chloride, weighed 108 mg. (81%) and melted at 156–157°. A mixture melting point determination with the benzoyl derivative of *p*-toluidine (m.p. 157–158°) was 157–158°. The infrared spectra of the samples were identical.

Pyrolysis of N-(2-Chloro-2-propyl)-N′-fluorodiimide N-Oxide in Chlorobenzene.—A solution of 0.55 g. (3.9 mmoles) of the N′-fluorodiimide in 15 ml. of chlorobenzene was refluxed for 2 hr. while a nitrogen stream swept the off-gases through a −20° condenser and through traps cooled to −78 and −196°. The chlorobenzene solution was cooled while the nitrogen sweep was maintained. The −196° trap collected only N_2O (by mass spectrum), 85.5 ml. (STP), 3.8 mmoles. No SiF_4 was detected. The −78° trap collected 64.3 ml. (STP), 2.9 mmoles, of 2-chloropropene. The infrared and mass spectra were identical with those of an authentic specimen.

Reaction of N-Phenyl-N′-fluorodiimide N-Oxide and the *n*-Butyl Grignard Reagent.—A solution of 0.71 g. of the above diimide in 25 ml. of tetrahydrofuran was stirred at ice-bath temperature while 9.5 ml. of 0.8 *M* *n*-butyl Grignard reagent in tetrahydrofuran was added over 10 min. The reaction mixture was allowed to warm to 25° (90 min.), and then was poured over an ice–dilute hydrochloric acid mixture. The organic product was isolated by extraction with methylene chloride and was chromatographed on silica gel. Elution of the column with pentane–methylene chloride (1:1) gave N-phenyl-N′-*n*-butyldiimide N-oxide, 0.306 g. (34%), as a yellow oil; ultraviolet (cyclohexane), λ_{max} 246 mμ (ϵ_{max} 10,300).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.46; H, 7.97; N, 16.08.

Reaction of the Phenyl Grignard Reagent and N-*p*-Chlorophenyl-N′-fluorodiimide N-Oxide.—A solution of 0.350 g. of the above diimide in 20 ml. of ether was stirred at ice-bath temperature while about 3 mmoles of the phenyl Grignard reagent in 2 ml. of ether was added dropwise. The reaction temperature was allowed to increase to 22° over 1 hr., then the mixture was quenched in ice–water and hydrochloric acid. The organic product was isolated by ether extraction. Chromatography of the organic residue over silica gel gave N-*p*-chlorophenyl-N′-phenyldiimide N-oxide, 0.264 g. (57%), m.p. 81–82°.[7]

Anal. Calcd. for $C_{12}H_9ClN_2O$: N, 12.04. Found: N, 12.23.

Reaction of the *p*-Chlorophenyl Grignard Reagent and N-Phenyl-N′-fluorodiimide N-Oxide.—A solution of 1.02 g. (7.3 mmoles) of the above diimide in 25 ml. of tetrahydrofuran was stirred at ice-bath temperature under an atmosphere of nitrogen while 7.7 ml. of 1.1 *M* *p*-chlorophenylmagnesium bromide in tetrahydrofuran was added dropwise. The mixture was allowed to warm to 20° over 1 hr., and then quenched in iced aqueous hydrochloric acid. The organic product was isolated by extraction with methylene chloride. The methylene chloride was removed at reduced pressure. The last traces of solvent were removed by pumping *in vacuo* through a −80° trap. An F^{19} n.m.r. scan of the material trapped at −80° showed peaks at −4800 c.p.s. (40 Mc., CF_3COOH standard), due to the starting N′-fluorodiimide, and at +1531 c.p.s., due to 4-chlorofluorobenzene. Chromatography of the residue over silica gel as usual gave an azoxybenzene fraction of 1.27 g. (74.6%). One recrystallization of this material from hexane gave N-phenyl-N′-*p*-chlorophenyldiimide N-oxide, 1.07 g., m.p. 68–69°, lit.[7] m.p. 68°.

Structure and Configuration of Isojervine[1]

TADASHI MASAMUNE, MITSUO TAKASUGI, MASATOSHI GOHDA, HIROSHI SUZUKI, SHOZO KAWAHARA, AND TOSHI IRIE

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

Received January 1, 1964

Isojervine, an isomer obtained on acid treatment of jervine, is shown to possess structure II from chemical and physical evidence.

The elucidated structure[2] of jervine (I) has been shown to explain all but one of the diverse reactions[3] of the alkaloid. Isojervine,[4] an unexpected product obtained on acid treatment of pseudojervine has received no generally accepted structural assignment.[5] In a preliminary communication[6] we reported that structure II was consonant with all chemical and spectral data obtained from isojervine[7] and the present paper describes the full details.

Isojervine (II), $C_{27}H_{39}O_3N$, m.p. 116–118°, was obtained in crystalline form by treatment of jervine according to Jacobs' procedure,[4] together with a new isomer, m.p. 262–263°. Isojervine is moderately stable toward acid and very sensitive to alkali, in contrast to jervine. It possesses a characteristic ultraviolet absorption spectrum[8] (Fig. 1), showing strong end absorption (ϵ 9200 at 220 mμ) with inflection at 252 mμ (ϵ 2900) and a maximum at 330 mμ, the intensity (ϵ 250) of which is considerably higher than that of usual ketones. The infrared spectrum[9] exhibits an α,β-unsaturated carbonyl peak at 1684 and 1630 cm.$^{-1}$ and the chemical data[4,8] show the presence of two hydroxyl groups and a secondary amino group; that is, the ether linkage of jervine is cleaved in isojervine. Isolation of 2-ethyl-3-hydroxy-5-methylpyridine on selenium dehydrogenation[10] proves that isojervine contains the same nitrogen ring skeleton as that of jervine.

Reduction of II with lithium in liquid ammonia at −70° in presence of methanol has now afforded "α-dihydrojervinol"[8] (III), showing that the carbocyclic ring system of jervine is still retained, and three double bonds are, therefore, present in isojervine. The result also established that not only the ketonic function of isojervine exists at C-11, but also that two hydroxyl groups are located at C-3 and C-23 in "α-dihydrojervinol" and isojervine.

The abnormal ultraviolet absorption spectrum of II and the higher pK_a value (7.12 in 50% ethanol) of N-methylisojervine (IV) than that (6.08) of N-methyljervine[11] (V) led us to assume, at first, that one of the three double bonds might be conjugated with nitrogen.

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(1) Part I of "C-Nor-D-homosteroids and Related Alkaloids."

(2) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin, and A. Klingsberg, *J. Am. Chem. Soc.*, **73**, 2970 (1951).

(3) K. J. Morgan and J. A. Barltrop, *Quart. Rev.* (London), **12**, 34 (1958).

(4) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **155**, 565 (1944).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 851.

(6) T. Masamune, M. Takasugi, H. Suzuki, S. Kawahara, M. Gohda, and T. Irie, *Bull. Chem. Soc. Japan*, **35**, 1749 (1962).

(7) After we had completed this work, Dr. O. Wintersteiner of the Squibb Institute and Professor W. G. Dauben of California University informed us that they also have arrived at the same structure as ours. Their results have now been published in (a) *Tetrahedron Letters*, 795 (1962), and (b) *J. Org. Chem.*, **28**, 293 (1963), respectively.

(8) W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.*, **170**, 635 (1947).

(9) B. M. Iselin and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 5318 (1955).

(10) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **181**, 55 (1949).

(11) K. Saito, H. Suginome, and M. Takaoka, *Bull. Chem. Soc. Japan*, **11**, 172 (1936).

This compound (IV), m.p. 221–222°, was obtained by acid treatment of V or by methylation of II with methyl iodide. However, the ultraviolet spectra of isojervine (II), the triacetate (IIa), and the N-methyl derivative (IV) in ethanol were completely identical with that of isojervine in ethanol containing hydrochloric acid (0.1 *N*). Furthermore, isojervinol (VI), m.p. 210–211°, which was formed by reduction of II with lithium aluminum hydride or sodium borohydride and was very unstable to acid, exhibited only weak end absorption (ϵ 2990 at 220 mμ). These facts[12,13] indicated that no double bond was conjugated with another or with the nitrogen.

Of three double bonds, one was shown to be located at C-5–C-6 by the Oppenauer oxidation; oxidation of isojervine with cyclohexanone and aluminum isopropoxide in toluene yielded isojervone[14] (VII), m.p. 112–114°, which was very unstable in air in contrast to the stable diacetate (VIIa), m.p. 202–204°. Hydrogenation of II led to saturation of this 5,6-double bond; that is, treatment of II with hydrogen and platinum in acetic acid gave stereoisomeric dihydroisojervines[15] (VIII, m.p. 154–155°, and IX, m.p. 114–115°). The absorption maxima of VIII and IX were not only shifted to the shorter wave length (239 and 236 mμ) but also intensified from 2900 to 10,000 (Fig. 1). The higher melting isomer (VIII) was presumed to be fused by A–B *trans* linkage, because VIII was a main product of the hydrogenation. The Oppenauer oxidation of VIII produced dihydroisojervone (X), m.p. 108–110°, only in a low yield, which exhibited ultraviolet absorption similar to VIII, and a considerable amount of the starting material was recovered unchanged. Compound X was also obtained by oxidation of VIII with chromic anhydride in better yield. Similarly, IX was oxidized to yield the corresponding dihydroisojervone (XI) which showed one spot on the paper chromatogram, though it was not isolated in crystalline form. Reduction of X with sodium borohydride gave the original alcohol (VIII) as a major product. In such a reduction of an unhindered ketone, the equatorial isomer is the major product.[16a] Since VIII has a 3β-hydroxyl group,[16b] VIII must possess an A–B *trans* configuration. The difference[17a,b] between the optical rotatory dispersion curves of X and VIII, considered to represent the absorption characteristics of the 3-ketone, showed a positive Cotton effect (Fig. 2). Application of the octant rule[17c] supported the conclusion on the stereochemistry of the A–B ring junction mentioned above.

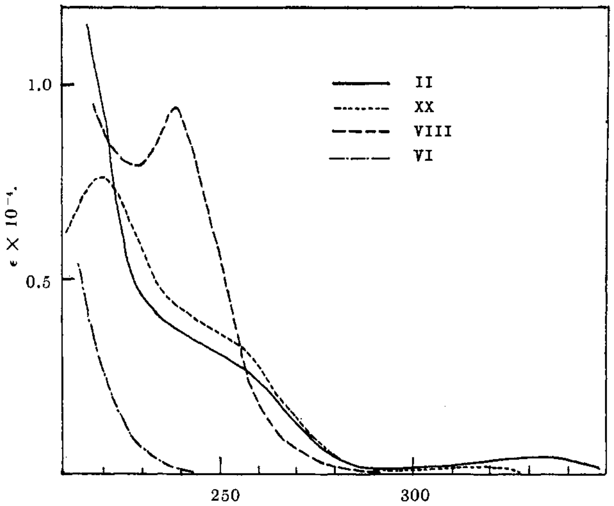

Fig. 1.—Ultraviolet absorption spectra of various isojervine derivatives; solvent, ethanol.

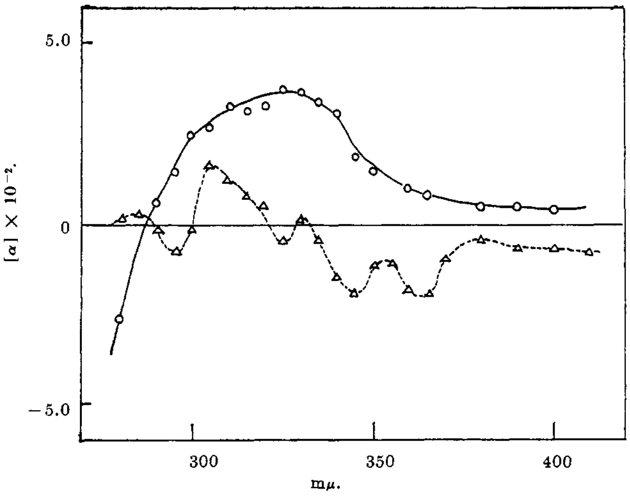

Fig. 2.—The differences in the optical rotatory dispersion curves of dihydroisojervones and dihydroisojervines: ○, *trans* (X–VIII); △, *cis* (XI–IX); solvent, ethanol.

A double bond conjugated with the carbonyl group is shown to exist at C-8–C-9. As mentioned above, the absorption maximum at 252 mμ in I was shifted to 239 mμ in VIII and also the carbonyl peak (1700 cm.$^{-1}$) of I was displaced to a longer wave length (1684 cm.$^{-1}$) in II, suggesting[18,19] that the double bond would occupy an endocyclic position; that is, it would be located at C-8–C-9 or C-12–C-14. Furthermore, the atypical spectrum of II with its relatively weak absorption near 250 mμ was changed to one typical for an α,β-unsaturated ketone (in VIII and IX) by saturation of the 5,6-double bond. On the other hand, the reduction of the keto group of II leading to VI caused the loss of absorption above 220 mμ. This spectroscopic behavior of II, VIII, and VI completely paralleled that of 1-acetyl-1,4-cyclohexadiene[20] and, thus, the double bond must be

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(12) R. Adams and L. E. Mahon, *J. Am. Chem. Soc.*, **64**, 2588 (1942); N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955); N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, **77**, 1552 (1955).

(13) N. J. Leonard and D. M. Locke, *ibid.*, **77**, 437 (1955).

(14) *Cf.* ref. 5, p. 177. The molecular rotation differences (ΔM_D) for the transformation II to VII, I to Δ^4-jervone, and III to "α-dihydrojervinolone" prepared by the Oppenauer oxidation of III were 748, 669, and 731°, respectively. To the contrary, the values were only 136 and 131° for the changes of VIII to X and IX to XI.

(15) The dihydroisojervine of m.p. 155° (as hydrate) described in the preliminary communication (ref. 6) was a mixture of the compounds VIII and IX. These gave almost the same R_f value on the paper chromatogram.

(16) (a) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956); O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962). (b) See ref. 37.

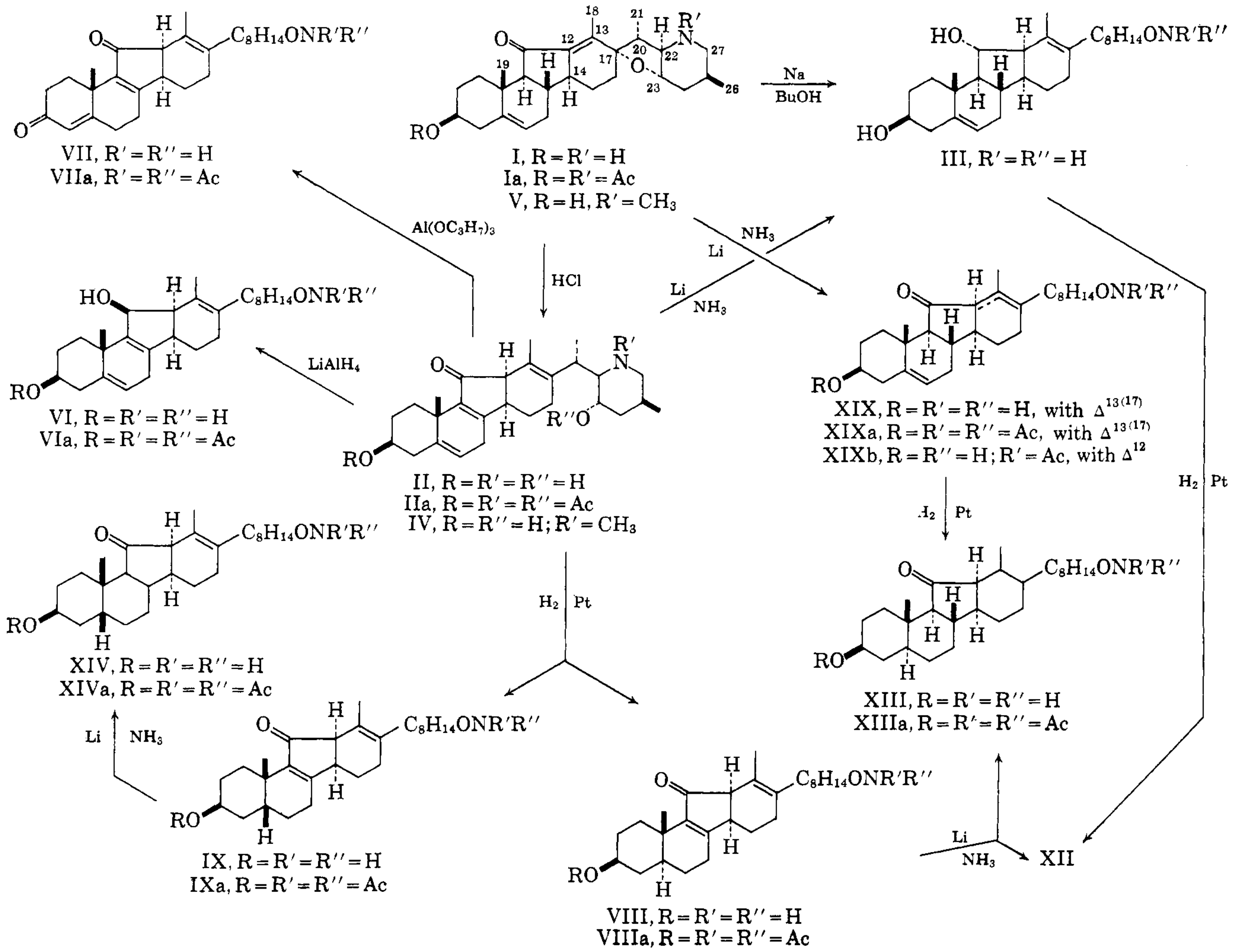
(17) (a) For additivity of the molecular rotatory dispersion curve, see W. Klyne, *Tetrahedron*, **13**, 29 (1961); C. Djerassi, E. Lunde, and A. A. Akhrem, *J. Am. Chem. Soc.*, **84**, 1249 (1962). (b) The corresponding difference between XI and IX indicated an unexplainable curve (Fig. 2). This suggests that IX would exist in a nonsteroid form. (c) C. Djerassi, *ibid.*, **78**, 6362 (1956); W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961).

(18) K. Hirayama, "Zikken Kagaku Koza," Vol. I, the Chemical Society of Japan, Ed., Maruzen Co., Tokyo, 1961, p. 71.

(19) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960).

(20) E. A. Braude, E. R. H. Jones, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, 607 (1947); E. R. H. Jones, G. H. Mansfield, and M. C. Whitig, *ibid.*, 4073 (1956).

Chart I



located at C-8–C-9. The n.m.r. spectral data, which will be discussed later, support this view.

Hydrogenation of VIII was found not to proceed under usual conditions, suggesting that a remaining double bond was sterically hindered, probably tetrasubstituted. The n.m.r. spectrum of IIa gave a sharp singlet at τ 8.09 due to a methyl group attached to an olefinic carbon comparable to that at τ 7.81 due to the 18-methyl of diacetyljervine (Ia). Thus the double bond must exist either at C-13–C-17 or C-17–C-20. The Birch reduction of VIII resulted in formation of a mixture of compounds. Chromatographic separation on paper led to the isolation of two crystalline substances, m.p. 142–143° and m.p. 167–168°, besides some unchanged starting material. The higher melting compound (XII) showed no carbonyl band in the infrared spectrum and was proved to be a dihydro derivative of the alcohol (III) by hydrogenation. This base (XII) was also formed in good yield by the Birch reduction of VIII in the presence of methanol. The compound XIII[21] of m.p. 143° showed an absorption band due to a saturated five-membered ring ketone at 1732 cm.$^{-1}$, which indicated the reduction of the 8,9-double bond. The Birch reduction of IX yielded a new compound (XIV),[21] m.p. 147–148°, which had a carbonyl peak at 1731 cm.$^{-1}$ and was isomeric with XIII. These tetrahydroisojervines (XIII and XIV) were acetylated for direct comparison with "22,27-imino-$\Delta^{17(20)}$-jervene-3,23-diol-11-one 3,23,N-triacetate" (XV) already prepared by Wintersteiner *et al.*[22] However, neither the triacetate (XIIIa), m.p. 167–169°, of XIII nor the corresponding isomer (XIVa), m.p. 190–191°, of XIV was found to be identical with the known compound (XV).[23] (See Chart I.)

5α-Dihydroisojervine (VIII) was treated with potassium *t*-butoxide in refluxing *t*-butyl alcohol; if the isolated double bond is located at C-13–C-17, one ought to expect the migration of the double bond to the α,β-position relative to the keto group.[24] Careful chromatographic fractionation of the product yielded a crystalline compound (XVI), $C_{27}H_{41}NO_3$, m.p. 143–145°. It had a maximum at 239 mμ (ϵ 8600) in the ultraviolet spectrum, indicating the presence of a simple α,β-unsaturated keto group. Acetylation of XVI with acetic anhydride and pyridine on a steam bath afforded a base which gave one spot on the paper. While it was obtained only in amorphous form, the elementary

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[21] In the preliminary communication (ref. 6), the compounds XIII and XIV were called β- and α-tetrahydroisojervines, respectively.

[22] O. Wintersteiner, M. Moore, and B. M. Iselin, *J. Am. Chem. Soc.*, **76**, 5609 (1954).

[23] The n.m.r. spectrum of Wintersteiner's compound (XV) showed a weak peak at τ 4.11 due to an olefinic proton. In view of the easy hydrogenation of this compound, the location of a double bond at C-17–C-20 seems to be improbable.

[24] R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

analysis fitted the molecular formula $C_{31}H_{45}NO_5$, corresponding to the diacetate (XVIa) of XVI. The infrared spectrum showed only three maxima at 1726, 1685, and 1629 cm.$^{-1}$ in the 6-μ region, showing the absence of an N-acetyl group. The n.m.r. spectrum of XVI or XVIa exhibited a new sharp singlet at τ 8.73 corresponding to three protons instead of the 18-methyl signal (τ 8.08) seen in the spectrum of the triacetate (VIIIa) of VIII. Thus, nitrogen is bonded with the carbon to which the 18-methyl is attached. Furthermore, XVI and XVIa were found to be weak bases, the pK_a values being 6.12 and 4.47, respectively. These results established that the compound of m.p. 145° possesses structure XVI, and that the formation of XVI took place through a reaction analogous to the formation of jervisine as elaborated by Wintersteiner, *et al.*[25] Apparently the reaction of VIII leading to XVI involves migration of the 13,17-double bond[26] to the 12,13-position followed by cyclization. Thus, II is the most probable structure for isojervine.

Consideration of the n.m.r. spectra (Fig. 3) confirms the disposition of a double bond at C-8–C-9 and the configuration of the 12-carbon. Triacetylisojervine (IIa) showed a doublet centered at τ 8.91 (J = 7 c.p.s.) involving six protons and a sharp singlet at τ 8.71 corresponding to three protons along with a singlet at τ 8.09 due to 18-methyl. While the doublet is associated with the C-26 and C-21 methyl groups and the signals due to those groups coincided fortuituously, the signal at τ 8.71 must be attributed to 19-methyl and is shifted abnormally to the lower field as compared with that of diacetyljervine (τ 8.99) or "diacetyl-Δ^{13}-jervine"[9] (τ 8.87). The resonance fields of the angular methyl at C-10 vary depending on the nature and position of other substituents nearby and the shifts of 19-methyl caused by the fields due to the magnetic anisotropy of those substituents have been found to be additive with normal steroids.[27,28] This principle of additivity was observed for a number of C-nor-D-homosteroids and related alkaloids,[29] though the magnitude of the shifts due to substituents in the C-ring do not correspond to those observed with normal steroids. The 19-methyl signals of XIIIa and "22,27-imino-Δ^{16}-jervene-3,23-diol-11-one triacetate"[22] (XVII) appeared at τ 9.17 and 9.16, respectively, and the corresponding peak of the 16,17-dihydro derivative[22] (XVIII) of XVII also appeared at the same region (τ 9.17). This indicated that there was no contribution from the 13,17- or 16,17-double bond. Contribution from 5,6- and 8,9-double bonds was estimated as follows; the Birch reduction of jervine afforded 8,9-dihydroisojervine (XIX), m.p. 162–163°. The structure of XIX was confirmed by transformation of XIX into XIII by hydrogenation.

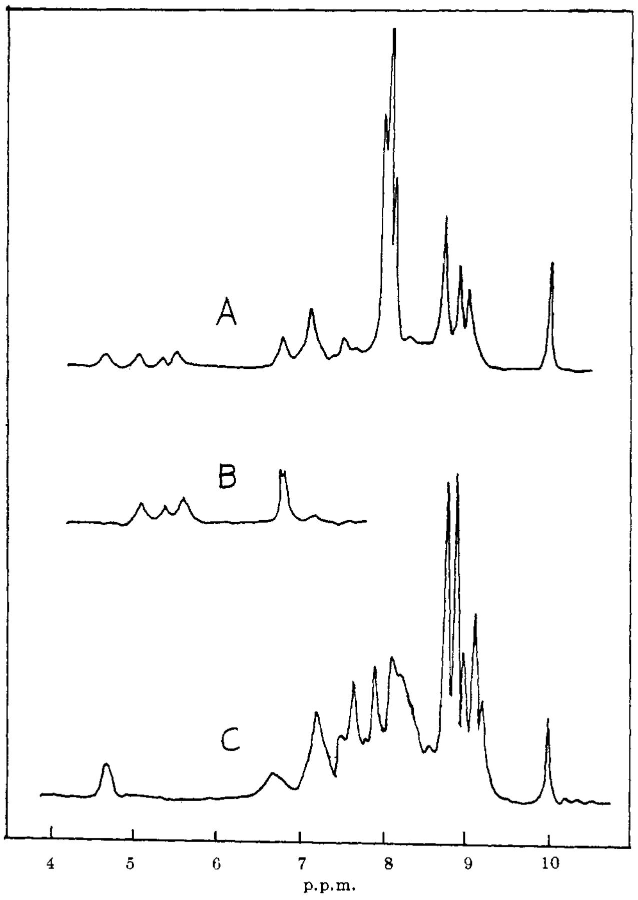
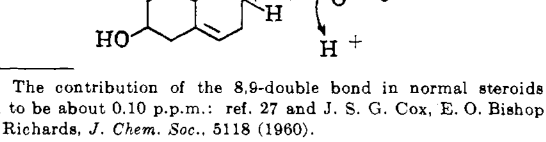


Fig. 3.—The n.m.r. spectra of isojervine derivatives: A, triacetylisojervine (IIa); B, triacetyltetrahydroisojervine (XIIIa); C, a new isomer (XX); solvent, deuteriochloroform; 60 Mc.; internal reference, tetramethylsilane.

As the angular methyl groups of VIIIa and the triacetate (XIXa), m.p. 163–164°, of XIX appeared at τ 8.99 and 8.98, the 5,6- and 8,9-double bonds[30] were shown to shift the 19-methyl signal to the lower field by 0.18 and 0.19 p.p.m., respectively. If the principle of additivity was applicable to triacetylisojervine (IIa), the angular methyl signal should appear at τ 8.80. In order to explain the abnormal ultraviolet absorption of 1-acetyl-1,4-cyclohexadiene, Braude[20] postulated that there would be interaction between the π-electrons of the two double bonds. If so, a similar interaction would be obtained between the 5,6- and 8,9-double bonds of IIa, and the discrepancy (0.09 p.p.m.) of the observed value from the calculated would be explicable by assuming the extra magnetic field associated with such interaction as mentioned above.[31]

The formation of isojervine from jervine is considered to involve the following sequence,[32] and thus there is a



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[25] O. Wintersteiner and M. Moore, *J. Am. Chem Soc.*, **75**, 4938 (1953); **78**, 6193 (1956).

[26] Migration of the 13,17-double bond to the 12,13-position followed by *no* cyclization was observed with triacetyl-8,9-dihydroisojervine (XIXa); treatment of XIXa with potassium hydroxide in refluxing methanol afforded an N-acetate (XIXb), $C_{29}H_{43}NO_4$, m.p. 213–215°. The spectra indicated the presence of an α,β-unsaturated keto group [ultraviolet, λ_{max} 254 mμ (ϵ 19,000); infrared, ν_{max} 1704 and 1610 cm.$^{-1}$; n.m.r., a singlet at τ 7.82 (3H, 18-methyl protons)] and an N-acetyl group [infrared, ν_{max} 1610 cm.$^{-1}$; n.m.r., a singlet at τ 7.90 (3H)].

[27] R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); E. R. Malinowski, M. S. Manhas, G. H. Müller, and A. K. Bose, *Tetrahedron Letters*, 1161 (1963).

[28] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

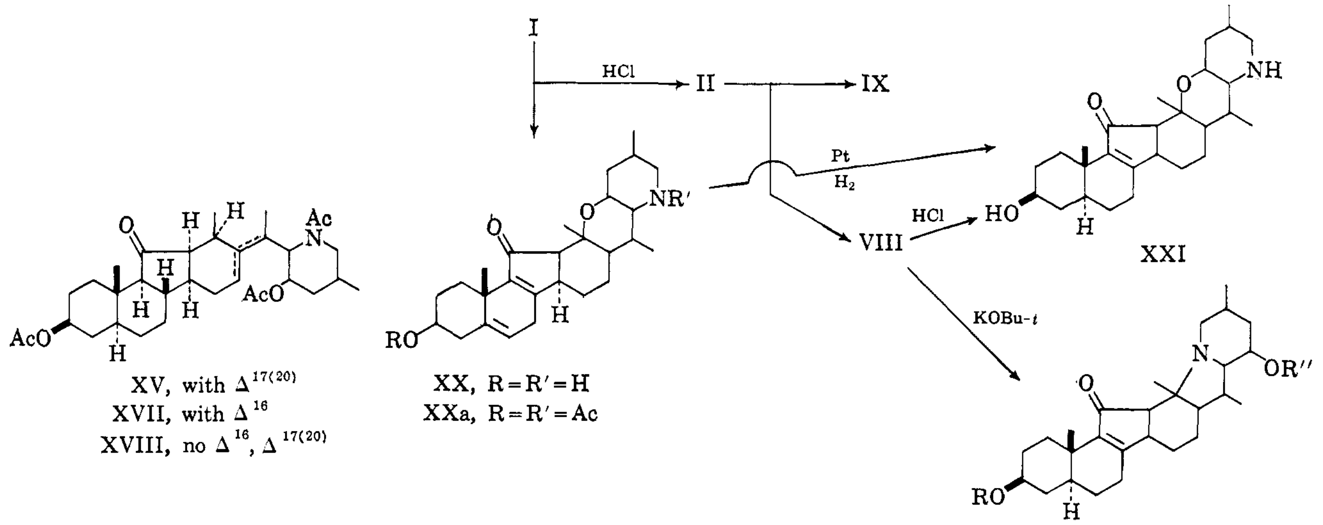
[29] T. Masamune, *et al.*, unpublished observations.

[30] The contribution of the 8,9-double bond in normal steroids was shown to be about 0.10 p.p.m.: ref. 27 and J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J. Chem. Soc.*, 5118 (1960).

[31] The angular methyl signals of IXa and XIVa appeared at τ 8.77 and τ 8.67, respectively, and these extraordinary shifts to the lower field will be discussed in the subsequent papers; *cf.* D. M. Bailey, D. P. G. Hamon and W. S. Johnson, *Tetrahedron Letters*, 555 (1963).

[32] W. G. Dauben, personal communication.

CHART II



XV, with $\Delta^{17(20)}$
XVII, with Δ^{16}
XVIII, no Δ^{16}, $\Delta^{17(20)}$

XX, R=R′=H
XXa, R=R′=Ac

XXI

XVI, R=R″=H
XVIa, R=R″=Ac

new asymmetric center in isojervine at C-12. The n.m.r. spectrum of XIIIa showed in low field absorptions for three protons on C-3, C-22, and C-23 as broad peaks[33a] in the region near τ 5 and for about two protons as a relatively sharp peak centered at τ 6.71. The latter signal was shown to be a doublet (J = 1.7 c.p.s. and half-width = 4.9 c.p.s.) and the doublet peak was attributed to the 12-hydrogen by comparison of the spectra of various isojervine derivatives (IIa, VIIIa, XIIIa, and XVIII).[33b] The coupling constant between the protons at C-12 and C-14 gives dihedral angles of about 60 or 105°, using Conroy's graph,[34] and these values are consistent with C–D *cis*-fused linkage. Models of isojervine with such C–D *cis* configuration indicate that there will be nonbonded interaction between the 11-keto group and the 13,17-double bond. The ultraviolet absorption of the carbonyl group at 330 mμ with high intensity[35,36] supports this view as mentioned above. Since the configuration[37] of jervine is known, the hydrogen on C-12 of isojervine must have the α-configuration.

The isomer XX of m.p. 263° obtained in the preparation of isojervine had the molecular formula $C_{27}H_{39}NO_3$. Acetylation of XX gave the O,N-diacetate (XXa), m.p. 201–202°, indicating that the hydroxyl group on C-23 of isojervine had recombined with the carbocyclic ring. The infrared spectrum of XX showed the presence of an α,β-unsaturated keto group (bands at 1683 and 1630 cm.$^{-1}$) and a double bond at C-5–C-6 (band at 1063 cm.$^{-1}$). The ultraviolet spectrum had maxima at 220 mμ (ϵ 7600) and at 316 mμ (ϵ 180) and also an inflection at 252 mμ (ϵ 3500), and the whole curve was similar to that of isojervine. Hydrogenation of XX led to the formation of the dihydro derivative (XXI), m.p. 230–232°, which was also obtained when 5α-dihydroisojervine (VIII) was treated with methanol saturated with hydrogen chloride at room temperature. The transformation of XX to XXI caused the same hypsochromic and hyperchromic effects on the ultraviolet absorption as observed on hydrogenation of isojervine. The n.m.r. spectrum (Fig. 3) of XX showed two sharp singlets at τ 8.72 and 8.84 and two doublets centered at τ 9.02 (J = 7 c.p.s.) and 9.13 (J = 6 c.p.s.), respectively. Apparently, the latter two signals are due to 21- and 26-methyl groups or *vice versa*[38a,b] and the τ 8.72 peak can be attributed to the 19-methyl. The second

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(33) (a) Contrary to the broad peak centered near τ 5.3 due to 3-hydrogen, absorption for 22- and 23-hydrogens is separated into three main signals centered near τ 4.9, 5.1, and 5.4. This absorption curve was characteristic for all acetylated jervine derivatives formed by cleavage of the ether linkage. (b) The absorption for the remaining one proton would be due to β-hydrogen at C-1; *cf.* D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2810 (1963).

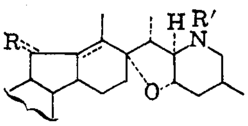
(34) H. Conroy, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 311.

(35) H. Birnbaum, R. C. Cookson, and N. Lewin, *J. Chem. Soc.*, 1224 (1962).

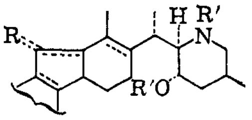
(36) The end absorption in the ultraviolet spectrum of IIa would be associated not only with this interaction but also with the isolated tetrasubstituted 13,17-double bond itself. *Cf.* R. A. Micheli and T. H. Applewhite, *J. Org. Chem.*, **27**, 345 (1962); P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(37) As for the stereochemistry of jervine, see the following papers: ref. 25; J. Sicher and M. Tichý, *Tetrahedron Letters*, 6 (1959); S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.* (London), 512 (1961); R. L. Augustine, *ibid.*, 1448 (1961); H. Mitsuhashi and Y. Shimizu, *Tetrahedron*, **19**, 1027 (1963).

(38) (a) Alkali treatment (1 N potassium hydroxide in refluxing ethanol under nitrogen stream for 1 hr.) of XXI gave a resinous product which showed at least five spots on the paper but not a spot corresponding to XXI. As 12,13-dihydrojervine is stable under the conditions, this result suggests that in XXI the oxygen on the 23-carbon would be attached to the β-carbon (13-carbon) relative to the 11-keto group. A compound corresponding to the main spot was isolated and had m.p. *ca.* 130° (from isopropyl ether); λ_{max} 237 mμ (ϵ 11,000); ν_{max} 1678, 1630, and 1037 cm.$^{-1}$. These physical constants and the R_f value suggested it was a crude dihydroisojervine but a small amount of the product did not permit further examination. (b) The structure in which the 23-oxygen is attached to the 17-carbon as in jervine can be excluded on the basis of the sharp *singlet* at τ 8.84, as far as the carbocyclic and nitrogen ring systems are retained. For reference, the chemical shifts of 18-, 21-, and 26-methyl protons of jervine and isojervine derivatives are shown in Table I. Those values depend on the substituents in the C- and/or D-rings and also in the nitrogen ring. In jervine derivatives (partial formula A), assignment was performed, assuming that the signals of 26-methyl protons are not affected by substituents in the C- and/or D-rings and the peaks of the 18-methyl protons by substituents in the nitrogen ring. In most of the isojervine derivatives (B), the signals of the 21- and 26-methyl protons coincided.



A



B

TABLE I

CHEMICAL SHIFTS OF THE 18-, 21-, AND 26-METHYL PROTONS OF JERVINE AND ISOJERVINE DERIVATIVES

Substituents			Number of compounds examined	Chemical shifts (τ) of methyl protons		
Double bond	R	R′		18-	21-	26-
			Jervine Derivatives (A)			
12, 13	O	Ac	2	7.77, 7.79	9.12, 9.14	8.96, 8.98
None	O	Ac	2	9.08, 9.09	9.18, 9.19	8.98, 8.99
12, 13	H_2	Ac	1	8.29	9.16	8.99
12, 13	β-OH	Ac	1	8.10	9.15	8.98
None	β-OH	Ac	1	9.07?	9.17	8.98
None	α-OH	Ac	1	9.07	9.18	8.96
12, 13	O	H	3	7.79–7.85	9.04–9.06	9.04–9.06
None	O	H	2[a]	9.07, 9.09	9.07, 9.09	9.07, 9.09
12, 13	O	CH_3	1	7.78	8.94	8.94
12, 13	H_2	CH_3	2	8.34, 8.37	8.93, 8.96	8.93, 8.96
None	O	CH_3	1	9.07	8.98	8.98
			Isojervine Derivatives (B)			
8, 9; 13, 17	O	Ac	4	8.05–8.09	8.89–8.92	8.89–8.92
13, 17	O	Ac	4	8.10–8.12	8.86–8.90	8.86–8.90
13, 17	H_2	Ac	1	8.35	8.92	8.92
11, 12; 13, 17	H	Ac	1	8.17	8.86	8.86
8, 9; 13, 17	β-OH	Ac	1	8.18	8.87	8.87
13, 17	β-OH	Ac	1	8.30	8.87	8.87
13, 17	O	H	1	8.12	(8.89 and 9.18)[b]	
8,9; 13, 17	O	H	2	7.99, 8.01	(8.88, 8.89 and 9.16, 9.18)[b]	

[a] 12,13-Dihydrojervine and tetrahydrojervine. [b] Assignment was not possible.

signal with a τ-value of 8.84 p.p.m. must be, therefore, absorption of the C-18 methyl. On the basis of these facts, one might conclude that the isomer of m.p. 263° possesses structure XX. (See Chart II.)

Experimental

The melting points are uncorrected. The optical rotations and the ultraviolet spectra were measured in ethanol and the infrared spectra in Nujol unless otherwise stated. The n.m.r. spectra were taken in deuteriochloroform at 60 Mc. using tetramethylsilane as an internal standard. The basicity measurements were carried out according to Thomson's procedure[39] in 50% ethanol at 20°.

Preparation of Isojervine[4,9] (II) and a New Isomer (XX).—To a methanol solution (210 ml.) saturated with hydrogen chloride was added jervine (7.0 g.) in 3 min. under stirring and cooling with ice, and the whole solution was continuously stirred for 1 hr. at room temperature. After removal of the solvent under reduced pressure below 45°, water (500 ml.) was added to the residue, which was made alkaline to pH 8.8 with 10% aqueous sodium carbonate. On treatment of the aqueous solution with chloroform, the chloroform compound of isojervine separated and was collected by filtration. Recrystallization from acetone yielded pure isojervine (6.0 g.), m.p. 116–118°. The chloroform solution obtained on filtration of the chloroform compound was evaporated to dryness and acetone was then added to the residue, yielding a crystalline substance (XX, 106 mg.) of m.p. 251–255°, which gave one spot on the paper chromatogram.[40] Two recrystallizations from methanol raised the melting point to 262–263°; $[\alpha]^{23}\text{D}$ +33° (*c* 0.126); $\lambda_{\max}$ 220 mμ (ϵ 7600) and 316 (180) and an inflection at 252 (3500); $\nu_{\max}$ 1683, 1630, and 1063 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_3$: C, 76.19; H, 9.24; N, 3.29. Found: C, 76.17, 75.91; H, 9.20, 9.42; N, 3.40.

Compound XX (100 mg.) was dissolved in a mixture of acetic anhydride (1 ml.) and pyridine (1 ml.), and the solution was allowed to stand at room temperature overnight and then heated on a steam bath for 30 min. The product crystallized on removal of acetic anhydride and pyridine and was recrystallized from aqueous ethanol. The diacetate (XXa, 95 mg.), m.p. 201–202°, was obtained; $\lambda_{\max}$ 220 mμ (ϵ 10,000) and an inflection at 252 mμ (ϵ 4500); $\nu_{\max}$ 1727, 1701, 1636, 1594, 1252, and 1031 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{43}NO_5$: C, 73.05; H, 8.50; N, 2.75. Found: C, 73.08, 73.25; H, 8.78, 8.68; N, 3.13, 3.19.

The Birch Reduction of Isojervine.—To liquid ammonia (80 ml.) containing methanol (3 ml.) was added isojervine (0.5 g.) dissolved in tetrahydrofuran (5 ml.) and to the solution was added lithium metal (0.16 g.) at −70° during 15 min. under stirring. The mixture was stirred for another 10 min. After addition of ammonium chloride (1.7 g.) and removal of the solvent, the residue was treated with water and chloroform. The chloroform solution gave a resinous substance after drying and evaporation, which crystallized on addition of acetone. Recrystallization from a mixture of acetone and methanol afforded white crystals (III, 0.19 g.), m.p. 200–222°.

Anal. Calcd. for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09. Found: C, 75.26; H, 10.14.

No depression of melting point was observed on admixture of the product (III) with "α-dihydrojervinol" obtained by reduction of jervine with sodium and butanol.[8] The infrared spectra of the two compounds were also identical in Nujol and chloroform.

Isojervone (VII).—Isojervine (502 mg.) was dissolved in toluene (100 ml.) and 35 ml. of the solvent was distilled to remove moisture by azeotropization. To the solution was added freshly distilled cyclohexanone (8 ml.), and 8 ml. of the solvent was again removed. A dry toluene solution (5 ml.) of aluminum isopropoxide (1.50 g.) was added, and the mixture was refluxed for 7 hr. After removal of the solvent by steam distillation, the residue was repeatedly extracted with chloroform. The chloroform solutions were combined, washed with water, dried over sodium sulfate, and evaporated *in vacuo* to yield an unstable resin which was crystallized from acetone. Recrystallization from acetone gave isojervone (VII, 62 mg.), m.p. 112–114° dec. Paper chromatography showed that the product was homogeneous, but no satisfactory analysis was obtained because it was unstable in the air; $[\alpha]^{19}\text{D}$ +140°; $\lambda_{\max}$ 234 mμ (ϵ 22,000) and 320 mμ (ϵ 310); $\nu_{\max}$ 1682, 1642, and 1620 cm.$^{-1}$.

The crude Oppenauer oxidation product, obtained from 500 mg. of isojervine, was directly acetylated with acetic anhydride (5 ml.) and pyridine (5 ml.). The crude acetate was chromatographed on Merck acid-washed alumina (10 g.). Fractions eluted with petroleum ether–benzene (1:1) and benzene were collected and triturated with acetone to afford crude diacetylisojervone (VIIa, 68 mg.), m.p. 188–195°. It had m.p. 202–204° after two recrystallizations from aqueous ethanol; $[\alpha]^{23}\text{D}$ +211°; $\lambda_{\max}$ 234 mμ (ϵ 27,000) and 320 mμ (ϵ 240); $\nu_{\max}$ 1736, 1675, and 1641 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{41}NO_5$: C, 73.34; H, 8.14; N, 2.76. Found: C, 73.60; H, 8.17; N, 2.70.

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(39) G. Thomson, *J. Chem. Soc.*, 1113 (1946).

(40) The paper chromatographic system used was that of J. Levine and H. Fischbach, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 191 (1957); ethylene chloride-Cellosolve Acetate-pyridine (15:10:1 v.v.).

Dihydroisojervines (VIII and IX).—Isojervine (6.00 g.) recrystallized from ethanol was hydrogenated in acetic acid (80 ml.) in the presence of prereduced Adams catalyst (1.07 g.), and 354 cc. of hydrogen (1.18 moles) was taken up after 7 hr. After removal of the catalyst and the solvent, the residue was diluted with water, made alkaline with aqueous sodium carbonate, and treated with chloroform. A large amount of material, consisting of chloroform addition compounds of dihydroisojervines (6.52 g., m.p. 129–140°), remained suspended between the aqueous and chloroform layers and was collected by filtration. The aqueous filtrate was further extracted with chloroform repeatedly and the extract was combined with the chloroform filtrate. The chloroform solution was washed with water, dried, and concentrated to give additional solid substances (0.13 g., m.p. 134–143°). These chloroform compounds were combined and recrystallized from aqueous acetone to yield a mixture of dihydroisojervines (VIII and IX, 3.35 g.), m.p. 147–149°. After three further recrystallizations from aqueous acetone, the pure 5α-dihydroisojervine (VIII, 1.74 g.) was obtained and had m.p. 154–155° (as hydrate) and 171.5–172.5° (after drying), $[\alpha]^{23}_{\mathrm{D}}$ −21.1°; $\lambda_{\max}$ 239 mμ (ε 9400) and 326 mμ (ε 210); $\nu_{\max}$ 1680, 1626, and 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.65; H, 9.55; N, 3.46.

After concentration of the first mother liquor and removal of a mixture of VIII and IX (1.13 g.), m.p. 135–140°, by filtration, the filtrate was further concentrated to give a single compound (0.46 g.), m.p. 128–133° dec., which was shown to be 5β-dihydroisojervine (IX) isomeric with VIII after purification by prolonged paper chromatography. The final product (IX), on recrystallization from acetone, had m.p. 114–115° dec., $[\alpha]^{23}_{\mathrm{D}}$ −49.0°; $\lambda_{\max}$ 236 mμ (ε 11,000) and 337 mμ (ε 250); $\nu_{\max}$ 1716 (acetone), 1687, 1631, and 1030 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3 \cdot CH_3COCH_3 \cdot H_2O$: C, 71.53; H, 9.81. Found: C, 71.44; H, 9.46.

5α-Dihydroisojervine (VIII, 203 mg.) was treated with acetic anhydride (1 ml.) and pyridine (2 ml.) at room temperature for 19.5 hr. and then heated at 100° for 10 min. The mixture was poured into cold water to give a crystalline product which was collected by filtration and recrystallized twice from aqueous ethanol, yielding 193 mg. of the triacetate (VIIIa), m.p. 208–210°, $[\alpha]^{23}_{\mathrm{D}}$ +68.8°; $\lambda_{\max}$ 234 mμ (ε 14,000) and 332 mμ (ε 180); $\nu_{\max}$ 1737, 1685, 1634, 1244, and 1024 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56; N, 2.53. Found: C, 71.68; H, 8.51; N, 2.43.

5β-Dihydroisojervine (IX, 99 mg.) was acetylated under the same conditions as mentioned above and the crude triacetate (IXa, 93 mg.) thus obtained was recrystallized from aqueous ethanol to yield the pure compound (72 mg.), m.p. 174–176°, $[\alpha]^{23}_{\mathrm{D}}$ +56°; $\lambda_{\max}$ 236 mμ (ε 11,000) and 328 mμ (ε 180); $\nu_{\max}$ 1740, 1683, 1633, 1242, and 1023 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56; N, 2.53. Found: C, 71.59; H, 8.64; N, 2.83.

Dihydroisojervones (X and XI). A.—A mixture of 5α-dihydroisojervine (VIII, 472 mg.) and cyclohexanone (8 ml.) was dissolved in toluene (100 ml.) and 40 ml. of the solvent was distilled. To the solution was added aluminum isopropoxide (1.50 g.) in dry toluene (5 ml.), and the whole solution was refluxed for 10 hr. After removal of the solvent by steam distillation, the residue was repeatedly extracted with chloroform. The chloroform solution was evaporated to yield a resin. The paper chromatogram indicated that it was a mixture of the starting material and an oxidation product, dihydroisojervone. The resin was chromatographed on ten sheets of paper (Toyō Roshi No. 50, 20 × 40 cm.) and bands corresponding to dihydroisojervone were cut out and treated with aqueous ammonia and chloroform. On concentration of the chloroform solution, 5α-dihydroisojervone (X, 20 mg.) crystallized and was collected by filtration. The filtrate was evaporated to dryness and chromatographed on silicic acid (1.5 g.) using chloroform as solvent to give additional crystals (40 mg.). Recrystallization from acetone yielded plates, m.p. 108–110° dec.; $[\alpha]^{23}_{\mathrm{D}}$ 0°, $[\alpha]^{23}_{350}$ +179° (dioxane); $\lambda_{\max}$ 238 mμ (ε 9900) and 325 mμ (ε 320); $\nu_{\max}$ 1714, 1679, and 1626 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_3 \cdot 2CH_3COCH_3$: C, 73.16; H, 9.49. Found: C, 73.52; H, 9.27.

B.[41]—To 5α-dihydroisojervine (VIII, 405 mg.) dissolved in dimethylformamide (12 ml.) were added chromic anhydride (405 mg.) and concentrated sulfuric acid (8 drops) under ice cooling, and the whole solution was allowed to stand at room temperature for 10 hr. After decomposition of the excess chromic anhydride with 10% aqueous sodium bisulfite (4 ml.), the solution was made alkaline to pH 8.2 with 10% aqueous sodium carbonate and extracted with four 10-ml. portions of chloroform. The chloroform solution was evaporated to dryness after being washed with water (30 ml.) and the residue was dissolved in ether. The mixture of bases in the ether solution was extracted with 2 *N* hydrochloric acid (2 × 12 ml.) and the acidic solution was made alkaline with 6 *N* ammonia and then treated with chloroform. The chloroform solution gave a brown oil (382 mg.), which crystallized on trituration with acetone and a small quantity of water. Recrystallization from aqueous acetone yielded 5α-dihydroisojervone (X, 147 mg.), m.p. 108–110° dec. Paper chromatography showed that more than 50% of the filtrate was the ketone X.

C.—5β-Dihydroisojervine (IX, 106 mg.) was oxidized and worked up in a manner similar to B, and gave an oily base (103 mg.). The oil was dissolved in chloroform and chromatographed on silicic acid (1 g.) using chloroform as solvent to yield oily 5β-dihydroisojervone (XI, 36 mg.), which showed one spot on the paper; $[\alpha]^{23}_{\mathrm{D}}$ −23°; $\lambda_{\max}$ 236 mμ (ε 10,000) and 326 mμ (ε 300); $\nu_{\max}$ 1714, 1684, and 1616 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_3$: C, 76.19, H, 9.24. Found: C, 75.98; H, 9.30.

Hydride Reduction[42] of 5α-Dihydroisojervone (X).—5α-Dihydroisojervone (XII, 50 mg.) was treated with sodium borohydride (20 mg.) in absolute ethanol at 20° for 1 hr. under stirring. After decomposition of the excess sodium borohydride with acetone (1 ml.) the solution was evaporated to dryness and the residue was shaken with chloroform and water. The chloroform solution gave a crystalline substance on removal of the solvent, which was recrystallized from aqueous acetone to yield 5α-dihydroisojervine (VIII, 28.1 mg.), m.p. 154–156°. The infrared spectrum and paper chromatography showed that more than 50% of the filtrate was the alcohol (VIII).

N-Methylisojervine (IV).—N-Methyljervine[11] (V, 4.50 g.) was added to methanol (135 ml.), saturated at 0° with hydrogen chloride, with stirring in the course of 6 min. and stirred at 0° for 1.5 hr. The red solution was evaporated *in vacuo* and diluted with water (500 ml.). It was made alkaline to pH 8.0 with 10% aqueous sodium carbonate and shaken with chloroform. Solid chloroform addition compounds were formed and collected by filtration. The aqueous layer of the filtrate was repeatedly extracted with chloroform and all chloroform solutions were combined, washed with water, and concentrated to 20 ml. to give solid materials (0.95 g.). The solid materials were combined and recrystallized from methanol–acetone to yield of N-methylisojervine (IV, 1.34 g.), m.p. 221–222°. It was also obtained by methylation of isojervine with methyl iodide and sodium carbonate in low yield; $[\alpha]^{23}_{\mathrm{D}}$ −9°; $\lambda_{\max}$ 327 mμ (ε 350), inflection at 245 (4400), and end absorption at 215 (11,000); $\nu_{\max}$ 1673, 1631, and 1066 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{41}NO_3$: C, 76.49; H, 9.40; N, 3.19. Found: C, 76.53; H, 9.68; N, 2.97.

Isojervinol (VI). A.—To a solution of isojervine (499 mg.) in dry tetrahydrofuran (25 ml.) was added lithium aluminum hydride (250 mg.) in the same solvent (7 ml.) and the whole mixture was stirred under nitrogen. After 18.6 hr., the reaction mixture was treated cautiously with water (1.4 ml.) and filtered. The filtrate was evaporated under reduced pressure, diluted with water, and extracted with chloroform repeatedly. The combined chloroform solution was washed with water, dried, and evaporated. The residue yielded a crystalline substance (VI, 134 mg.), m.p. 198–203°, on trituration with acetone. After two recrystallizations from methanl–acetone, it had m.p. 210–211°, $[\alpha]^{23}_{\mathrm{D}}$ −33.2°; ultraviolet spectrum, only end absorption (ε 6400 at 212 mμ), $\lambda_{\max}^{0.1\,N\ \mathrm{HCl-EtOH}}$ 311 mμ (ε 12,000); infrared spectrum, no band near 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.54; H, 9.76; N, 3.27.

B.—Sodium borohydride (150 mg.) was added to a solution of isojervine (300 mg.) in tetrahydrofuran (20 ml.) and the reaction mixture was refluxed for 10 hr. under nitrogen and then kept at room temperature for 14 hr. The excess reducing agent was decomposed with acetone (3 ml.) and the mixture was evaporated under reduced pressure. Water was added to the residue, and the mixture was repeatedly extracted with chloroform. The

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(41) *Cf.* G. Snatzke, *Ber.*, **94**, 729 (1961).

(42) *Cf.* O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953).

combined chloroform solutions were washed with water, dried, and evaporated. Trituration of the residue with acetone yielded isojervinol (VI, 142 mg.), m.p. 204–208°, which after recrystallization from methanol–acetone had m.p. 206.5–207.5°.

Isojervinol (30 mg.) was treated with acetic anhydride (0.5 ml.) and pyridine (0.5 ml.) at room temperature for 12 hr. The excess of acetic anhydride was decomposed with methanol and the solution was evaporated to give an oily residue. On addition of water the residue crystallized gradually and recrystallization from aqueous ethanol yielded triacetylisojervinol (VIa, 26 mg.) which melted at 123°, solidified, and again melted at 181–183° dec.; ν_{max} 3400, 1728, 1617, 1237, and 1026 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56. Found: C, 71.40; H, 8.68.

The Birch Reduction of Dihydroisojervines (VIII and IX).—To a refluxing solution of liquid ammonia (100 ml.) containing lithium (41 mg.) was added 5α-dihydroisojervine (VIII, 498 mg.) in tetrahydrofuran (6 ml.) during 2 min. under stirring. The mixture was continuously stirred for 5 min., when the blue color of the reaction mixture almost disappeared. Ammonium chloride (1 g.) was added and the resulting colorless solution was kept at room temperature to remove ammonia. When the residue was diluted with water and shaken with chloroform, a solid material (487 mg.) insoluble in the two layers appeared and was collected by filtration. The chloroform extract of the aqueous filtrate and the chloroform layer were combined, washed with water, dried over sodium sulfate, and evaporated to dryness. The residue and the solid material mentioned above were mixed and chromatographed on twelve sheets of paper. There appeared three bands when developed with bromophenol blue indicator. Each of the bands was cut out, collected, made alkaline with aqueous ammonia, and extracted with chloroform repeatedly.

The residue from the chloroform extract of the most mobile band yielded on trituration with chloroform crude 5α-tetrahydroisojervine needles (XIII, 152 mg.), m.p. 138–142°, m.p. 142–143° on recrystallization from aqueous acetone, $[\alpha]^{23}{}_{D}$ +12°; λ_{max} 310 mμ (ϵ 240) and end absorption (ϵ 4300 at 215 mμ); ν_{max} 1732, 1039, and 1029 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09; N, 3.26. Found: C, 75.29; H, 10.05; N, 3.21.

The middle band gave a crystalline product which was shown to be the unchanged 5α-dihydroisojervine by comparison of its chromatographic behavior and infrared spectrum with that of the starting material (VIII). The least mobile band afforded a crystalline product which upon recrystallization from chloroform gave hexahydroisojervine leaflets (XII, 13 mg.), m.p. 167–168°, $[\alpha]^{23}{}_{D}$ −51°; ultraviolet spectrum, only end absorption (ϵ 3100 at 215 mμ); infrared spectrum, no carbonyl band near 1700 cm.$^{-1}$

Anal. Calcd. for $C_{27}H_{45}NO_3$: C, 75.13; H, 10.51; N, 3.25. Found: C, 74.85; H, 10.30; N, 3.28.

Hexahydroisojervine (XII) was also obtained by catalytic hydrogenation of "α-dihydrojervinol"; "α-dihydrojervinol" (III, 514 mg.) was dissolved in acetic acid (25 ml.) and hydrogenated over Adams platinum oxide (108 mg.) at room temperature. During 2.5 hr., 34 ml. of hydrogen (1.2 moles) was absorbed. After removal of the catalyst and the solvent, the residue was made alkaline with aqueous sodium carbonate and extracted with chloroform. The extract was dried over sodium sulfate and concentrated to yield a crystalline product (XII, 296 mg.), m.p. 163–165°. The infrared spectrum was identical with that of hexahydroisojervine. For analysis it was recrystallized twice from acetone, m.p. 122° dec.

Anal. Calcd. for $C_{27}H_{45}NO_3 \cdot CH_3COCH_3$: C, 73.57; H, 10.50; N, 2.86. Found: C, 73.53; H, 10.37; N, 3.01.

In another experiment where a mixture of dihydroisojervines (VIII and IX) was used as a starting material, the product showed a new spot on the paper beside those corresponding to the three compounds XII, VIII, and XIII, which appeared between the spots of XIII and VIII. A compound corresponding to the new spot was isolated by a treatment similar to that described above, and it crystallized on trituration with chloroform. Recrystallization from aqueous acetone gave isomeric 5β-tetrahydroisojervine leaflets (XIV), m.p. 147–148°. The yield was comparable with that of XIII. XIV had $[\alpha]^{23}{}_{D}$ +83.0°; λ_{max} 302 mμ (ϵ 200) and end absorption (ϵ 5700 at 215 mμ); ν_{max} 1731, 1066, and 1029 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09; N, 3.26. Found: C, 75.37; H, 10.08; N, 3.43.

5α-Tetrahydroisojervine (XIII, 95 mg.) was dissolved in acetic anhydride (1 ml.) and pyridine (1 ml.). The mixture was kept at room temperature for 11 hr. and then heated at 100° for 10 min. It was poured into cold water and the solid material thus obtained was recrystallized twice from aqueous ethanol to yield the triacetyl derivative as needles (XIIIa, 84 mg.), m.p. 167–169°, $[\alpha]^{23}{}_{D}$ +83°; λ_{max} 307 mμ (ϵ 250) and end absorption (ϵ 7,400) at 215 mμ); ν_{max} 1738, 1632, 1238, and 1026 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{49}NO_6$: C, 71.32; H, 8.89; N, 2.52. Found: C, 71.49; H, 8.83; N, 2.71.

5β-Tetrahydroisojervine (XIV, 28 mg.) was similarly acetylated with acetic anhydride (0.4 ml.) and pyridine (0.4 ml.). The reaction mixture was worked up as usual and gave the corresponding triacetyl derivative as needles (XIVa, 25 mg.), m.p. 190–191° on recrystallization from aqueous ethanol, $[\alpha]^{23}{}_{D}$ +110°; λ_{max} 308 mμ (ϵ 250) and end absorption (ϵ 8100 at 215 mμ); ν_{max} 1732, 1639, 1237, and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{49}NO_6$: C, 71.32; H, 8.89; N, 2.52. Found: C, 71.54; H, 9.07; N, 2.55.

Alkali Treatment of 5α-Dihydroisojervine (VIII).—A solution of 5α-dihydroisojervine (VIII, 1.02 g.) in *t*-butyl alcohol (20 ml.) containing 1 *N* potassium *t*-butoxide was refluxed for 1 hr. under a stream of nitrogen. The solution was evaporated *in vacuo*, diluted with water (40 ml.), and treated with chloroform. The chloroform solution gave a resin (1.03 g.) after being washed with water and dried. A paper chromatogram indicated that no starting material had survived. The resin was chromatographed on silicic acid (22 g.) using chloroform as eluent to yield crystalline material (283 mg.). Two recrystallizations from aqueous methanol yielded XVI as rods, m.p. 143–145°; $[\alpha]^{23}{}_{D}$ +19°, $[\alpha]^{23}{}_{350}$ −382°; λ_{max} 239 mμ (ϵ 8600); ν_{max} 1670 and 1621 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1684 and 1629 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.69; H, 9.66; N, 3.51.

The rearranged prduct (XVI, 193 mg.) was treated with acetic anhydride (3 ml.) and pyridine (3 ml.) and heated on a steam bath for 1 hr. The solution was worked up as usual to yield a resin (227 mg.), which was chromatographed on silicic acid using chloroform as eluent to afford an amorphous base, $[\alpha]^{23}{}_{D}$ −11°, $[\alpha]^{23}{}_{350}$ −383°; λ_{max} 237 mμ (ϵ 8900); ν_{max} 1738, 1696, and 1640 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1726, 1685, and 1629 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{45}NO_5$: C, 72.76; H, 8.86; N, 2.74. Found: C, 72.65; H, 8.68; N, 2.72.

8,9-Dihydroisojervine (XIX).—To a refluxing solution of liquid ammonia (90 ml.) containing lithium (163 mg.) was added jervine (999 mg.) in dioxane (about 30 ml.) during 2 min. under stirring, and the whole mixture was stirred for another 5 min. The blue color of the reaction mixture disappeared on addition of ammonium chloride (3 g.) and then the ammonia was removed. The residue was treated with chloroform (100 ml.), and the chloroform solution was washed with water to remove dioxane and dried. The chloroform solution gave crude XIX, which crystallized as the chloroform compound (1.0 g.), m.p. 130°, on scratching. Recrystallization from acetone gave 8,9-dihydroisojervine (770 mg.), m.p. 159–160°. Two recrystallizations from acetone yielded an analytical sample (330 mg.), m.p. 162–163°; λ_{max} 312 mμ (ϵ 300) and end absorption (ϵ 5000 at 220 mμ); ν_{max} 1735 and 1060 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 76.04; H, 9.66; N, 3.06.

8,9-Dihydroisojervine (102 mg.) was acetylated with acetic anhydride (1 ml.) and pyridine (1 ml.) at room temperature. The product (86 mg.) crystallized on trituration with ethyl acetate and had m.p. 160–162°. Recrystallization from aqueous ethanol yielded pure triacetate (XIXa, 45 mg.), m.p. 163–164°, ν_{max} 1732 and 1638 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{47}NO_6$: C, 71.58; H, 8.56. Found: C, 71.88, 71.40; H, 8.47, 8.59.

Hydrogenation of 8,9-Dihydroisojervine (XIX).—8,9-Dihydroisojervine (100 mg.) was hydrogenated over Adams platinum (50 mg.) in acetic acid (2 ml.) at room temperature for 3 hr. After removal of the catalyst and the solvent, the residue was treated with chloroform and 6 *N* ammonia (1 ml.) when a solid material (86 mg.), insoluble in the two layers, appeared and was collected by filtration. The solid and an amorphous base (38 mg.) obtained from the chloroform solution were mixed and chromatographed on seven sheets of paper. There appeared three bands when developed with bromophenol blue indicator. Each of the bands was cut out, collected, and treated with aqueous ammonia and chloroform. The residue (34 mg.) obtained from the most mobile band crystallized on trituration with chloroform. Two recrystallizations from aqueous acetone gave 5α-tetrahydroisojervine (XIII, 13.5 mg.), m.p. 143–144°. The infrared spectrum was identical with that of the 5α-tetrahydroisojervine obtained by the Birch reduction of VIII. The middle band yielded a crystalline product (16.8 mg.), which had m.p. 135–137° on recrystallization from aqueous ethanol. The infrared spectrum showed no absorption of a carbonyl group and was different from that of III or XII.

Alkali Treatment of Triacetyl-8,9-dihydroisojervine (XIXa).—A solution of triacetyl-8,9-dihydroisojervine (XIXa, 30 mg.) in methanol (2 ml.) containing 10% potassium hydroxide was refluxed for 2 hr. under a stream of nitrogen. The solution was evaporated *in vacuo*, diluted with water, and treated with chloroform. The chloroform solution afforded a crystalline material (XIXb, 20 mg.), which had m.p. 213–215° on recrystallization from aqueous methanol; λ_{max} 254 mμ (ε 19,000); ν_{max} 3370, 1704, 1610, and 1055 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{43}NO_4$: C, 74.16; H, 9.23. Found: C, 74.01; H, 9.15.

The Dihydro Derivative of The Isomer (XX). A.—The compound (XX, 0.23 g.) was hydrogenated over prereduced Adams platinum (0.1 g.) in acetic acid (10 ml.) at room temperature, and after 6 hr. 13.4 ml. of hydrogen was absorbed (calculated for 1 mole, 12.7 ml.). The crystalline substance obtained after the usual work-up was recrystallized from acetone and the dihydro derivative (XXI, 0.12 g.), m.p. 230–232°, was obtained; λ_{max} 239 mμ (ε 12,800); ν_{max} 1691, 1630, and 1035 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.52; H, 9.76; N, 3.31.

B.—The dihydro derivative (XXI) was also obtained from 5α-dihydroisojervine (VIII); a solution of VIII (60 mg.) in methanol (8 ml.) was saturated with hydrogen chloride and allowed to stand at room temperature for 2 days. Water was added to the residue obtained on removal of the solvent under reduced pressure. The aqueous solution was made alkaline to pH 8 with 5% aqueous sodium carbonate, when a solid material (the starting material, 35 mg.) separated. After filtration, the aqueous solution was repeatedly extracted with chloroform. The chloroform solution gave a resin on removal of the solvent, which was chromatographed on paper. Five bands appeared on the chromatogram. The middle band was cut out and treated with aqueous ammonia and chloroform. The chloroform solution gave an amorphous substance which crystallized on trituration with acetone. On recrystallization from acetone, a crude sample of XXI (3.5 mg.), m.p. 220–227°, was obtained, which showed the practically same infrared spectrum and R_f value as the pure dihydro derivative mentioned above.

Acknowledgment.—The authors wish to express their appreciation to Professor S. M. Kupchan, University of Wisconsin, for providing them with an abundant amount of crude jervine, to Mr. S. Ohnishi, Toyo-rayon Company, Ltd., and to Mr. S. Shimokawa, Hokkaido University, for measurement of the n.m.r. spectra, and also to Miss A. Maeda for microanalysis.

Syntheses of Jasmone and the Related Compounds. II.[1] Preparation of *trans*-Jasmone and Allethrone

KEIITI SISIDO, SIGERU TORII, AND MITUYOSI KAWANISI

Department of Industrial Chemistry, Faculty of Engineering, Kyôto University, Kyôto, Japan

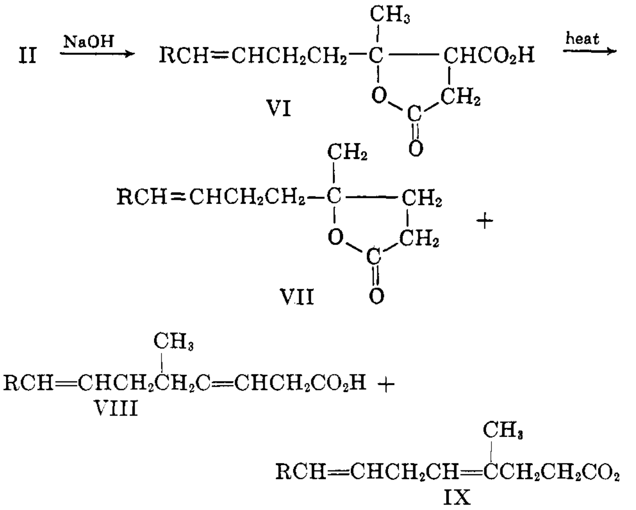
Received December 30, 1963

trans-Jasmone (Vb) and allethrone (Va) were synthesized from γ-methyl-γ-(3,4-dibromoalkyl)paraconic acids (III) by cyclodehydration with polyphosphoric acid followed by debromination with zinc. The acids III were obtained by bromination of γ-methyl-γ-alkenyl-α,β-dicarbethoxybutyrolactones (II) followed by heating with hydrochloric acid. Care was required in order to avoid the migration of and addition to the side-chain double bond.

In the previous paper,[2] a synthesis of 2,3-dialkyl-2-cyclopenten-1-ones including dihydrojasmone from γ,γ-dialkylparaconic acids was described. A synthesis of cyclopentenones (V) with an unsaturated side chain such as *trans*-jasmone[3–5] (Vb) and allethron[6] (Va) was undertaken. In order to avoid the migration of and addition to the double bond, a reaction sequence as illustrated in Scheme I was followed.

Reaction of ethyl β-methyl-β-alkenylglycidates (I) with sodium malonate afforded γ-methyl-γ-alkenyl-α,β-dicarbethoxybutyrolactones (II). Bromination of II followed by heating with hydrochloric acid gave γ-methyl-γ-(3,4-dibromoalkyl)paraconic acids (III). Treatment of III with polyphosphoric acid as described previously[2] resulted in the formation of methyldibromoalkylcyclopentenones (IV) which were subsequently debrominated with activated zinc[7] to give the expected cyclopentenones (V), including *trans*-jasmone (Vb) and allethrone (Va). The structures of these cyclopentenones were established by infrared spectra as well as conversion into the well-defined crystalline derivatives.

Saponification of II with aqueous sodium hydroxide followed by decarboxylation in glacial acetic acid[2] gave paraconic acids (VI). These were identical with the paraconic acids obtained by debromination of III, indicating that during the treatment of the lactone diesters (II) with alkali no shift of the double bond in the alkenyl group took place. Further evidence supporting the



VI

$RCH{=}CHCH_2CH_2C(CH_3)(O\text{-}CO\text{-}CH_2)CHCO_2H$

VII

$RCH{=}CHCH_2CH_2C(CH_2)(O\text{-}CO\text{-}CH_2)CH_2$

VIII

$RCH{=}CHCH_2CH_2C(CH_3){=}CHCH_2CO_2H$

IX

$RCH{=}CHCH_2CH{=}C(CH_3)CH_2CH_2CO_2$

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[1] Part I[2] concerned the preparation of dihydrojasmone and the homologs from γ,γ-dialkyl paraconic acid.

[2] K. Sisido, S. Torii, and M. Kawanisi, *J. Org. Chem.*, **29**, 904 (1964).

[3] W. Treff and H. Werner, *Chem. Ber.*, **68**, 640 (1935).

[4] H. Hunsdiecker, *ibid.*, **75**, 460 (1942).

[5] L. Crombie and S. H. Harper, *J. Chem. Soc.*, 869 (1952).

[6] L. Crombie, A. J. B. Edger, S. H. Harper, M. W. Lowe, and D. Thompson, *ibid.*, 3552 (1950).

[7] F. Bohlmann and K. Kieslich, *Chem. Ber.*, **87**, 1363 (1954).