Reaction of Cyclobuxine D with Epoxides

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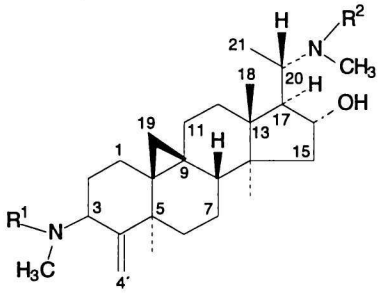
Received 17 December 1992

By the reaction of buxus alkaloid cyclobuxine D with 1,2-epoxypropane and 6-*O*-(2,3-epoxypropyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, corresponding C-3-, C-20-mono- and C-3-, C-20-bisalkanolamines were synthesized; the structure of the prepared compounds was confirmed by spectral data.

Cyclobuxine D (*I*) and cyclovirobuxine D (*II*) belong to the major alkaloids, secondary metabolites of plants of *Buxus* species [1—5]. From these two natural bases, cyclovirobuxine D (*II*) exhibited remarkable pharmacological antiarrhythmic properties [6, 7] and it was tested clinically [8]. Because there is an assumption that structurally related cyclobuxine D (*I*) could exhibit similar effects, we prepared six new derivatives of alkaloid *I* for biological evaluation. We have studied reaction of cyclobuxine D with selected epoxides and the possibility of preparation of all three alkanolamine types derived from cyclobuxine D, *i.e.* C-3- and C-20-mono- and C-3-, C-20-bisalkanolamines, was followed.



I $R^1 = R^2 = H$

III $R^1 = R^2 = CH_2CH(OH)CH_3$

IV $R^1 = H$ $R^2 = CH_2CH(OH)CH_3$

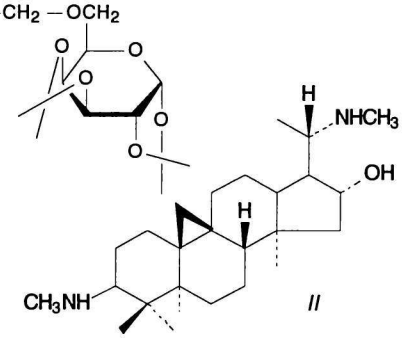
V $R^1 = CH_2CH(OH)CH_3$ $R^2 = H$

VI $R^1 = R^2 = CH_2CH(OH)CH_2$-*Z*

VII $R^1 = H$ $R^2 = CH_2CH(OH)CH_2$-*Z*

VIII $R^1 = CH_2CH(OH)CH_2$-*Z* $R^2 = H$

Z: —CH_2—CH(OH)—CH_2—OCH_2—



II

As a secondary diamine, cyclobuxine D can react with two equivalents of epoxide. By heating with 1,2-epoxypropane, alkaloid *I* afforded a mixture of three compounds (*III*—*V*), which were separated using column chromatography. In the mass spectrum of all three isolated compounds, a distinct peak of molecular ion was observed indicating that compound *III* is derivative of cyclobuxamine where both secondary amino groups reacted with epoxide (M^+ at *m/z* = 502); compounds *IV* and *V* are monoalkanolamines (M^+ at *m/z* = 444). The base peak which is formed in the case of cyclobuxine D by generating of CH_3—CH=N^+HCH_3 fragment (*m/z* = 58) owing to splitting of C-17—C-20 bond [9], enabled us to determine position of alkanolamine grouping in the structures of *IV* and *V*. In the spectrum of compound *IV*, the base peak was observed at *m/z* = 116 ($CH_3CH=N^+(CH_3)CH_2CH(OH)CH_3$) indicating that 1,2-epoxypropane reacted with C-20—N methylamino group; the occurrence of base peak at *m/z* = 58 in the spectrum of compound *V* is indicative for derivative with alkanolamine grouping at the C-3 position. In the spectra of all three compounds, further significant peaks corresponding to the fragmentations M – 45 (M – $CH_3CHOH^•$) and M – 15 were registered. Because (±)-1,2-epoxypropane was used for the synthesis, prepared compounds *III*—*V* are mixtures of diastereoisomers exhibiting duplication of some signals in the ^1H NMR spectra. In the spectrum of compounds *III* and *V*, the signals of C-4′—H_a, C-4′—H_b were shifted downfield; the signal of C-4′—H_a atom, situated in the *cis*-position with regard to the C-3—H hydrogen atom, was duplicated. For compounds with the 2-hydroxypropyl group attached to C-20—N (*III*, *IV*), a change of signal position of H-21 protons (δ = 1.08 for *I*, δ = 0.87 + 0.91 for *III*) was indicative; in the spectra of compounds *III* and *V* prepared by the reaction of epoxide on C-3—N, a shift of H-3 signal (δ = 2.90 for *I*, δ = 3.05 for *V*) was registered. In the ^{13}C NMR spectra, the change of substituent on C-3—N re-

Table 1. ^{13}C NMR Data of Cyclobuxine D (*I*) and Compounds *III*—*VIII*

Compound	C-3	C-4	C-17	C-20	C-21	C-4′	C-3—NMe	C-20—NMe
I	63.6	153.9	61.9	58.9	19.1	100.8	34.5	34.5
III	68.8	151.8	57.5	63.7	11.4	103.4	44.5	44.5
IV	63.8	153.8	57.6	63.6	11.5	100.8	34.5	44.4
V	68.9	151.5	61.2	58.9	19.1	103.5	45.2	34.2
VI	68.5	151.5	57.2	63.4	11.2	103.6	44.9	44.9
VII	63.4	152.8	57.2	63.5	11.2	101.4	34.0	44.8
VIII	68.4	151.5	61.5	58.9	19.2	103.5	44.5	33.4

sulted in the change of shifts for C-3, C-4, C-3—NCH_3, and C-4′. Substitution on C-20—N resulted in the change of signals position for C-17, C-20, C-21, and C-20—NCH_3 (Table 1). Alkanolamines *VI*—*VIII* were synthesized by the reaction of (+)-6-*O*-(2,3-epoxypropyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with alkaloid *I* using the similar method as for *N*-(2-hydroxypropyl) derivatives of cyclobuxamine D. Considering that compounds *VI*—*VIII* were optically pure compounds, duplication of signals in the NMR spectra was not observed; synthesized compounds were characterized on the basis of NMR data applying knowledge obtained during studies on structure of compounds *III*—*V* (Table 1).

EXPERIMENTAL

Mass spectra (70 eV) were measured on a spectrometer JMS-100D (Jeol) at an emission current of 300 μA, applying direct sample-introduction technique. ^1H and ^{13}C NMR spectra (in $CDCl_3$ solutions) were registered on a spectrometer AM-300 (Bruker) operating at 300.13 or 75.46 MHz working frequencies. For TLC, Silufol plates in the mixture of chloroform—methanol—ammonia (φ_r = 18 : 7 : 1.5) were used; detection was performed by the spraying with $KMnO_4$ solution (1 g/100 cm^3 of water).

6-*O*-(2,3-Epoxypropyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose was prepared from 3-chloro-1,2-epoxypropane and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose according to the known method [10].

Reaction of Cyclobuxine D (*I*) with Epoxides

A mixture of *I* (500 mg; 1.3 mmol) and 1,2-epoxypropane (1.5 g; 25.8 mmol) or 6-*O*-(2,3-epoxypropyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (820 mg; 2.6 mmol) in methanol (25 cm^3) was heated at 30 °C for 3 h. Solvent was removed *in vacuo* and the residue was chromatographed on silica gel using a mixture of chloroform—methanol—ammonia (φ_r = 18 : 7 : 1.5) as an eluent; individual fractions were monitored by TLC using the same eluent. Corresponding fractions were combined, solvents removed and the residue was dried. Amorphous products were obtained.

N-3,*N*-20-Bis(2-hydroxypropyl)cyclobuxine D (*III*)

Yield = 320 mg (49 %), R_f = 0.84; for $C_{31}H_{54}N_2O_3$ (M_r = 502.9) w_i(calc.): 74.04 % C, 10.82 % H, 5.57 % N; w_i(found): 73.97 % C, 10.93 % H, 5.55 % N. Mass spectrum, *m/z* (I_r/%): 502 (11), 487 (3, M-15), 457 (36, M-45), 414 (16), 398 (5), 386 (2), 369 (3), 367 (3), 116 (100).

N-20-(2-Hydroxypropyl)cyclobuxine D (*IV*)

Yield = 84 mg (15 %), R_f = 0.47; for $C_{28}H_{48}N_2O_2$ (M_r = 447.7) w_i(calc.): 75.63 % C, 10.88 % H, 6.30 % N; w_i(found): 75.53 % C, 10.79 % H, 6.26 % N. Mass spectrum, *m/z* (I_r/%): 444 (4), 429 (2), 412 (1), 399 (53), 356 (7), 313 (4), 116 (100).

N-3-(2-Hydroxypropyl)cyclobuxine D (*V*)

Yield = 73 mg (13 %), R_f = 0.21; for $C_{28}H_{48}N_2O_2$ (M_r = 444.7) w_i(calc.): 75.63 % C, 10.88 % H, 6.30 % N; w_i(found): 75.55 % C, 10.92 % H, 6.27 % N. Mass spectrum, *m/z* (I_r/%): 444 (32), 429 (32), 414 (35), 399 (51), 386 (15), 369 (6), 367 (7), 355 (8), 342 (27), 322 (8), 58 (100).

N-3,*N*-20-Bis(2-hydroxy-3-(1,2:3,4-di-*O*-isopropylidene-6-*O*-(α-D-galactopyranosyl)propyl))cyclobuxine D (*VI*)

Yield = 280 mg (21 %), R_f = 0.75; for $C_{55}H_{90}N_2O_{15}$ (M_r = 1019.3) w_i(calc.): 64.81 % C, 8.90 % H, 2.75 % N; w_i(found): 64.70 % C, 8.94 % H, 2.73 % N. ^1H NMR spectrum, δ: 5.53 (d, 1H, H-1″, $J_{1'',2''}$ = 5.03 Hz), 4.93 (s, 1H, C-4′—H_a), 4.65 (s, 1H, C-4′—H_b), 4.10 (m, 1H, H-16), 3.05 (m, 1H, H-3), 2.54 (s, 6H, N-3—CH_3, N-20—CH_3), 1.54 (s, 6H, $C(CH_3)_2$), 1.46 (s, 6H, $C(CH_3)_2$), 1.33 (s, 12H, 2 × $C(CH_3)_2$), 1.16

(s, 3H, H-28), 0.97 (s, 3H, H-18), 0.95 (d, 3H, H-21, $J_{20,21}$ = 6.8 Hz), 0.27 (d, 1H, H-19$_a$, $J_{19a,19b}$ = 3.8 Hz), 0.07 (d, 1H, H-19$_b$). ^{13}C NMR spectra are given in Table 1.

N-20-(2-Hydroxy-3-(1,2:3,4-di-*O*-isopropylidene-6-*O*-(α-D-galactopyranosyl)propyl)) cyclobuxamine D (*VII*)

Yield = 180 mg (20 %), R_f = 0.52; for $C_{40}H_{66}N_2O_8$ (M_r = 703.0) w_i(calc.): 68.28 % C, 9.46 % H, 3.98 % N; w_i(found): 68.16 % C, 9.58 % H, 3.95 % N. ^{1}H NMR spectrum, δ: 5.54 (d, 1H, H-1˝, $J_{1'',2''}$ = 5.1 Hz), 4.81 (s, 1H, C-4′—H$_a$), 4.59 (s, 1H, C-4′—H$_b$), 4.13 (m, 1H, H-16), 2.90 (m, 1H, H-3), 2.54 (s, 3H, N-20—CH$_3$), 2.29 (s, 3H, N-3—CH$_3$), 1.54, 1.44, 1.33, 1.32 (4 × s, 12H, 2 × C(CH$_3$)$_2$), 1.16 (s, 3H, H-28), 0.97 (s, 3H, H-18), 0.94 (d, 3H, H-21, $J_{20,21}$ = 6.5 Hz), 0.30 (d, 1H, H-19$_a$, $J_{19a,19b}$ = 4.0 Hz), 0.08 (d, 1H, H-19$_b$). ^{13}C NMR spectra are given in Table 1.

N-3-(2-Hydroxy-3-(1,2:3,4-di-*O*-isopropylidene-6-*O*-(α-D-galactopyranosyl)propyl))cyclobuxine D (*VIII*)

Yield = 120 mg (13 %), R_f = 0.24; for $C_{44}H_{66}N_2O_8$ (M_r = 703.0) w_i(calc.): 68.28 % C, 9.46 % H, 3.98 % N; w_i(found): 68.15 % C, 9.63 % H, 3.92 % N. ^{1}H NMR spectrum, δ: 5.54 (d, 1H, H-1˝, $J_{1'',2''}$ = 5.1 Hz), 4.95 (s, 1H, C-4′—H$_a$), 4.65 (s, 1H, C-4′—H$_b$), 4.01 (m, 1H, H-16), 3.04 (m, 1H, H-3), 2.47 (s, 3H, N-3—CH$_3$), 2.33 (s, 3H, N-20—CH$_3$), 1.54, 1.45, 1.37, 1.34 (4 × s, 12H, 4 × CH$_3$), 1.13 (s, 3H, H-28), 1.08 (d, 3H, H-21, $J_{20,21}$ = 6.2 Hz), 0.98 (s, 3H, H-18), 0.27 (d, 1H, H-19$_a$, $J_{19a,19b}$ = 4.0 Hz), 0.09 (d, 1H, H-19$_b$). ^{13}C NMR spectra are given in Table 1.

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Translated by M. Kóóš