Structure of Isojervine[1]

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Isojervine[2], $C_{27}H_{39}O_3N$, an unexpected product obtained on acid treatment of pseudojervine or jervine[3] (I), has received no generally accepted structural assignment. We

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[1] When we have completed this work, Dr. O. Wintersteiner, the Squibb Inst., and Prof. W. G. Dauben, California Univ., kindly informed us that they have arrived at the same structure as ours.

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

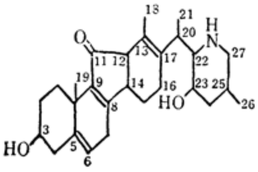
[3] J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin

wish to report that the structure II is consonant with all chemical and spectral data for isojervine[4], which is a secondary base with two acylable hydroxyl groups and one $\alpha\beta$-unsaturated keto group. IR[5], 1684, 1630 and 1063 cm^{-1}, UV[4], 330 mμ (ε, 250), 252 mμ (inflexion, ε, 2900) and end absorption (ε, 9000 at 211 mμ).

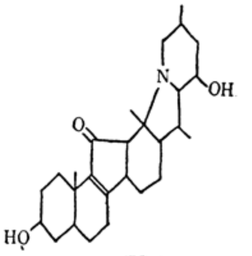
Reduction of II with lithium and methanol in liquid ammonia at -70°C has now afforded α-dihydrojervinol[4], thus establishing the skeleton and the position of all oxygen-containing functional groups of II.

The location of a double bond at C_5–C_6 was confirmed by the Oppenauer oxidation of II with cyclohexanone and aluminum isopropoxide to isojervone[6], m. p. 112~114°C, $[\alpha]_D$ $+140°$ (ethanol), IR, 1682, 1642 and 1620 cm^{-1}, UV, 234 mμ (ε, 22000). Hydrogenation of II over platinum in acetic acid resulted in preferential reduction of the C_5–C_6 double bond to yield dihydroisojervine (III), m. p. 153~155°C (as hydrate) and 171.5~172.5°C (after drying), IR, 1679, 1625 and 1040 cm^{-1}, UV, 238 mμ (ε, 9400) ; that is, the Oppenauer oxidation of III produced dihydroisojervone, m. p. 108~110°C, IR, 1712, 1687 and 1629 cm^{-1}, UV, 238 mμ (ε, 9900), only in a low yield. Hydride reduction of II yielded isojervinol (IV), m. p. 210~211°C, which exhibited only a weak end absorption (ε, 6400 at 212 mμ). The spectroscopic behavior of II, III and IV completely paralleled that of 1-acetyl-1, 4-cyclohexadiene[7], suggesting that another double bond would exist at C_8–C_9. The NMR spectral data (deuterochloroform, 60 Mc.) supported this view; the C_{19}-methyl signal of triacetate (IIa) of II appeared at the lower field (8.68 τ) as compared with that (8.97 τ) of diacetate (Ia) of I. The observed shift would be explained by assuming the field due to magnetic anisotropy not only of the C_8–C_9 double bond itself[8,9] but also associated with interaction[7] between the C_5–C_6 and C_8–C_9 double bonds. The C_{19}-methyl signals of triacetate, m. p. 203~205°C, of III and of diacetyl-Δ^{13}-jervine[5] appeared at the normal positions (8.98 and 8.87 τ) and the ultraviolet absorptions of these compounds were devoid of anomalies as observed with II.

The NMR spectrum of IIa showed a broad multiplet centered at 4.53 τ due to *one* olefinic proton (C_6-hydrogen) and a sharp singlet of methyl group attached to olefinic carbon at 8.06 τ instead of that at 7.77 τ due to C_{18}-methyl of Ia. The Birch reduction of III led to reduction of the C_8–C_9 double bond to yield two crystalline substances, α-tetrahydroisojervine (V), m. p. 147~149°C, IR, 1731 cm^{-1}, and β-isomer (VI), m. p. 138~142°C (chloroform addition compound), IR, 1741 cm^{-1}. However, neither triacetate, m. p. 179~182°C, of V, nor the corresponding β-isomer, m. p. 168~168.5°C, was found to be identical with 22, 27-imino-Δ^{17-20}-jervene-3, 23-diol-11-one triacetate prepared by Wintersteiner et al.[10] Treatment of III with 1 N potassium *t*-butoxide in refluxing *t*-butanol[11] under nitrogen for an hour yielded a crystalline compound (VII), m. p. 142~144°C, IR, 1670, 1621 and 1036 cm^{-1}, chloroform, 1678 and 1630 cm^{-1}, UV 239 mμ (ε, 8600). It was a *weak* tertiary base ; (1) the pK_a value of VII, II and III were 6.12, 6.92 and 7.08 in 50 % ethanol. (2) Acetylation of VII with acetic anhydride and pyridine on steam bath for 3 hr. gave exclusively an amorphous *O,O*-diacetate, IR, chloroform, 1725, 1685 and 1632 cm^{-1}, pK_a, 4.47. In view of the analogous examples[12], the formula VII was assigned to the m. p. 144°C compound. Similar reactions were observed with V and VI. Apparently these reactions involve migration of C_{13}-C_{17} double bond to $\alpha\beta$-position of the carbonyl group followed by cyclization. Thus, the formula II is the most favorable structure of isojervine.



(II)



(VII)

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and A. Klingsberg, *J. Am. Chem. Soc.*, **73**, 2970 (1951).

4) W. A. Jacobs and C. F. Heubner, *J. Biol. Chem.*, **170**, 635 (1947) ; W. A. Jabobs and Y. Sato, ibid., **181**, 55 (1949).

5) B. M. Iselin and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 5318 (1955). Unless otherwise stated, IR spectra were taken in Nujol and UV spectra in ethanol.

6) All new compounds reported in this paper had acceptable carbon, hydrogen and nitrogen analyses.

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9) J. S. G. Cox, E. O. Bishop and R. E. Richards, *J. Chem. Soc.*, **1960**, 5118.

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

11) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, ibid., **76**, 4013 (1954).

12) O. Wintersteiner and M. Moore, ibid., **78**, 6193 (1956).