Phytochemistry, 1971, Vol 10, pp 1385 to 1388. Pergamon Press. Printed in England.

A NEW ALKALOID FROM *RAUWOLFIA VOMITORIA*

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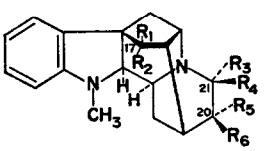
(*Received* 28 *July* 1970, *in revised form* 6 *October* 1970)

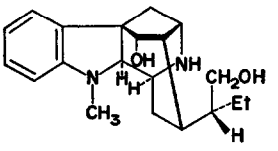
Abstract—Two new dihydroindole alkaloids were isolated from *Rauwolfia vomitoria* Afz One of them proved to be sandwicine, previously isolated from *Rauwolfia sandwicensis* The structure of isosandwicine was assigned to the other substance on the basis of its spectroscopic and chemical properties and by correlation with sandwicine and ajmaline

IN THE course of research on the constituents of *Rauwolfia vomitoria* Afz we isolated, besides known alkaloids, small quantities of tetraphyllicine and the new alkaloid 17-acetylajmaline.[1]

We now wish to report the isolation, from the same plant, of two other alkaloids. The first, obtained in small quantity, proved to be identical with sandwicine[2] (I) on the basis of the optical rotatory measurements and IR spectrum. However, in contrast to earlier authors who obtained only an amorphous acetate from sandwicine, we succeeded in obtaining crystalline a 17-monoacetate (III) and a diacetate (II).

The second alkaloid proved to have the structure of isosandwicine (IV) on the basis of the following data: the molecular formula $C_{20}H_{26}N_2O_2$ as indicated by elemental analysis and mass spectrometry, corresponded to that of ajmaline (V) or sandwicine (I); the UV





VIII

I ; R_1, R_4, R_5=H, R_2, R_3=OH, R_6=Et
II ; R_1, R_4, R_5=H, R_2, R_3=OAc, R_6=Et
III ; R_1, R_4, R_5=H, R_2=OAc, R_3=OH, R_6=Et
IV ; R_1, R_3, R_6=H, R_2, R_4=OH, R_5=Et
V ; R_2, R_4, R_5=H, R_1, R_3=OH, R_6=Et
VI ; R_1, R_3, R_6=H, R_2, R_4=OAc, R_5=Et
VII ; R_1, R_3, R_6=H, R_2=OAc, R_4=OH, R_5=Et
IX ; R_2, R_3, R_6=H, R_1, R_4=OH, R_5=Et
X ; R_1, R_2=O, R_3, R_6=H, R_4=OH, R_5=Et

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[2] M. GORMAN, N NEUSS, C. DJERASSI, J. P. KUTNEY and P J. SCHEUER, *Tetrahedron* **1**, 328 (1957).

spectrum was typical of a dihydroindole alkaloid and the IR spectrum showed remarkable similarities to that of ajmaline (V). Treatment of the compound with acetic anhydride-pyridine yielded a crystalline diacetate $C_{24}H_{30}N_2O_4$ (VI) from which a crystalline monoacetate $C_{22}H_{28}N_2O_3$ (VII) was obtained by transesterification with 70% ethanol. The presence of a carbinolamine moiety was shown by the fact that reduction with $NaBH_4$ transformed the compound into a dihydroderivative ($C_{20}H_{28}N_2O_2$) (VIII). All the above reported data strongly suggested a close structural similarity to ajmaline and sandwicine.

The NMR spectrum of isosandwicine (IV) showed, in addition to other signals, a doublet (δ 4·72, $J = 9$ Hz) which could be attributed to the proton at C-17; this doublet is shifted to δ 5·64 ($J = 9$ Hz) in the NMR spectrum of the diacetate VI and to δ 5·66, with the same coupling constant, in the spectrum of the monoacetate VII. Furthermore, the signal of the protons of the acetate group in the last spectrum is at δ 2·03. The NMR data, when compared with the spectra of similar compounds,[3,4] indicated that in isosandwicine the hydroxyl group at C-17 had the configuration opposite to that of the corresponding hydroxyl group in ajmaline.[3] The stereochemistry of the hydroxyl group at C-21 was clearly revealed by the NMR spectra of isosandwicine (IV) and of its mono- (VII) and diacetylderivatives (VI). In these spectra the proton at C-21 was seen as a doublet ($J \simeq 6$ Hz), similar to the signal found in the spectrum of isoajmaline (IX). However, the spectrum of ajmaline showed the signal corresponding to the same proton as a broad singlet. Moreover isosandwicine remained unchanged when boiled with methanolic KOH under the same conditions which convert ajmaline into isoajmaline.

The spectroscopic and chemical data above reported indicated that the stereochemistry at C-20 and C-21 of isosandwicine is identical with that of the same centres in isoajmaline. The structure IV of isosandwicine was eventually confirmed by correlation with sandwicine and ajmaline. By isomerization of sandwicine at C-20 and C-21 with methanolic KOH a compound was obtained which was isolated as its dihydrochloride salt; this was identical with isosandwicine dihydrochloride. Furthermore, mild oxidation of isosandwicine with acetic anhydride-dimethyl sulfoxide[5] produced isoajmalidine (X) in good yields. This last compound was also obtained, by the same oxidation procedure, from isoajmaline (IX). Since the only asymmetric centre involved in the oxidation is C-17, isosandwicine and isoajmaline differ only at C-17. Isosandwicine has therefore the structure IV of 17-epiisoajmaline.

EXPERIMENTAL

Melting points were uncorrected; all the compounds had elemental analyses consistent with the assigned structures

Isolation of Alkaloids from Rauwolfia vomitoria *Afz*

10 kg of *Rauwolfia vomitoria* Afz powdered roots were extracted with boiling CH_3OH (4 × 30 l.).

The combined methanolic extracts were evaporated *in vacuo* and the residue was dissolved in 5 l. of 5% phosphoric acid. The acidic solution was extracted three times with $CHCl_3$, NH_4OH was added until pH 9 was reached and the basic solution was again extracted with $CHCl_3$. The last organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue (0·9 kg) was dissolved in 2 parts (w/w) CH_3OH; after standing 15 hr at 0°, crystalline ajmaline was recovered by filtration and the mother liquors were evaporated *in vacuo*.

The residue was dissolved in 3 parts (w/w) CH_3COCH_3, 1 part HCl added and the resulting crystals filtered, washed with CH_3COCH_3 and dissolved in 2 parts H_2O; after standing 12 hr at 4°, a further quantity of ajmaline, as hydrochloride, crystallized and was filtered. Adding NaOH to the cooled mother liquors until

[3] M. F. BARTLETT, R. SKLAR, W. I. TAYLOR, E. SCHLITTER, R. L. S. AMAI, P. BEAK, N. V. BRINGI and E. WENKERT, *J. Am. Chem. Soc.* **84**, 622 (1962)

[4] J. L. KAUL, J. TROJÁNEK and A. K. BOSE, *Chem. & Ind.* 853 (1966).

[5] J. D. ALBRIGT and L. GOLDMAN, *J Am Chem. Soc.* **89**, 2416 (1967).

pH 10 was reached, an amorphous solid was obtained, which was washed with H_2O, dried under high *vacuum* (P_2O_5) and stirred with $CHCl_3$ in the cold. The insoluble residue was filtered and dried (50 g, fraction A) and the $CHCl_3$ solution was evaporated *in vacuo* (44 g, fraction B)

17-*Acetylsandwicine* (III). Fraction A was acetylated with acetic anhydride-pyridine and the acetylated material was dissolved in acetone–hexane (8:2) and chromatographed on 100 parts of silica gel, using the solvent mixture as eluent

After 50 fractions containing 17,21-diacetylajmaline and 17,21-diacetylisosandwicine (VI), there were obtained 5 g of 17-acetylsandwicine* (III) which, after crystallization from CH_3OH, had m.p. 153–156°, $[\alpha]_D^{20°} = +188.5°$ ($c = 1$, $CHCl_3$), $\lambda_{max}^{CH_3OH}$ 251 ($\epsilon = 7700$) and 294 ($\epsilon = 2570$) nm; ν_{max} ($CHCl_3$) 1730 and 1614 cm^{-1}, NMR ($CDCl_3$) 6·61–7·28 δ (4 H, *m*, aromatic protons), 5·71 (1 H, *d*, $J = 9$ Hz, C-17HOAc), 4·24 (1 H, *s*, C-21HOH), 3·76 (1 H, *m*, CHN), 3·10 (1 H, *s*, C-2H), 2·98 (1 H, *m*, CHN), 2·84 (3 H, *s*, NCH_3) 2·06 (3 H, *s*, $OCOCH_3$).

Sandwicine (I) 1 g of 17-acetylsandwicine (III) was dissolved in 100 ml of 0·1% methanolic KOH. The solution was allowed to stand at room temp. for 2 hr, neutralized with acetic acid and evaporated *in vacuo* The residue was dissolved in water and the solution was adjusted to pH 9 with NH_4OH: the precipitated sandwicine was collected and obtained as amorphous powder from CH_3OH–H_2O, $[\alpha]_D^{20°} = +174°$ ($c = 1$, CH_3OH); its IR spectrum was identical with the published one,[2] $\lambda_{max}^{CH_3OH}$ 250 ($\epsilon = 7600$) and 294 ($\epsilon = 2560$) nm; m.s.· 326, 183, 182, 158, 157, 145, 144 *m/e*.

17,21-*Diacetylsandwicine* (II) 1 g of 17-acetylsandwicine (III) was dissolved in 5 ml of C_6H_6 and 5 ml of Ac_2O and the solution was refluxed for 6 hr The solvent was evaporated *in vacuo* and the residue was crystallized from petroleum ether. The compound exhibited m.p. 105–108°, $[\alpha]_D^{20} = +104°$ ($c = 1$, $CHCl_3$), $\lambda_{max}^{CH_3OH}$ 251 ($\epsilon = 7700$) and 295 ($\epsilon = 2570$) nm; ν_{max} (nujol) 1735 and 1610 cm^{-1}, NMR ($CDCl_3$). 6·55–7·32 δ (4 H, *m*, aromatic protons), 5·70 (1 H, *d*, $J = 9$ Hz, C-17 HOAc), 3·70 (1 H, *d*, $J = 7$ Hz, CHN), 3·43 (1 H, *m*, CHN), 3·04 (1 H, *s*, C-2H), 2·80 (3 H, *s*, NCH_3), 2·1 (3 H, *s*, $OCOCH_3$), 2·04 (3 H, *s*, $OCOCH_3$)

Isosandwicine (IV)

(a) *Isosandwicine dihydrochloride.* Fraction B was dissolved in 3 parts CH_3COCH_3 and 1 part conc HCl was added· the precipitated crystalline dihydrochloride (20 g) was recrystallized from CH_3OH containing a little HCl; m.p. 244–245°, $[\alpha]_D^{20°} = +133°$ ($c = 1$, CH_3OH), ν_{max} (nujol). 3200, 3180, 3080, 1140, 1120 and 770 cm^{-1}.

A dihydrochloride identical with that described above (m.p., mixed m.p., $[\alpha]_D^{20°}$, IR spectrum) was obtained from sandwicine in the following way: 50 mg of sandwicine were boiled for 8 hr with 2% methanolic KOH; the solution was poured into H_2O and extracted with $CHCl_3$. The residue obtained from evaporation of the solvent was treated as above with acetone–conc. HCl and the precipitated dihydrochloride recrystallized from CH_3OH–HCl

(b) *Isosandwicine from isosandwicine dihydrochloride.* 10 g of isosandwicine dihydrochloride were dissolved in 10 ml H_2O· the solution was made basic with NH_4OH and the precipitated isosandwicine (IV) was crystallized from CH_3OH–H_2O, m.p. 250° (after sintering at 160°); $[\alpha]_D^{20°} = +130°$ ($c = 1·18$, $CHCl_3$), $\lambda_{max}^{CH_3OH}$ 250 ($\epsilon = 7750$) and 295 ($\epsilon = 2600$) nm; ν_{max} (nujol) 3380, 1614, 1120, 1100, 1075, 745 cm^{-1}, NMR ($CDCl_3$): 7 δ (4 H, *m*, aromatic protons), 4·72 (1 H, *d*, $J = 9$ Hz, C-17HOH), 4·0 (1 H, *d*, $J = 6$ Hz, C-21HOH), 3·47 (2 H, *m*, C-3H and C-5H), 3·04 (1 H, *s*, C-2H), 2·81 (3 H, *s*, NCH_3); MS: 326, 183, 182, 158, 157, 145, 144 *m/e*.

Isosandwicine remained unchanged when boiled with 2% MeOH–KOH for 8 hr

17,21-*Diacetylisosandwicine* (VI) 1 g of isosandwicine (IV) was acetylated with acetic anhydride-pyridine to yield 17,21-diacetylisosandwicine (VI), which was crystallized from C_2H_5OH–H_2O, m.p. 160° (after sintering at 110°), $[\alpha]_D^{20°} = +101°$ ($c = 1$, $CHCl_3$), $\lambda_{max}^{CH_3OH}$ 250 ($\epsilon = 7680$) and 294 ($\epsilon = 2580$) nm, ν_{max} 1730 and 1615 cm^{-1}; NMR ($CDCl_3$): 6·5–7·3 δ (4 H, *m*, aromatic protons), 5·64 (1 H, *d*, $J = 9$ Hz, C-17HOAc), 5·24 (1 H, broad *d*, $J \simeq 6$ Hz, C-21HOAc), 3·68 (1 H, *d*, $J = 7$ Hz, CNH), 3·39 (1 H, *m*, CNH), 3·02 (1 H, *s*, C-2H), 2·78 (3 H, *s*, NCH_3), 2·03 (6 H, *s*, $OCOCH_3$)

17-*Acetylisosandwicine* (VII) 0·1 g of (VI) were refluxed with 20 ml of 70% aq EtOH for 30 min The solution was concentrated *in vacuo* to a small volume and after standing at 4° for 12 hr, 17-acetylisosandwicine (VII) was obtained in crystals, m.p. 220–221°, $[\alpha]_D^{20} = +124°$ ($c = 1$, $CHCl_3$), $\lambda_{max}^{CH_3OH}$ 252 ($\epsilon = 7750$) and 293 ($\epsilon = 2630$) nm, ν_{max} ($CHCl_3$): 1730, 1615, cm^{-1}, NMR ($CDCl_3$): 6·62–7·29 δ (4 H, *m*, aromatic protons), 5·68 (1 H, *d*, $J = 9$ Hz, C-17HOAc), 4·10 (1 H, broad *d*, $J \simeq 6$ Hz, C-21HOH), 3·62 (2 H, *m*, C-3NH and C-5NH), 3·08 (1 H, *s*, C-2H), 2·83 (3 H, *s*, NCH_3), 2·03 (3 H, *s*, $OCOCH_3$).

Isoajmalidine (X). (a) *From isoajmaline.* 200 mg of isoajmaline were oxidized with Ac_2O–DMSO, using the published procedure [5] The crude product was chromatographed on 20 g of silica gel. Elution with $CHCl_3$–CH_3OH (99·1) afforded 130 mg of product, crystallized from CH_3COCH_3, m.p. 192°; $[\alpha]_D^{20°} = +304°$ ($c = 1$, $CHCl_3$), ν_{max} ($CHCl_3$): 1740 and 1615 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 250 ($\epsilon = 7700$) and 294 ($\epsilon = 2600$) nm; NMR

* The product is eluted as 17-monoacetate instead of 17,21-diacetate because the labile 21-acetate is hydrolyzed during the silica-gel chromatography

($CDCl_3$): 7 3–6 7 δ (4 H, *m*, aromatic protons), 4 12 (1 H, *d*, *J* = 6Hz, C-21HOH), 3 89 (1 H, *m*, CHN), 3·58 (1 H, *d*, *J* = 9 Hz, CHN), 2·78 (3 H, *s*, NCH_3), 2 65 (1 H, *s*, C-2H)

(b) *From isosandwicine* 200 mg of isosandwicine (IV), processed as in (a), yielded 115 mg of isoajmalidine (X), whose m.p , $[\alpha]_D^{20°}$ and IR spectrum were identical with those of the product obtained from isoajmaline.

Dihydroisosandwicine (VIII). Isosandwicine was reduced with $NaBH_4$ using the described procedure:[2] the dihydroisosandwicine (VIII) obtained was crystallized from CH_3COCH_3–H_2O, m.p 181–182°, $[\alpha]_D^{20°}$ = +98° (*c* = 1, $CHCl_3$); its dihydrobromide crystallized from MeOH–diisopropylether, m.p. 253–258°.

Acknowledgements—We thank Prof. L Canonica for his useful advice, Dr. G. Severini Ricca for the NMR spectra and Dr. T Salvatori for the m s. spectra