CONVERSION OF AJMALINE, ISOAJMALINE, SANDWICINE AND ISOSANDWICINE TO THEIR ACYLATION PRODCUTS

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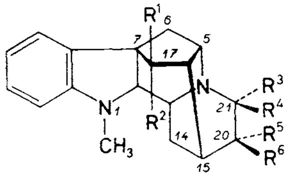
Ajmaline, isoajmaline, sandwicine and isosandwicine were converted to their new acylation products in 68—94% yields using isobutyric anhydride and isovaleric anhydride. The structures of these compounds were established on the basis of their spectroscopic studies.

Ajmaline[1], the main alkaloid of *Rauwolfia serpentina*, and sandwicine[2] have been used as drugs of choice for the treatment of cardiac arrythmiasis[3-5] and a number of pharmaceutical preparations containing ajmaline hydrochloride have gained an important position in cardiac theraphy. The earlier established coronary dilating and antiarrythmic effects of ajmaline[6] have led to the preparation of its various derivatives which were found to be more potent than ajmaline[7-9]. We report here the preparation of new acylation products of ajmaline, isoajmaline, sandwicine and isosandwicine.

In preparation of diisobutyrates and diisovalerates, considerable difficulty was experienced with the method employed by Robinson (refluxing with anhydride in $C_6H_6/CHCl_3$ solution for 12 h). Apart from being time consuming and complicated



I $R^2, R^4, R^5 = H$; $R^1, R^3 = OCOCH(CH_3)_2$, $R^6 = C_2H_5$
II $R^2, R^3, R^6 = H$; $R^1, R^4 = OCOCH(CH_3)_2$; $R^5 = C_2H_5$
III $R^1, R^4, R^5 = H$; $R^2, R^3 = OCOCH(CH_3)_2$; $R^6 = C_2H_5$
IV $R^1, R^3, R^6 = H$; $R^2, R^4 = OCOCH(CH_3)_2$; $R^5 = C_2H_5$
V $R^2, R^4, R^5 = H$; $R^1, R^3 = OCOCH_2CH(CH_3)_2$; $R^6 = C_2H_5$
VI $R^2, R^3, R^6 = H$; $R^1, R^4 = OCOCH_2CH(CH_3)_2$; $R^5 = C_2H_5$
VII $R^1, R^4, R^5 = H$; $R^2, R^3 = OCOCH_2CH(CH_3)_2$; $R^6 = C_2H_5$
VIII $R^1, R^3, R^6 = H$; $R^2, R^4 = OCOCH_2CH(CH_3)_2$; $R^5 = C_2H_5$

it was also noted that slight impurity in the reaction mixture adversely affected the product yield. In order to overcome this, a more convenient method was worked out for the acylation of these bases with isobutyric anhydride and isovaleric anhydride, and as a result following compounds were prepared in high yields (68–94%), and their structures were established through spectral studies.

EXPERIMENTAL

Melting points were recorded in glass capillary tubes and were uncorrected. The purity of samples was checked by TLC using precoated silica gel (GF-254) 0·2 mm plates. The spectra were recorded on Shimadzu UV-240 spectrophotometer, Shimadzu A-302 IR spectrophotometer, Finnigan MAT-112 and MAT-312 mass spectrometer connected to PDP 11/34 computer system, Bruker WP-100 SY FT-NMR spectrometer. The UV spectra were measured in methanol, IR spectra were recorded in KBr, and ^{1}H NMR spectra were recorded in deuteriochloroform. All chemical shifts (δ) are related to tetramethylsilane as internal standard and spectral details are reported as: δ ppm (number of protons, multiplicity, coupling constant Hz, and assignments). The multiplicity of signals is expressed by the following symbols: s singlet, d doublet, t triplet, m multiplet.

Ajmaline diisobutyrate I: Ajmaline (100 mg) was heated with 3 ml isobutyric anhydride for 5 min at 70°C. The mixture was cooled, neutralized with dilute ammonia, extracted with ethyl acetate, washed with water, dried with Na_2SO_4 (anhyd.) and freed of the solvent under reduced pressure. The product was obtained in 92% yield, m.p. 189–191°C. For $C_{28}H_{38}N_2O_4$ (466·3) calculated: 72·10% C, 8·15% H, 6·01% N, 13·74% O; found: 72·51% C, 8·00% H, 6·23% N, 13·26% O. Mass spectrum *m/z* observed: 466·2832, calculated 466·2831 ($C_{28}H_{38}N_2O_4$), (M^+, 72%); 395 (12), 324 (18), 278 (8), 236 (12), 182 (54), 144 (100). IR spectrum ν_{max} (KBr): 1 708, 1 720 cm^{-1} (C=O). UV spectrum, λ_{max} methanol: 208, 250, 292 nm. ^{1}H NMR spectrum (C^2HCl_3): δ 7·24–6·62 (4 H, m, aromatic protons), 5·59 (1 H, d, J = 1·8 Hz, $C_{(17)}$HOCOCH—), 5·28 (1 H, d, J = 6 Hz, $C_{(21)}$HOCOCH—), 3·35 (2 H, m, $C_{(3)}C_{(5)}$, 5 H), 2·71 (3 H, s, N—CH_3), 2·42–2·26 (2 H, m, —CH, isobutyrate), 1·65 (6 H, d, J = 6·9 Hz, $C_{(17)}$ $(CH_3)_2$-isobutyrate), 1·50 (6 H, d, J = 7·0 Hz, $C_{(21)}$ $(CH_3)_2$-isobutyrate), 1·27 (2 H, m. $C_{(19)}$H), 0·96 (3 H, t, $C_{(18)}$H).

Under similar reaction conditions following derivatives were prepared.

Isoajmaline diisobutyrate II: in 68% yield, m.p. 198–199°C. For $C_{28}H_{38}N_2O_4$ (466·3) calculated: 72·10% C, 8·15% H, 6·01% N, 13·74% O; found: 71·92% C, 8·02% H, 6·41% N, 13·65% O. Mass spectrum *m/z* observed: 466·2833, calculated 466·2 831 ($C_{28}H_{38}N_2O_4$), (M^+, 84%), 395 (20), 324 (18), 278 (19), 236 (32), 182 (100), 144 (42). IR spectrum ν_{max}: 1 710, 1 722 cm^{-1} (C=O). UV spectrum, λ_{max}: 208, 251, 292 nm. ^{1}H NMR spectrum: δ 5·59 (1 H, d, J = 2 Hz, $C_{(17)}$HOCO. .CH—), 5·26 (1 H, d, J = 6 Hz, $C_{(21)}$HOCOCH—).

Sandwicine diisobutyrate III: 94% yield and melted at 173–174°C. For $C_{28}H_{38}N_2O_4$ (466·4) calculated: 72·10% C, 8·15% H, 6·01% N, 13·74% O; found: 71·87% C, 8·01% H, 6·23% N, 13·98% O. Mass spectrum *m/z* observed: 466·2829, calculated 466·2831 ($C_{28}H_{38}N_2O_4$), (M^+, 68%), 395 (18), 324 (21), 278 (12), 236 (28), 182 (56), 144 (100). IR spectrum ν_{max}: 1 708, 1 720 cm^{-1} (C=O). UV spectrum: λ_{max}: 210, 250, 292 nm. ^{1}H NMR spectrum: δ 5·58 (1 H, d, J = 9·0 Hz, $C_{(17)}$HOCOCH—), 5·31 (1 H, d, J = 6·0 Hz, $C_{(21)}$HOCOCH—).

Isosandwicine diisobutyrate IV: 86% yield, m.p. 205–206°C. For $C_{28}H_{38}N_2O_4$ (466·3) calculated: 72·10% C, 8·15% H, 6·01% N, 13·74% O; found: 71·79% C, 8·36% H, 6·42% N, 13·43% O. Mass spectrum *m/z* observed: 466·2839, calculated 466·2831 ($C_{28}H_{38}N_2O_4$), M^+, 72%), 395 (17), 324 (32), 278 (14), 236 (31), 182 (100), and 144 (47). IR spectrum ν_{max}: 1 701, 1 725 cm^{-1}

(C=O). UV spectrum, λ_{max}: 209, 248, 293 nm. ^{1}H NMR spectrum: δ 5·56 (1 H, d, J = 9·0 Hz, $C_{(17)}$HOCOCH—), 5·28 (1 H, d, J = 6·0 Hz, $C_{(21)}$HOCOCH—).

Ajmaline diisovalerate V: 100 mg ajmaline was heated with 3 ml isovaleric anhydride for 3 min at 70°C. The mixture was cooled, neutralized with dilute ammonia and extracted with ethyl acetate. On work up of the ethyl acetate layer, *V* was obtained in 78% yield, m.p. 217–218°C. For $C_{30}H_{42}N_2O_4$ (494·3) calculated: 72·87% C, 8·50% H, 5·67% N, 12·96% O; found: 72·80% C, 8·21% H, 5·72% N, 13·27% O. Mass spectrum m/z observed: 494·3145, calculated 494·3144 ($C_{30}H_{42}N_2O_4$), (M^+, 10%), 409 (9), 324 (12), 236 (34), 182 (46), 144 (100). IR spectrum, ν_{max}: 1 705, 1 720 cm^{-1} (C=O). UV spectrum, λ_{max}: 207, 248, 290 nm. ^{1}H NMR spectrum: δ 5·64 (1 H, d, J = 1·8 Hz, $C_{(17)}$HOCOCH$_2$—), 5·28 (1 H, d, J = 6·0 Hz, $C_{(21)}$HOCOCH$_2$—).

Isoajmaline diisovalerate VI: 71% yield, melted at 231–232°C. For $C_{30}H_{42}N_2O_4$ (494·3) calculated: 72·87% C, 8·50% H, 5·67% N, 12·96% O; found: 72·73% C, 8·54% H, 5·47% N, 13·26% O. Mass spectrum m/z observed 494·3159, calculated 494·3144 ($C_{30}H_{42}N_2O_4$), (M^+, 42%), 409 (27), 324 (18), 278 (22), 236 (37), 182 (100), 144 (49). IR spectrum, ν_{max}: 1 700, 1 715 cm^{-1} (C=O). UV spectrum, λ_{max}: 207, 292 nm. ^{1}N NMR spectrum: δ 5·60 (1 H, d, J = 2·0 Hz, $C_{(17)}$HOCOCH$_2$—), 5·28 (1 H, d, J = 6·0 Hz, $C_{(21)}$HOCOCH$_2$—).

Sandwicine diisovalerate VII: 98% yield melted at 199–201°C. For $C_{30}H_{42}N_2O_4$ (494·3) calculated: 72·87% C, 8·50% H, 5·67% N, 12·96% O; found: 72·29% C, 8·63% H, 5·74% N, 13·34% O. Mass spectrum, m/z observed: 494·3144, calculated 494·3144 ($C_{30}H_{42}N_2O_4$), (M^+, 12%), 409 (67), 324 (14), 278 (12), 236 (20), 182 (48), 144 (100). IR spectrum, ν_{max}: 1 702, 1 720 cm^{-1} (C=O). UV spectrum, λ_{max}: 207, 249, 290 nm. ^{1}H NMR spectrum: δ 5·56 (1 H, d, J = 9·0 Hz, $C_{(17)}$HOCOCH$_2$—), 5·29 (1 H, d, J = 6·0 Hz, $C_{(21)}$HOCOCH$_2$—).

Isosandwicine diisovalerate VIII: 87% yield, m.p. 251–253°C. For $C_{30}H_{42}N_2O_4$ (494·3) calculated: 72·87% C, 8·50% H, 5·67% N, 12·96% O; found: 73·01% C, 8·61% H, 5·31% N, 13·08% O- Mass spectrum m/z observed: 494·3139, calculated 494·3144 ($C_{30}H_{42}N_2O_4$), (M^+, 28%), 409 (12), 324 (40), 278 (14), 182 (100), 144 (84). IR spectrum ν_{max}: 1 705, 1 720 cm^{-1} (C=O). UV spectrum, λ_{max}: 208,250, 280 nm. ^{1}H NMR spectrum: δ 5·56 (1 H, d, J = 9·0 Hz, $C_{(17)}$HOCO.CH$_2$—), 5·28 (1 H, d, J = 6·0 Hz, $C_{(21)}$HOCOCH$_2$—).

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