cooling the solution in ice–water almost pure 4-bromo-3-hydroxyquinolizinium nitrate (**3**, X = NO_3) was obtained (0.57 g., 75%) crystallizing from ethanol as colorless needles, decomposing at 135–140°, melting above 200°.

Anal. Calcd. for $C_9H_7BrN_2O_4$: C, 37.64; H, 2.46; N, 9.76. Found: C, 38.13; H, 2.49; N, 9.32.

When a solution of the nitrate was passed through Amberlite IRA 400 (Br), 4-bromo-3-hydroxyquinolizinium bromide was obtained, identical with that obtained by direct bromination of 3-hydroxyquinolizinium bromide.

1-Hydroxyquinolizinium Betaine (**8**).—Saturated aqueous sodium carbonate solution (5 ml.) was added to 1-hydroxyquinolizinium bromide (1.00 g.) dissolved in water (2 ml.). Effervescence occurred and needles of the hydrated betaine were precipitated. The almost pure betaine was dried for several hours under reduced pressure (0.415 g., 58%). It sublimed as a yellow solid: m.p. 187–191°; $\lambda_{max}^{95\%\ EtOH}$ 2660, 3740 (sh), and 4000 Å. (log ϵ 3.91, 3.91, and 3.94); $\lambda_{max}^{CHCl_3}$ 2500, 2780, 3820, and 4310 Å. (log ϵ 3.85, 3.85, 3.85, and 3.85).

Anal. Calcd. for $C_9H_7NO \cdot H_2O$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.69; H, 5.57; N, 8.61.

3-Hydroxyquinolizinium Betaine (**9**).—A saturated solution of aqueous sodium carbonate (15 ml.) was added to 3-hydroxyquinolizinium bromide (1.00 g.) dissolved in water (2 ml.). Effervescence and the formation of yellow oily droplets were noticed during the addition. The mixture was continuously extracted with chloroform for 12 hr., and the dried (Na_2SO_4) chloroform extracts were evaporated. The oily residue was dissolved in acetone and the acetone was evaporated to small bulk. Cooling gave crystals of the betaine which recrystallized from acetone as yellow needles: m.p. 143–146°; 0.39 g. (48%); $\lambda_{max}^{CHCl_3}$ 2500, 2690, 2780, and 3620 Å. (log ϵ 4.38, 4.36, 4.36, and 4.18). The analysis specimen was dried overnight at room temperature (0.01 mm.) and then for 6 hr. at 100° (0.0005 mm.).

Anal. Calcd. for $C_9H_7NO \cdot 2A_2O$: C, 59.66; H, 6.12; N, 7.73. Found: C, 60.10; H, 6.31; N, 8.06.

1-Benzyloxyquinolizinium Bromide (**10**).—A solution of 1-hydroxyquinolizinium betaine (**8**, 0.175 g.) in benzene (40 ml.) was evaporated to approximately 10 ml. Benzene (40 ml.) was added followed by benzyl bromide (0.29 g.) and the mixture was boiled under reflux for 4 hr. The crystalline solid which had separated was filtered off and recrystallized from ethanol–ethyl acetate as colorless needles: m.p. 167–170°; 0.156 g. (38%); $\lambda_{max}^{H_2O}$ 2460 and 3500 Å. (log ϵ 4.33 and 4.27).

Anal. Calcd. for $C_{16}H_{14}BrNO \cdot 2H_2O$: C, 54.55; H, 5.15; N, 3.97. Found: C, 54.68; H, 4.98; N, 3.87.

The ether **8** gave a precipitate with a silver nitrate–nitric acid mixture but gave no color with neutral ferric chloride solution.

Jervine. XIV. Isojervin-11β-ol and Related Reduction Products of Isojervine

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Isojervine (Ia) is reduced by lithium borohydride to isojervin-11β-ol (IIa), the 3,23,N-triacetate of which (IIb) reverted on oxidation to the triacetate Ib of the parent ketone. N-acetylisojervine (Ic) yielded in this reduction, however, a crystalline mixture containing, in addition to the expected N-acetyl-isojervin-11β-ol (IIc), a more dextrorotatory 11β-ol, the triacetate of which on oxidation gave a ketone resembling in its ultraviolet characteristics the unconjugated ketone VI (triacetyl-8β,9α-dihydroisojervine) rather than Ic, but differing from both VI and Ic by its very high dextrorotation. This ketone was eventually assigned the 8ξ,9ξ-dihydro structure V on the basis mainly of the ultraviolet characteristics of the α,β-unsaturated enone IX obtained from Vb *via* its 5,6-dihydro derivative VII and the 17,17a-epoxide VIII.

Long before the structure of isojervine (Ia) was established[1–3] we had studied the reduction of this compound with borohydrides in order to make sure that the 11-keto group was part of the chromophor responsible for its abnormal ultraviolet absorption spectrum. Since lithium borohydride gave better yields of the resulting crystalline base (m.p. 219°, $[\alpha]_D$ −54°) than sodium borohydride, it was used in all subsequent experiments. That the reduction product is isojervin-11β-ol (IIa, m.p. 217–219°, recently also reported by Masamune, *et al.*,[2] with m.p. 210–211°) is evidenced (1) by the lack of specific absorption in the region 220–360 mμ; (2) the presence of only weak bands at 6.05 and 6.20 μ in the double bond stretching vibration region of the infrared spectrum; (3) the formation on mild acetylation of a triacetate (IIb, m.p. 186°, $[\alpha]_D$ +24°) which with alkali gave the N-acetyl derivative IIc (m.p. 211°, $[\alpha]_D$ +6°) and on Jones oxidation[4] reverted to triacetylisojervine (Ib) (Chart I).

Isojervin-11β-ol and its acetylated derivatives give a strong Rosenheim reaction (purple), and on addition of dilute hydrochloric acid to their alcoholic solutions produce a rose-colored, orange-fluorescing pigment. This instability to acid is also evident in the formation of yellow decomposition products on chromatography of the acetates on acid-washed or neutral alumina. These color reactions are not dependent only, however, on the presence of the allylic alcohol grouping in II, but, as will appear later, also of the 5,6-double bond. On the other hand, isojervin-11β-ol does not display the characteristic instability of isojervine towards strong alkali which manifests itself in the formation of a deep red pigment.

It was then surprising to find, in the face of these straightforward results, that the lithium borohydride reduction of N-acetylisojervine (Ic) did not lead to the N-acetylisojervin-11β-ol IIc, m.p. 211°, but to higher-melting, more dextrorotatory products (m.p. 230–232°, $[\alpha]_D$ +65 to 75°) which on acetylation yielded triacetates, m.p. 183–186°, $[\alpha]_D$ +78 to 98°. It soon became clear that these new acetylated reduction products were mixtures, respectively, of the normal triacetyl- and N-acetylisojervin-11β-ols IIb and IIc and the corresponding derivatives of a more dextrorotatory entity which to judge from the analytical results was isomeric with the normal isojervin-11β-ol IIa. These derivatives (triacetate, m.p. 162–167°, $[\alpha]_D$ +133°; N-acetyl derivative, m.p. 240–241°, $[\alpha]_D$ +132°) differed from the crystalline mixtures originally obtained by no longer giving the color reactions char-

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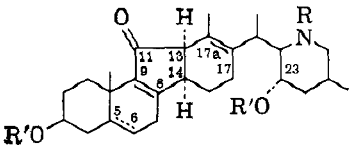
(1) (a) O. Wintersteiner and M. Moore, *Tetrahedron Letters*, 795 (1962); (b) *J. Org. Chem.*, **29**, 262 (1964).

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

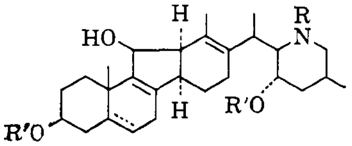
(3) W. G. Dauben, W. W. Epstein, M. Tanabe, and B. Weinstein, *J. Org. Chem.*, **28**, 293 (1963).

(4) K. Bowden, I. M. Heilbron, E. R. H. Jones, and C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

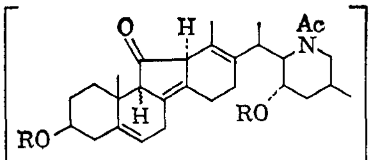
Chart I



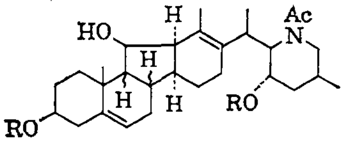
Ia, R = R' = H; Δ^5
b, R = R' = Ac; Δ^5
c, R = Ac; R' = H; Δ^5
XIIIa, R = R' = Ac; no Δ^5
b, R = Ac; R' = H; no Δ^5



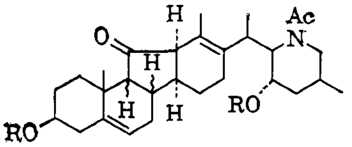
IIa, R = R' = H; Δ^5
b, R = R' = Ac; Δ^5
c, R = Ac; R' = H; Δ^5
XIVa, R = R' = Ac; no Δ^5
b, R = Ac; R' = H; no Δ^5



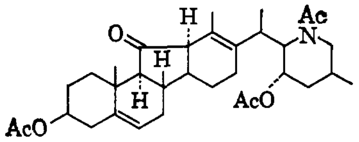
III



IVa, R = Ac
b, R = H



Va, R = Ac
b, R = H



VI

acteristic for IIb and IIc. The reason for this became clear when the triacetate, m.p. 167°, was subjected to Jones oxidation.[4] The resulting highly dextrorotatory oxidation product (m.p. 206–209°, $[\alpha]_D$ +199°) exhibited spectral characteristics (low intensity peaks at 308, 319, and 330 mμ, and end absorption; infrared bands at 5.77 and 5.80 μ) indicative of a *nonconjugated* ketone. These ultraviolet characteristics and the infrared band at 5.77 μ persisted in the spectra of the N-acetyl derivative (m.p. 254–255°, $[\alpha]_D$ +209°) obtained from the triacetylated ketone by hydrolysis with alkali. The new ketone thus differs from isojervine by its stability to strong base, and its acetylated derivatives can thus be easily distinguished from those of isojervine by their failure to give on alkalinization the red pigment mentioned earlier.

Reduction of the triacetylated ketone with lithium borohydride followed by alkaline hydrolysis gave the "abnormal" N-acetyl 11β-ol, m.p. 241°, showing that no other but the 11β-ol → 11-ketone change had occurred on Jones oxidation.

As with the "abnormal" 11β-ol derivatives, the analyses of the new 11-keto compounds derived from them indicated persistence of all three of the original double bonds; *i.e.*, they appeared to be isomers of triacetyl- and N-acetylisojervine rather than 8,9-dihydro derivatives, a supposition which also seemed to find some support in the perbenzoic acid uptake of the triacetyl derivative and its 11β-ol precursor (2.5–3.0 moles after 48 hr.). Taking these data at their face value, one would then have to assume that the 8,9-double bond has not been saturated in the reduction, but has moved into a neighboring position where, in the ketone, it is in conjugation neither with the 11-keto group nor with the 5,6-double bond, *i.e.*, into the 8,14-position, so that the new ketone would have to be formulated as III. However, to our knowledge there is no precedence for such a migration occurring in the metal hydride reduction of an α,β-unsaturated ketone, whereas there are on record numerous instances of the simultaneous reduction by sodium borohydride of the keto group and conjugated ethylenic bond.[5] More importantly, the additional facts outlined below cannot be well reconciled with III, and we therefore provisionally assign to the ketone in question the 8ξ,9ξ-dihydroisojervine structure V, and shall refer to it as 8,9-dihydroisojervine A to distinguish it from the 8,9-dihydroisojervine which is obtained from isojervine by reduction with lithium in liquid ammonia and unquestionably is the 8β,9α-stereoisomer VI.[1b] The 11β-ol giving rise (as the triacetate) to the triacetate Va on oxidation is then written as IVa and called (triacetyl)-8,9-dihydroisojervin-11β-ol A.[6]

The evidence militating against the triolefinic structure III for the highly dextrorotatory ketone now called 8,9-dihydroisojervine A (V) comprises the following findings. The ultraviolet characteristics of the triacetate Va showed no changes on refluxing with 2% methanolic potassium hydroxide or on prolonged treatment with hydrochloric acid at room temperature, conditions one would expect to shift the 8,14-double bond of III into one of the positions (8,9 or 13,14) conjugated with the keto group. For more conclusive proof the triacetate was converted to the 13,17a-unsaturated ketone IX *via* the 5,6-dihydro derivative VII and the 17,17a-epoxide VIII. The saturation of the 5,6-double bond of Va could be easily effected,

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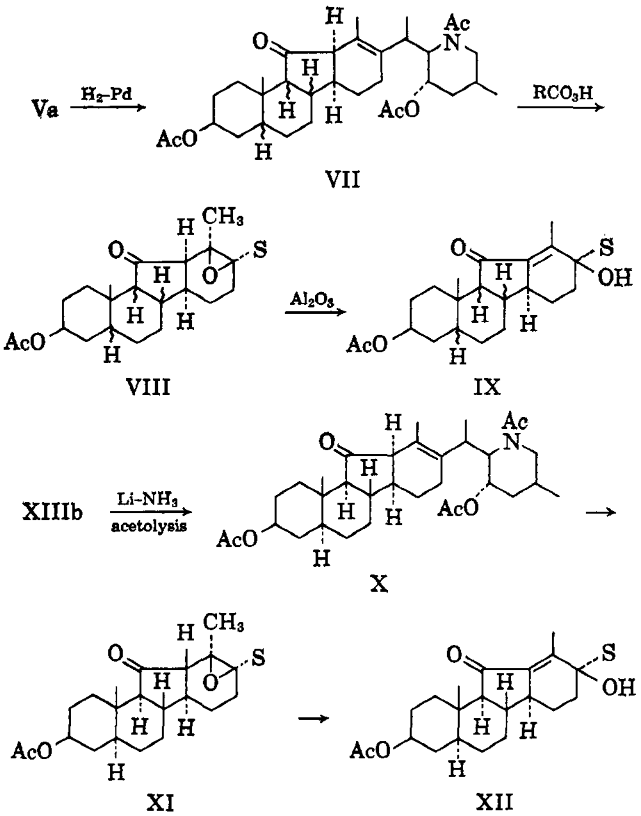
[5] For instance, F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. Ind.* (London), 1482 (1954); J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955); R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957); D. H. R. Barton, P. F. deMayo, and M. Shafig, *J. Chem. Soc.*, 929 (1957).

[6] In 1947 W. A. Jacobs and C. F. Huebner [*J. Biol. Chem.*, **170**, 635 (1947)] described a reduction product of jervine, "α-dihydrojervinol," which was obtained from the native alkaloid with sodium and butanol, and was believed to be 13,17a-dihydrojervin-11α-ol. It was subsequently shown in this laboratory by Fried and Klingsberg [*cf.* B. M. Iselin, M. Moore, and O. Wintersteiner, *J. Am. Chem. Soc.*, **78**, 403 (1956), footnote 4] that "α-dihydrojervinol" was actually a *dienic* hydrogenolysis product of jervine in which the oxidic ring had been opened with the establishment of the veratramine (or isojervine) side chain, and recently by Masamune, *et al.*,[2] and by Dauben, *et al.*,[3] that it is, in fact, a derivative of isojervine, namely, 8β,9α-dihydroisojervin-11α-ol (although these configurations were not specified in their papers). This designation should then be used for this compound to distinguish it from IV.

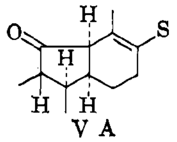
CHART II

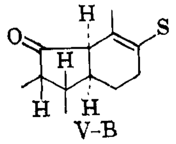


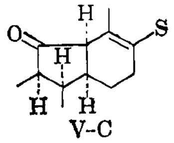
as with isojervine,[1] by catalytic hydrogenation with palladium on charcoal as the catalyst. The crystalline dihydro derivative VII gave on treatment with *m*-chloroperbenzoic acid[7] the amorphous epoxide VIII, which on neutral alumina was isomerized to the crystalline enone IX, $\lambda_{\max}$ 257 mμ (ϵ 6800) and 342 mμ (ϵ 80). Now the sequence VII → IX is completely analogous to the previously reported[1] conversion of triacetyl-5,6,8,9-tetrahydroisojervine (Xi) *via* the oxide XI to the enone XII, $\lambda_{\max}$ 261 mμ (ϵ 10,300) and 355 mμ (ϵ 120). Were the enone IX actually a 8,14,-13,17a-dienic 11-ketone such as would arise in the above sequence from III, one would expect its absorption spectrum to differ from that of XII by a markedly higher ϵ and possibly also $\lambda_{\max}$ value of the main maximum, whereas, in fact, the numerical values of both these parameters are decreased (we have been unable to locate in the literature ultraviolet data for the cross-conjugated dienone system in question). The spectral properties of the amorphous reduction product obtained from IX with lithium borohydride [$\lambda_{\max}$ 291 mμ (ϵ 810); broad high bands in the infrared spectrum at 2.95 and 6.16 and no bands in the 5.8–6.0-μ region] likewise support this structure, unless it is contended that the low ultraviolet band at 291 mμ originates in the $\Delta^{8-14,13-17a}$-dienol which would be formed from III, but was then for the most part further reduced to a singly unsaturated alcohol (Chart II).

Since it could be expected that N-acetyl-5,6-dihydroisojervine (XIIIb) on reduction with lithium borohydride would in analogy with the findings on N-acetylisojervine give rise to a mixture of the normal N-acetyl-5,6-dihydroisojervin-11β-ol (XIVb) and of the "abnormal" product, N-acetyl-5α?,6,8ξ,9ξ-tetrahydroisojervin-11β-ol A, this reaction was essayed in the hope that these two compounds could be more easily separated from each other, as the triacetates, than IVa from IIb, and a less wasteful procedure for securing the ketone VII would thus come to hand. However, the only pure substance which could be obtained from the reduced material was N-acetyl-5,6-dihydro-isojervine-11β-ol (XIVb), m.p. 251°, $[\alpha]_D$ +25.6°, which was shown to belong to the normal series by the conversion with chromic acid of its triacetate XIVa to the triacetate XIIIa of the starting ketone. These N-acetylated and triacetylated derivatives of 5,6-dihydroisojervin-11β-ol (XIVb and a) do not give the color reactions characteristic for IIa, b, and c, indicating that the pigments produced from the latter probably arise *via* conjugated trienes formed by dehydration at C-11 *and* $\Delta^5 \rightarrow \Delta^6$ migration.

It is then proposed that the compounds of the "abnormal," highly dextrorotatory series (IV and V) differ sterically from 8β,9α-dihydroisojervine (VI) by epimerism at C-8 or C-9, or both, but share with it the α-configuration at C-13 and C-14. The latter conclusion is supported not only by the equivalence of the transformations VII → VIII → IX and X → XI → XII, the last step of which can be assumed to depend on the *trans*-diaxial relationship between the 13α-hydrogen and the 17a-oxygen bond,[1b] but also by the similarity of the ultraviolet characteristics of V, VI, and X (multiple peaks in the 300–330-mμ region, indicative of *cis*-junction of rings C and D[1b]). Of the three spatial structures then under consideration for the ketone V (V-A, V-B, and V-C) the 8α,9α-isomer with *cis-syn-cis* arrangement of the ring junctions (V-C) appears the least probable, since the scale model shows that on account of the double folding of the molecule about the 8,9- and 13,14-axes rings B and C badly crowd the space above ring C, causing the 15β-hydrogen to impinge severely on the 19-methyl group, which effect is only partly mitigated by making ring B a half-boat. In the 8β,9β isomer V-B-the only nonbonded interaction of comparable severity is between the 1α-hydrogen and the 11-carbonyl oxygen (which could, however, through hydrogen bonding, increase rather than decrease stability), while the essentially flat molecule of the 8α,9β-isomer V-A with "unnatural" B/C *trans* fusion is devoid altogether of unfavorable interactions. There is also an experimental fact which would seem to favor one of the latter two expressions, insofar as they both have the 9β-configuration: the 19-methyl signal in the n.m.r. spectrum of Va appears at τ 8.65 (comparable with 8.45 in N-acetyl-11-keto-5β(?),6-dihydro-9β-veratramin-3-one[8]), whereas the spectrum of the 8β,9α-isomer VI exhibits this signal at τ 9.01 (comparable


V A


V-B


V-C

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[7] Technical Data, *m*-Chloroperbenzoic Acid, Food Machinery and Chemical Corp., New York, N. Y.; N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).

[8] D. M. Bailey, D. F. G. Hamon, and W. S. Johnson, *Tetrahedron Letters*, No. **9**, 555 (1963).

with 8.97[9] in N-acetyl-11-keto-5α,6-dihydroveratramine). Isomer V-B is, however, less attractive than V-A, for two reasons. First, it is not apparent from the model of V-B, in which the 19-methyl group has a pronounced tilt removing it from vicinity to the 11-carbonyl, why V should be as unreactive to ketone reagents as it is. Second, V is stable to boiling alkali and hence is the stable epimer with respect to its 13- and 9-epimers (the latter being VI), but VI is likewise stable to alkali, in the sense that it is not epimerized by it at C-9.[10] It would seem then that the difference between V and VI cannot be solely due to epimerism at C-9. This leaves V-A as the most likely expression for V. However, in the absence of any positive evidence favoring it over V-B and V-C we prefer leaving the C-8 and C-9 configurations undefined, nor do we wish at this point to discount entirely the trienic structure III.

It should also be noted that in VII, the 5,6-dihydro product of V, and in the compounds derived from it (VIII and IX) the configuration of C-5 is likewise left undefined. This uncertainty stems from the unexpected finding that the molecular rotation change accompanying the saturation of the 5,6-double bond of V has a high negative value, −225°, whereas in the isojervine and normal isojervin-11-ol series as well as in the jervine and veratramine series, in all of which this reaction without any doubt establishes the 5α-configuration, this value is always positive, though of variable magnitude (average values +72, +265, and +400°, respectively). Whatever the configuration of C-5 in VII may be, the above anomaly clearly reflects a profound change in the geometry of ring B such as would result from an abnormal type of B/C ring junction.

Finally, there remains the question why the "abnormal" 11β-ol IV is formed only when the reduction with lithium borohydride is carried out on an N-acetylated derivative of isojervine. We are inclined to believe that this difference in the course the reduction takes with the free base Ia and with its acetylated derivatives Ib and Ic is only apparent, not real, in the sense that the free base corresponding to IVa and IVb is actually produced in the reduction along with isojervin-11β-ol (IIa), though possible as a minor product, but fails to crystallize together with IIa or from the mother liquor of the latter, whereas its acetylated derivatives IVa and IVb tend to form, as the infrared data show, mixed crystals with the corresponding normal reduction products IIb and c. At any rate, the search for the abnormal products in the strongly pigmented mother liquor from isojervin-11β-ol before and after acetylation was unsuccessful.

Experimental

The melting points were taken in open Pyrex glass capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semimicrotube, with chloroform as the solvent, unless indicated otherwise. The ultraviolet spectra were measured in absolute ethanol in a Cary self-recording instrument, Model 11 M. The infrared spectra were determined on Nujol mulls in the Perkin-Elmer double-beam self-recording spectrophotometer, Model 21. The characteristics of the infrared bands are expressed in the text as follows: (s), strong; (m), medium; (l), low; (v.l.), very low; (br), broad; (sh), shoulder.

Isojervin-11β-ol (IIa).—To a solution of isojervine acetonate (340 mg.) in tetrahydrofuran (20 ml.) lithium borohydride (320 mg.) in the same solvent (20 ml.) was added slowly with stirring. The solution was allowed to stand for 2 hr. and then was boiled under reflux for 0.5 hour. After cooling and the addition of water (50 ml.) it was brought to pH 6.5 with 10% acetic acid (13 ml.) and, when gas evolution ceased, was brought to pH 8 with 2 *N* sodium carbonate solution (20 ml.). The material was recovered by extraction with two 100-ml. portions of chloroform. The glassy residue of the water-washed and dried extract (324 mg.) was recrystallized from ethyl acetate and then twice from methanol–ethyl acetate. The resulting product (needles, 124 mg., m.p. 217–219°) showed no specific ultraviolet absorption above 220 mμ; $[\alpha]^{24}\text{D}$ −57° (*c* 0.412), −54.5° (*c* 0.515, absolute ethanol); $\lambda_{\max}^{\text{Nujol}}$ 2.95 (s), 3.05 (s), 6.05 (v.l.), 6.20 (v.l.) μ.

Anal. Calcd. for $C_{27}H_{41}NO_3$ (427.6): C, 75.83; H, 9.66. Found: C, 75.49, 76.00; H, 9.46, 9.41.

The substance did not give the red color reaction with strong alkali characteristic for isojervine, but addition of a few drops of 2 *N* hydrochloric acid to a methanolic solution produced an intense pink color with orange fluorescence; the Rosenheim test (90% trichloroacetic acid added to chloroform solution) gave an intense red color.

For the preparation of the **3,23-N-triacetate (IIb)**, isojervinol (525 mg.) was treated with acetic anhydride (10 ml.) in pyridine (20 ml.) at room temperature for 6 hr. (reaction with an 1:1 mixture of the reagents for 20 hr. gave inferior yields). The crude product (702 mg.) was recrystallized twice from aqueous methanol, from which it formed small needles with m.p. 183–186°; $[\alpha]^{23}\text{D}$ +24° (*c* 0.781); $\lambda_{\max}^{\text{Nujol}}$ 2.95 (m), 5.76 (s), 6.18 (s), 8.09 (s) μ; $\lambda_{\max}^{\text{CHCl}_3}$ 2.95 (v.l.), 5.76 (s), 6.12 (m.s.), 8.00 (s) μ.

Anal. Calcd. for $C_{33}H_{47}NO_6$ (553.7): C, 71.58; H, 8.58; $3COCH_3$, 23.3. Found: C, 71.45, 71.53; H, 8.36, 8.63; $COCH_3$ 20.2.

N-Acetylisojervinol (IIc) was obtained from the triacetate (111 mg.) by hydrolysis with 2% methanolic potassium hydroxide at room temperature (20 hr.). Repeated recrystallization of the crude product (106 mg.) from ethyl acetate yielded small rods (57 mg.) with m.p. 209–211°; $[\alpha]^{24}\text{D}$ +6.6° (*c* 0.969); $\lambda_{\max}^{\text{Nujol}}$ 3.00 (s), 6.22 (s) μ.

Anal. Calcd. for $C_{29}H_{43}NO_4$ (469.6): C, 74.16; H, 9.23. Found: C, 73.88; H, 9.20.

On acetylation in pyridine, N-acetylisojervinol reverted to the triacetate, m.p. 182°, $[\alpha]\text{D}$ +23°.

Oxidation of Triacetylisojervinol (IIb) to Triacetylisojervine (Ib).—The triacetate (103.4 mg., 0.187 mmole) was dissolved in reagent grade acetone (15 ml.), and 1.10 ml. of a solution, prepared by diluting 0.62 ml. of the chromic acid–sulfuric acid reagent of Djerassi, *et al.*,[10] with acetone to 10 ml., was added dropwise from a buret (0.188 matom of oxygen). The mixture was allowed to stand for 10 min. and, after the addition of a few drops of ethanol and excess water, freed from the acetone by dis-

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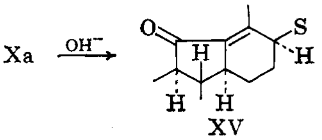
[9] Paper XIII of this series: O. Wintersteiner and M. Moore, *Tetrahedron*, **20**, 1947 (1964).

[10] This conclusion rests on the following indirect evidence: N-acetyl-5,6,8,9-tetrahydroisojervine (X with 3- and 23-hydroxyls free), which unquestionably has the normal 8β,9α-configuration,[1b] is quantitatively converted by boiling 5% methanolic potassium hydroxide to its 13,17a-double bond isomer, the conjugated ketone XV (partial formula below). The



XV

latter ketone on catalytic hydrogenation afforded a 13,17a-dihydro derivative identical with a compound which had previously been obtained from diacetyltetrahydrojervine by a sequence of reactions not involving C-8, C-9, or C-14 and, therefore, having at these carbon atoms the "natural" configurations shown in XV. (O. Wintersteiner and M. Moore, to be published). It follows from this that X is not epimerized by hot alkali either before or after migration of its double bond into the conjugated position, and the same must be true of VI, the more so as its 5,6-double bond would lend additional stability to the normal 8β,9α-*trans* junction of rings B and C.[8] The fact that N-acetyl-8,9-dihydroisojervine A (Vb) is *not* isomerized by hot alkali to a conjugated ketone analogous to XV must have its cause in conformational factors residing in ring C which prevent enolization towards C-13. It is interesting that in this respect V resembles N-acetyl-5,6-dihydroisojervine (XIIIb), in which it is the 8,9-double bond that prevents the formation of the Δ^{11-13}-enol requisite for migration of the 17,17a-double bond into the conjugated position.[1b]

tillation under reduced pressure. The product was recovered by chloroform extraction. The residue from the carbonate-washed and dried extract (89 mg.) after several recrystallizations from aqueous ethanol yielded needles identified as triacetylisojervine by melting point (187°, undepressed by authentic sample), rotation (+27°), and infrared and ultraviolet characteristics.

Reduction of N-Acetylisojervine with Lithium Borohydride.—N-acetylisojervine (663 mg.) was reduced with lithium borohydride (603 mg.) in tetrahydrofuran (35 ml.), and the mixture was worked up in the manner described above for isojervine, except that ether instead of chloroform was used for extracting the product. The ether residue (472 mg.) on trituration with ethyl acetate yielded crystalline material, 352 mg., m.p. 223–229°. It was purified by recrystallization from aqueous methanol, from which it formed irregularly shaped platelets melting at 229–232°, $[\alpha]^{23}\text{D}$ +65° (*c* 0.915), after drying at 110° (1 mm.). The product showed no specific ultraviolet absorption, and its infrared spectrum (Nujol) was identical with that of N-acetylisojervinol, except for slight differences in the heights of some of the bands in the "fingerprint" region.

Other runs gave products melting in the same range, but showing somewhat higher rotational values (+69, +74, and +83°). Material of the same description, m.p. 231–233°, $[\alpha]\text{D}$ +71°, was obtained by lithium borohydride reduction of triacetylisojervine followed by alkaline hydrolysis at room temperature.

Acetylation of these high-rotating N-acetylated products with acetic anhydride and pyridine at room temperature gave homogenous-looking rods melting from 181 to 186°; an analysis sharply indicated $C_{33}H_{47}NO_6$, *i.e.*, a triacetylisojervinol. Their rotations varied from +78 to +98°, and they slightly depressed the melting points of comparable preparations of triacetylisojervinol. It is worth noting that the infrared spectra of these mixtures in chloroform solution or in potassium bromide disks were identical with those of triacetylisojervinol; only the much better resolved Nujol spectra revealed slight differences in the "fingerprint" region.

Triacetyl-8,9-dihydroisojervinol A (IVa).—The crude, but mostly crystalline reduction product, $[\alpha]\text{D}$ +57°, from 729 mg. of N-acetylisojervine was treated with pyridine (28 ml.) and acetic anhydride (14 ml.). The mixture was worked up after 5.25 hr., and the acetylated product (711 mg.) was chromatographed in benzene solution on neutral alumina. The fractions eluted with ether–benzene 1:9 were combined (156 mg.) and recrystallized repeatedly from aqueous methanol to yield what appeared to be substantially pure triacetyl-8,9-dihydroisojervinol A in small rods: m.p. 171–177° after drying at 100° at 2 mm.; $[\alpha]^{23}\text{D}$ +133°; $\lambda_{\max}^{\text{Nujol}}$ 2.98 (m), 5.77 (s), 6.14 (s), 8.10 (s) μ. The differences from the spectrum of triacetylisojervinol in the "fingerprint" region were now easily recognizable, as was the hypsochromic displacement of the N-acetyl band at 6.14 μ. The spectra of the mixtures with intermediate rotations are clearly composites of the curves of the pure normal and abnormal products.

Anal. Calcd. for $C_{33}H_{47}NO_6$ (553.7): C, 71.58; H, 8.56. Calcd. for $C_{33}H_{49}NO_6$ (555.7): C, 71.32; H, 8.89. Found: C, 71.68; H, 8.52.

The other chromatographic fractions were either amorphous or yielded only small amounts of crystalline, but inhomogeneous products. To judge from the positive Rosenheim test, they all contained triacetylisojervinol, but most of this compound seemed to have suffered destruction on the column.

N-Acetyl-8,9-dihydroisojervinol A (IVb) was prepared from the triacetate (37 mg.) with methanolic potassium hydroxide in the usual manner. The crude product (30 mg., m.p. 238–240°) after recrystallization from methanol–ethyl acetate had m.p. 240–241°; $[\alpha]^{20}\text{D}$ +132° (*c* 0.725); $\lambda_{\max}^{\text{Nujol}}$ 3.00 (s), 6.24 (s) μ.

Anal. Calcd. for $C_{29}H_{43}NO_4$ (469.6): C, 74.16; H, 9.23. Calcd. for $C_{29}H_{45}NO_4$ (471.7): C, 73.84; H, 9.62. Found: C, 74.31; H, 9.07.

Reacetylation of 10 mg. yielded triacetyl-8,9-dihydroisojervinol A: m.p. 171–176° after drying at 100° at 2 mm., $[\alpha]^{21}\text{D}$ +140°.

Triacetyl-8,9-dihydroisojervine A (Va).—Impure triacetyl-8,9-dihydroisojervinol A (m.p. 180°, $[\alpha]\text{D}$ +91°, 121 mg.) was oxidized in acetone solution with chromium trioxide (1 equiv. of oxygen) in the manner described above for triacetylisojervinol. The oxidized material (120 mg.) was recrystallized three times from aqueous ethanol from which it formed needles (61 mg.) melting at 206–209°: $[\alpha]^{23}\text{D}$ +199°; $\lambda_{\max}^{\text{alc}}$ 309 mμ (ϵ 64), 319 mμ (59) sh, 330 mμ (38), unchanged in 0.15 *N* ethanolic potassium hydroxide or in aqueous ethanol containing 5% hydrochloric acid; $\lambda_{\max}^{\text{Nujol}}$ 5.75 (sh s.), 5.79 (s), 6.10 (s), 8.09 (s) μ.

Anal. Calcd. for $C_{33}H_{45}NO_6$ (551.7): C, 71.84; H, 8.22. Calcd. for $C_{33}H_{47}NO_6$ (553.7): C, 71.58; H, 8.56. Found: C, 71.71; H, 8.44.

Another specimen, prepared from a triacetyl-8,9-dihydroisojervinol, $[\alpha]\text{D}$ +98°, showed m.p. 206–208° and $[\alpha]\text{D}$ +203°.

Anal. Found: C, 71.76; H, 8.44.

A solution of the ketone in ethanol stayed colorless on addition of aqueous potassium hydroxide.

A 25-mg. sample was subjected to reduction with lithium borohydride followed by alkaline hydrolysis. The purified product melted at 238–239° and showed $[\alpha]^{27}\text{D}$ +117°. The infrared spectrum was identical with that of N-acetyl-8,9-dihydroisojervinol A, m.p. 241°.

N-Acetyl-8,9-dihydroisojervine A (Vb) was prepared by refluxing a solution of the triacetate (32 mg.) in 2% methanolic potassium hydroxide for 0.5 hr. Two recrystallizations of the recovered material from methanol–ethyl acetate yielded hexagonal plates, melting at 254–255°: $[\alpha]^{23}\text{D}$ +209° (*c* 0.746); $\lambda_{\max}^{\text{alc}}$ 309 mμ (ϵ 60), 319 (60), sh. 330 (39); $\lambda_{\max}^{\text{Nujol}}$ 3.0 (s), 5.77 (s), 6.19 (s) μ.

Anal. Calcd. for $C_{29}H_{41}NO_4$ (467.6): C, 74.47; H, 8.84. Calcd. for $C_{29}H_{43}NO_4$ (469.6): C, 74.16; H, 9.23. Found: C, 74.42; H, 8.87.

Conversion of Triacetyl-8,9-dihydroisojervine A (Va) to the Enone IX.—Only 69 mg. of pure triacetyl-8,9-dihydroisojervine A (Va) was available for effecting its conversion to the α,β-unsaturated ketone IX *via* VII and VIII. This amount of Va, dissolved in absolute ethanol (6 ml.), was hydrogenated in the presence of prehydrogenated 5% palladium–charcoal catalyst. The reaction ceased after 1.5 hr. when 1.14 molar equiv. had been consumed. The crude product was recrystallized from aqueous ethanol, giving 44 mg. of **triacetyl-5,6,8,9-tetrahydroisojervine A** (VII, small needles, m.p. 190–193°, $[\alpha]^{23}\text{D}$ +152°), which without further purification was dissolved in benzene (15 ml.) containing 23.6 mg. of 88.5% *m*-chloroperbenzoic acid (1.55 molar equiv.). Titration of an aliquot after standing 2 hr. at room temperature showed that 1.00 mole/mole of substance had been consumed. After the addition of more solvent the solution was washed consecutively with aqueous sodium sulfite, sodium bicarbonate, and water, dried over sodium sulfate, and brought to dryness. The residue (42 mg.), which could not be crystallized, must have consisted, as the subsequent conversion to IX shows, of substantially pure triacetyl-5,6,8,9-tetrahydroisojervine A 17,17a-oxide (VIII). The rotation measurement, $[\alpha]^{23}\text{D}$ +89°, and analysis were carried out on a sample of VIII which was obtained by similar treatment of a second crop of crystals of VII melting at 185–187° (peracid consumption, 1.17 moles/mole).

Anal. Calcd. for $C_{33}H_{49}NO_7 \cdot H_2O$ (589.7): C, 67.20; H, 8.72. Found: C, 67.43; H, 8.39.

To a solution of the oxide VIII (42 mg.) in benzene (2 ml.) Woelm neutral alumina (1.7 g.) was added, and the suspension was stirred mechanically for 40 min., whereupon it was transferred to a small chromatography tube (diameter 6 mm.) and washed with three 20-ml. portions each of benzene, ether, and ether containing 2% of methanol. The last benzene and first ether eluate contained crystalline material (28 mg.) which on recrystallization from ethyl acetate–hexane gave hexagonal plates (15 mg.) melting at 204–207°. The ether and ether–methanol eluates were amorphous (difference from the conversion by the same procedure of the oxide XI to the enone XII, where the latter was eluted by ether–methanol): $[\alpha]^{21}\text{D}$ +60° (*c* 0.688); $\lambda_{\max}^{\text{alc}}$ 257 mμ (ϵ 6800), 342 mμ (ϵ 80); $\lambda_{\max}^{\text{Nujol}}$ 2.95 (m), 5.79, 5.84 (v.s., broad doublet), 6.08 (s) μ. In the spectrum of the structurally identical enone XII the O-acetyl and C=O bands are located at 5.80 and 5.85 μ, respectively, while the C=C and N-acetyl bands, contracted into a broad band at 6.08 μ in the spectrum of IX, appear as separate peaks at 6.03 and 6.11 μ.

Anal. Calcd. for $C_{33}H_{49}NO_7$ (571.7): C, 69.32; H, 8.64. Found: C, 69.19; H, 8.63.

N-Acetyl-5,6-dihydroisojervin-11β-ol (XIVb).—To a solution of N-acetyl-5,6-dihydroisojervine (XIIIb, 307 mg.) in tetrahydrofuran (30 ml.) lithium borohydride (315 mg.) dissolved in the same solvent (30 ml.) was added slowly with mechanical stirring. The solution was boiled under reflux for 4 hr., cooled, and, after the addition of cold water (150 ml.) and 10% acetic acid (15 ml.), was extracted twice with chloroform. Since the partly crystalline residue of the extract still showed in its infrared spectrum a band at 5.92 μ indicating the presence of unreduced starting material, it was re-treated with the reducing agent as described above. The crude crystalline product obtained from the residue with ethyl acetate (162 mg., m.p. 214–222°) had to be recrystallized four times from methanol–ethyl acetate before the melting point became constant at 250–252°: $[\alpha]^{22}\text{D}$ +25.6° (*c* 0.952); ultraviolet end absorption only; $\lambda_{\max}^{\text{Nujol}}$ 3.05 (m), 6.25 (m, s.), 8.08 (l) μ. The Rosenheim and hydrochloric acid color reactions were negative.

Anal. Calcd. for $C_{29}H_{45}NO_4$ (471.7): C, 73.84; H, 9.62. Found: C, 73.51; H, 9.34.

Acetylation of XIVb with acetic anhydride and pyridine gave the triacetate **XIVa** as needles from aqueous ethanol: m.p. 202–203°; $[\alpha]\text{D}$ +26.9° (*c* 0.595); $\lambda_{\max}^{\text{Nujol}}$ 2.95 (m), 5.77 (s), 6.20 (vs), 8.05–8.11 (vs) μ.

Anal. Calcd. for $C_{33}H_{49}NO_6$ (555.7): C, 71.32; H, 8.89. Found: 71.24; H, 8.95.

Acetylation of crystalline material (m.p. 187–193°) isolated rom the first two mother liquors from the purification of the N-acetyl derivative XIVb from another reduction run yielded a product, m.p. 196–198°, $[\alpha]\text{D}$ +32°. This rotation value shows that little, if any, of the abnormal 11β-ol corresponding to triacetyl-8,9-dihydroisojervin-11β-ol A (IVa) could have been formed in the lithium borohydride reduction of XIIIb, since this compound, having the 5α-configuration, should be even more dextrorotatory than IVa, $[\alpha]\text{D}$ +133°.

For the re-oxidation to triacetyl 5,6-dihydroisojervine (XIIIa), the triacetate (37.5 mg., 0.0674 mmole) was treated with the equivalent amount of the chromium trioxide–sulfuric acid reagent of Djerassi, *et al.*, as described for the reaction IIb → Ib. The residue of the chloroform extract (28.3 mg.) was recrystallized three times from aqueous ethanol, giving 13.4 mg. of needles: m.p. 212–213°, undepressed by admixture of an authentic sample of XIIIa; $[\alpha]^{21}\text{D}$ +38.5° (*c* 0.509), lit.[1b] $[\alpha]\text{D}$+37.5°; $\lambda_{\max}^{\text{alc}}$ 237 mμ (ε 8550). The infrared spectrum was identical with that of XIIIa.

Anal. Calcd. for $C_{33}H_{47}NO_6$ (553.7): C, 71.58; H, 8.56. Found: C, 71.45; H, 8.59.

A Novel Method for the Preparation of Bicyclooctane Systems[1]

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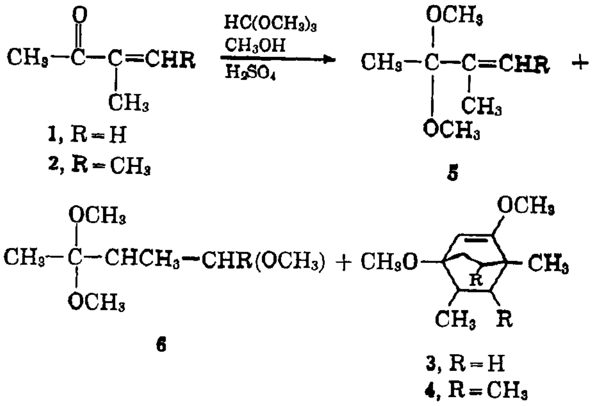
Reaction of 3-methyl-3-buten-2-one (**1**), *trans*-3-penten-2-one (**7**), and *trans*-3-methyl-3-penten-2-one (**2**) each with trimethyl orthoformate in the presence of orthophosphoric acid gave substituted 4-methoxybicyclo[2.2.2]-octanones (**8**, **9**, and **10**), respectively. The intermediate of the reaction was found to be a 1-methoxy-4-(1-methoxyvinyl)-1-cyclohexene derivative (**13**). An acid-catalyzed cyclization of 4-substituted 4-(1-methoxyvinyl)-1-methoxy-1-cyclohexenes gave 4-substituted 1,3-dimethoxybicyclo[2.2.2]oct-2-enes, whereas of cyclization 1,4-di-phenyl-4-vinyl-1-cyclohexene (**30**) gave 1,4-diphenylbicyclo[3.2.1]oct-3-ene (**31**).

It has previously been found[2] that the reaction of a methanol solution of 16-dehydropregnenolone acetate with trimethyl orthoformate in the presence of an acid catalyst furnished a bicyclo[2.2.2]octane system.[3] The reaction has now been extended to methyl vinyl ketone derivatives and the mechanism of the reaction was studied. In the course of this work, there was encountered an acid-catalyzed cyclization of 1,4-diphenyl-4-vinyl-1-cyclohexene (**30**) to 1,4-diphenylbicyclo[3.2.1]oct-3-ene (**31**).

When a methanol solution of *trans*-3-methyl-3-penten-2-one (2) was treated with trimethyl orthoformate in the presence of sulfuric acid, there was obtained 2,4-dimethoxy-1,5,6,7-tetramethylbicyclo[2.2.2]-oct-2-ene (**4**) in 50% yield (identified as 4-methoxy-1,5,6,7-tetramethylbicyclo[2.2.2]octan-2-one (**10**) after mild acid hydrolysis) and 24% yield of a mixture of 4,4-dimethoxy-3-methyl-2-pentene (**5**, R = CH_3) and 2,2,4-trimethoxy-3-methylpentane (6, R = CH_3) which was separated by vapor phase chromatography. An analogous reaction of 3-methyl-3-buten-2-one (**1**) also gave a similar set of the products. Methyl vinyl ketone, on the other hand, gave no bicyclooctane compound but 4-methoxy-2-butanone under the similar conditions.[4] A similar reaction of mesityl oxide gave a mixture of at least nine compounds from which no bicyclooctane derivative could be separated.



It was later found that methanol is not necessary for this reaction and the best yields of the bicyclooctane derivatives were obtained when orthophosphoric acid was used as a catalyst. Among other catalysts examined were boron trifluoride etherate and *p*-toluenesulfonic acid, where bicyclooctane derivatives were also obtained. Treatment of 3-methyl-3-buten-2-one (**1**), *trans*-3-penten-2-one (**7**), or *trans*-3-methyl-3-penten-2-one (**2**) each with an equivalent amount of trimethyl orthoformate in the presence of orthophosphoric acid gave the corresponding bicyclooctanes, **8** (72% yield), **9** (10%), and **10** (54%), respectively. Formation of methyl formate followed by that of methanol was observed in each case. The low yield observed

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[1] (a) Bridged Ring Compounds. Part II. For part I, see ref. 2. (b) A preliminary account of part of this work has appeared: K. Morita and Z. Suzuki, *Tetrahedron Letters*, **No. 6**, 263 (1964).

[2] K. Morita, G. Slomp, and E. V. Jensen, *J. Am. Chem. Soc.*, **84**, 3779 (1962).

[3] For the syntheses of bicyclooctane systems, see "Elsevier's Encyclopaedia of Organic Chemistry," Series III, Vol. 12A, E. Josephy and F. Radt, Ed., Elsevier Publishing Co., Amsterdam, 1948, p. 1066 ff; R. A. Raphael, "Chemistry of Carbon Compounds," Vol. IIA, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam 1953, p. 346 ff.

[4] M. F. Ansel, J. W. Lown, D. W. Turner, and D. A. Wilson, [*J. Chem. Soc.*, 3036 (1963)] reported that trimethyl orthoformate, in methanol with a trace of hydrochloric acid, and ethyl vinyl ketone gave 1,3,3-trimethoxypentane and that an analogous reaction of 2-methyl-1-penten-3-one gave 3,3-dimethoxy-2-methyl-1-pentene.