in 80 ml. of water. The resulting two-phase system was heated under reflux with vigorous stirring for 6 hr. The organic layer was separated, washed to neutrality with water, and connected *in vacuo*. The residual oil was triturated with methanol and the mixture was allowed to stand at −25° for several hours until solidification was complete. The yellow solid was recrystallized from methanol–benzene as short golden needles. The infrared spectrum of the compound (carbon tetrachloride) showed in addition to the carbonyl band at 1710 cm.$^{-1}$, and other bands, the two absorption bands at 1105 and 995 cm.$^{-1}$ characteristic of mono-ring substitution of ferrocene.[8]

Reduction of acetylferrocene[9] (22 g., 0.1 mole) with magnesium (1.44 g., 0.069 g.-atom) and 1.6 g. of mercuric chloride (50 ml. of tetrahydrofuran and 15 ml. of benzene) as described above gave 18.1 g. of solid with m.p. 146–175°. Even upon temporary storage *in vacuo* it began to decompose to a dark liquid. It was therefore immediately dissolved in 125 ml. of chlorobenzene and added to a solution of 48 ml. of concentrated sulfuric acid in 192 ml. of water. The two-phase system was treated as described above to yield 3.4 g. of solid, m.p. *ca.* 240° dec. The infrared spectrum of the material showed no carbonyl absorption bands at either 1685 or 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{24}Fe_2O$: C, 65.49; H, 5.50; Fe, 25.38. Found: C, 65.73; H, 5.72; Fe, 23.00.

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(8) M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).

(9) P. J. Graham, *et al.*, *ibid.*, **79**, 3416 (1957).

The Structure of Alantolactone

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The sesquiterpene lactones alantolactone (I), isoalantolactone (II), and dihydroisoalantolactone (III) were related to eudalene by Ruzicka and co-workers.[1] Subsequently, Tsuda, *et al.*,[2] proved the correct placement of the lactone oxygen and assigned structure IV to alantolactone and structure II to isoalantolactone.

Asselineau and Bory[3] questioned the validity of IV on the grounds that dihydroisoalantolactone (III) and dihydroalantolactone (V)[4] do not give the same chloride with hydrochloric acid.[5] The French workers saponified and oxidized dihydroalantolactone to a keto acid which was isomerized by alkali to a conjugated ketone VI [$\lambda_{\max}^{\mathrm{EtOH}}$ 240 mμ (ϵ 6000)].[3] This evidence supports formulation I for alantolactone.

Recently, Nakazawa[6] obtained identical bromides by hydrobromination of dihydroisoalantolactone and di-

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(1) L. Ruzicka, P. Pieth, T. Reichstein, and L. Ehmann, *Helv. Chim. Acta*, **16**, 268 (1933). These workers favored structure IV (lactone at C-6). The stereochemistry of these compounds has been reviewed by W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

(2) K. Tsuda, K. Tanabe, I. Iwai, and K. Funakoshi, *J. Am. Chem. Soc.*, **79**, 5721 (1957).

(3) C. Asselineau and S. Bory, *Compt. rend.*, **246**, 1874 (1958).

(4) The configuration at C-11 has recently been proved by W. Cocker and M. A. Nisbet, *J. Chem. Soc.*, 534 (1963).

(5) K. F. W. Hansen [*Chem. Ber.*, **64**, 1904 (1931)] obtained two isomeric hydrochlorides from dihydroisolantolactone. J. Bredt and W. Pcsth [*Ann.*, **285**, 349 (1895)] prepared the hydrochloride of dihydroalantolactone.

(6) S. Nakazawa, *J. Am. Chem. Soc.*, **82**, 2229 (1960).

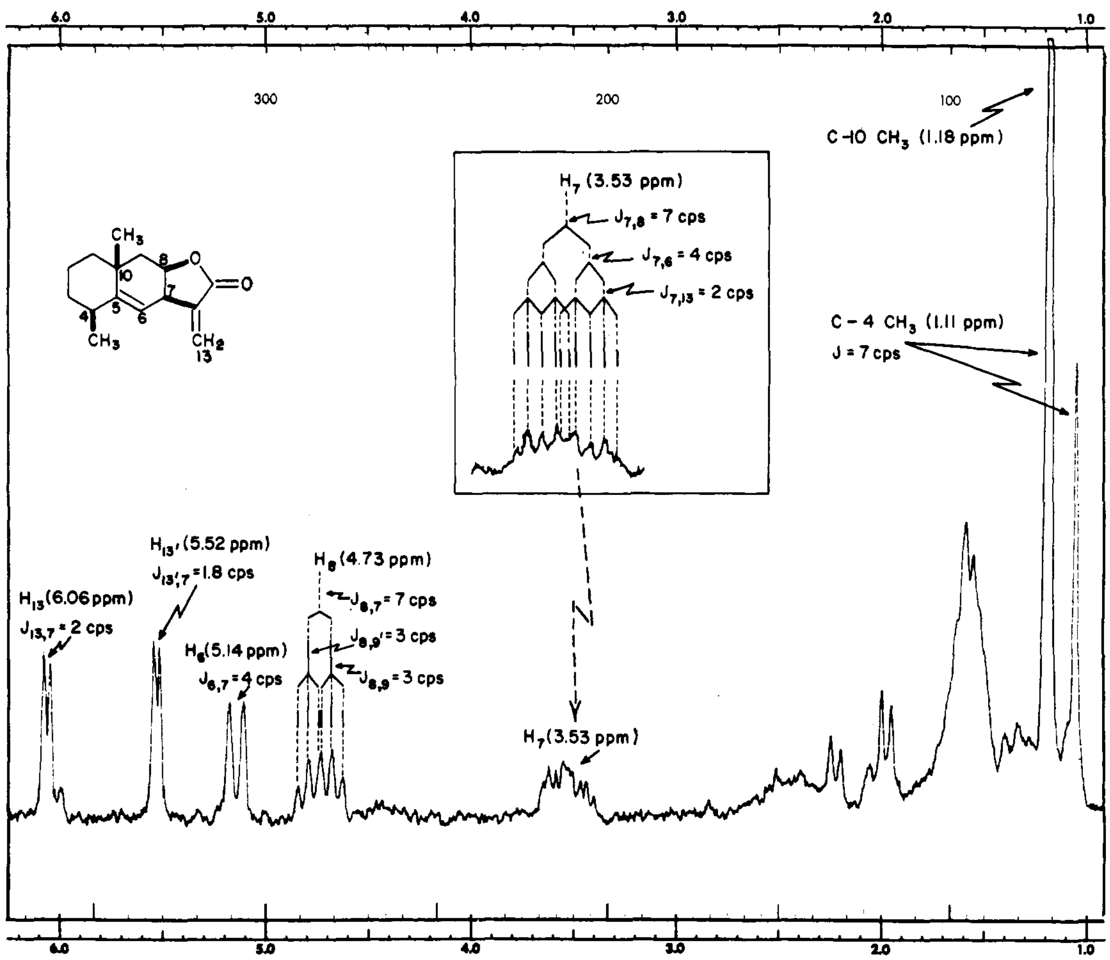
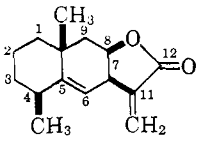
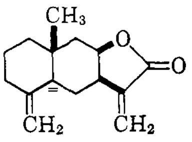


Figure 1.

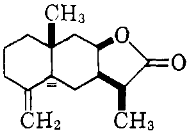
hydroalantolactone under comparable conditions. Furthermore, Ukita and Nakazawa[7] found that ozonation of dihydroalantolactone yielded a lactone keto acid which gave an iodoform test. Seemingly, these results are compatible only with formulation IV for alantolactone.



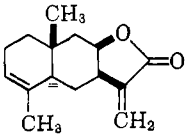
I



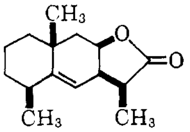
II



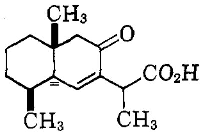
III



IV



V



VI

Our interest in this structural dilemma arose from projected synthetic approaches to the alantolactone family of sesquiterpenes. In view of the differing synthetic problems posed by I and IV we decided to seek evidence which would allow a clear choice between the two. For this task, nuclear magnetic resonance spectroscopy served admirably to define alantolactone as I and dihydroalantolactone as V.

The proton resonance peaks (Fig. 1) which are crucial to the choice of I in preference to IV occur at $\delta_{\text{TMS}}^{\text{CCl}_4}$ = 5.14 (H-6 doublet; $J_{6,7}$ = 4 c.p.s.) and 1.11 p.p.m. (C-4 CH_3 doublet; J = 7 c.p.s.). Additional structural details in support of I are furnished by peaks at 4.73 (H-8 quintet; $J_{8,9} = J_{8,9'}$ = 3 c.p.s., $J_{8,7}$ = 7 c.p.s.) and 3.53 p.p.m. (H-7 multiplet; $J_{7,6}$ = 4 c.p.s., $J_{7,8}$ = 7 c.p.s., $J_{7,13}$ = 2 c.p.s.).[8] The coupling constants between H-8 and H-9 (dihedral angle θ = 60°), H-8 and H-9′ (θ = 60°), and H-7 and H-8 (θ = 15°) are in good agreement with the predicted values.[9] Inspection of Dreiding models reveals that the long-range coupling between H-7 and H-13 in alantolactone (I) should be about 2 c.p.s., (observed J = 2 and 1.8 c.p.s.) while the analogous $J_{7,13}$ in isoalantolactone (II) should be less than 2 c.p.s. (observed J = 0.8 and 0.6 c.p.s.).[10] Thus the spectrum of alantolactone (Fig. 1) confirms not only the placement of the carbocyclic double bond at C-5 but the stereochemical details of I as well. As expected, the multiplet at 3.5 p.p.m. due to the C-7 proton of alantolactone is shifted down-

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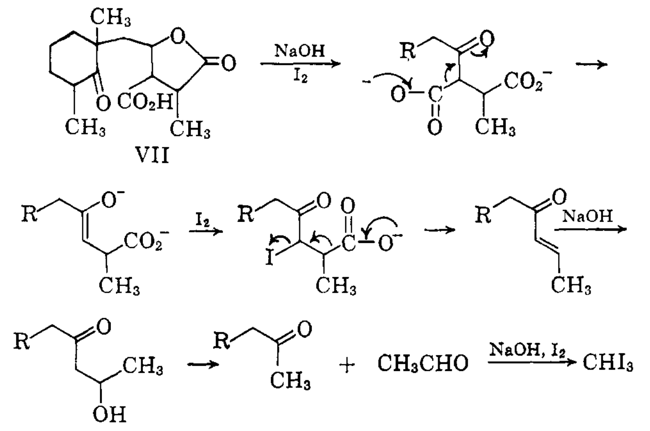
[7] T. Ukita and S. Nakazawa, *J. Am. Chem. Soc.*, **82**, 2224 (1960).

[8] The internal consistency of the splitting patterns appears to justify this first-order interpretation.

[9] H. Conroy, "Advances in Organic Chemistry," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 311.

[10] T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963).

Scheme I



field in the spectrum of dihydroalantolactone but the doublets at 5.1 and 1.1 p.p.m., attributed to the C-6 proton and the C-4 methyl group, remain. It is noteworthy that neither alantolactone (I) nor isoalantolactone (II) show appreciable $H_{13}/H_{13'}$ spin–spin coupling.[11]

We repeated the low-temperature hydrobromination of dihydroisoalantolactone (III) and obtained Nakazawa's[6] 120–121° bromo derivative which, on the basis of its n.m.r. spectrum, is 4-bromotetrahydroalantolactone. Since the same bromo compound is obtained by hydrobromination of dihydroalantolactone (V),[6] it is clear that this reaction is accompanied by double-bond (or carbonium ion) rearrangement. We were unable to prepare the 189–191° bromo derivative which is reported[6] for both dihydroalantolactone (V) and dihydroisoalantolactone (III). All attempts produced colored oils which evolved hydrogen bromide on exposure to air and during attempted crystallization at room temperature or below. Similar behavior was noted for the 120–121° bromo derivative.

Hydrochlorination of dihydroisoalantolactone (III)[5] was effected smoothly and afforded a mixture of isomeric 4-chlorotetrahydroalantolactones in good yield. The chloro compounds were easily handled and showed no tendency to dehydrochlorinate. Therefore, structural conclusions based on these derivatives[3] must be considered more compelling than conclusions based on the hydrobromides.[6]

The lactone keto acid obtained by ozonation of dihydroalantolactone (V)[7] must now be formulated as VII. A reasonable pathway for the formation of iodoform from this compound is pictured (R = 1,3-dimethyl-2-ketocyclohexyl) in Scheme I.

Experimental[12]

Alantolactone was purchased from Chemicals Procurement Laboratories, Inc., College Point, N. Y. The commercial material was about 60% isoalantolactone which was largely removed by crystallization from aqueous methanol. The remaining alantolactone was purified to the reported melting point[3] by numerous recrystallizations, first from hexane and finally ethanol at −20°. This material retained 5–10% of isoalantolactone (detected by the n.m.r. spectrum and estimated by integration) which could not be removed by further crystallization.[1]

Alantolactone (I) gave $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 6.06 (H–13 doublet, J = 2 c.p.s.), 5.52 (H-13′ doublet, J = 1.8 c.p.s.), 5.14 (H-6 doublet, J = 4 c.p.s.), 4.73 (H-8 multiplet), 3.53 (H-7 multiplet), 1.18 (C-10 CH_3), and 1.11 (C-4 CH_3 doublet, J = 7 c.p.s.) p.p.m.; m.p. 78.5–80°, lit[3] m.p. 78–79°.

Isoalantolactone (II) gave $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 6.02 (H-13 doublet, J = 0.8 c.p.s.), 5.55 (H-13′ doublet, J = 0.6 c.p.s.), 4.76, 4.55 ($C{=}CH_2$), 4.45 (H-8), and 0.82 (C-10 CH_3) p.p.m.; m.p. 112–113°, lit.[3] m.p. 111–113°.

Dihydroisoalantolactone (III) gave $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 4.78, 4.51 ($C{=}CH_2$) 4.3–4.6 (H-8), 1.17 (C-11 CH_3 doublet, J = 7 c.p.s.), and 0.82 (C-10 CH_3) p.p.m.; m.p. 172–173°, lit.[7] m.p. 171–172°. This material was prepared by hydrogenation of isoalantolactone over reduced platinum oxide in methanol until 1 mole equiv. was taken up.

Dihydroalantolactone (V) gave $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 5.18 (H-6 doublet, J = 3 c.p.s.), 4.5–4.8 (H-8), 1.22 (C-10 CH_3), and 1.17 (C-4 CH_3 and C-11 CH_3 doublet, J = 8 c.p.s.) p.p.m.; m.p. 132–132.5°, lit.[7] m.p. 133.5–134°. This material was prepared in the manner described for dihydroisoalantolactone.

4-Bromotetrahydroalantolactone gave $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 4.2–4.5 (H-8), 1.78 (C-4 CH_3), 1.18 (C-10 CH_3), and 1.18 (C-11 CH_3 doublet, J = 7 c.p.s.) p.p.m.; m.p. 119–121°, lit.[6] m.p. 120–121°. This material was obtained in only 10% yield by hydrobromination of dihydroisoalantolactone at 0° according to the published method.[6]

Hydrobromination of dihydroisoalantolactone at room temperature by the published procedure[6] afforded a brown oil which fumed in air. Crystallization of the oil could not be induced and dissolution in ether and hexane was attended by fuming and separation of a red-brown oil.

4-Chlorotetrahydroalantolactone gave $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 4.6–4.2 (H-8), 1.52 (C-4 CH_3), 1.20 (C-11 CH_3 doublet, J = 7 c.p.s.), and 1.00 (C-10 CH_3) p.p.m.; m.p. 142–145°, lit.[5] m.p. 145°. The procedure of Hansen[5] was followed using 0.50 g. of dihydroisoalantolactone. The crude hydrochloride, m.p. 104–137°, was obtained in 97% yield. Several recrystallizations from ethanol afforded 0.10 g., m.p. 142–145°.

The mother liquors were evaporated and the residue was recrystallized from ethanol. A second recrystallization afforded 0.05 g., m.p. 127–136°. This material is a mixture of 4-chloro isomers since the n.m.r. spectrum exhibited a new peak at 0.81 p.p.m. (C-10 CH_3) in addition to intense peaks at 1.52 (C-4 CH_3) and 1.00 p.p.m. (C-10 CH_3) present in the 145° isomer.

The chloro derivatives (in distinct contrast to the bromo derivatives) showed no tendency to fume. Solution in boiling 95% ethanol could be effected with no sign of decomposition.

Acknowledgment.—We thank the U. S. Public Health Service for support of this work through a research grant (AI-04965, National Institute of Allergy and Infectious Diseases) and a fellowship (5-F1-GM-19,-839 to N. Cohen). The A-60 spectrometer was purchased with funds furnished Northwestern University by the National Science Foundation. We are indebted to Professor R. E. Ireland for his kind assistance in obtaining spectra of dihydroalantolactone and dihydroisoalantolactone.

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[11] This result might be expected if the C-13 H–C–H bond angle assumes a value near 125° (ref. 9, p. 310).

[12] Melting points were taken on a Fisher-Johns hot stage and are corrected. N.m.r. spectra were determined with a Varian A-60 spectrometer.

Preparation of Triaminoguanidine

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During the course of a research program involving the use of triaminoguanidinium salts, a convenient method for the preparation of triaminoguanidine was discovered. The synthesis of this compound in its