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THE STRUCTURE OF BUXENINE-G

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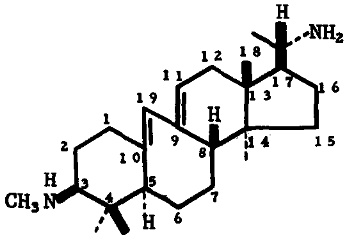
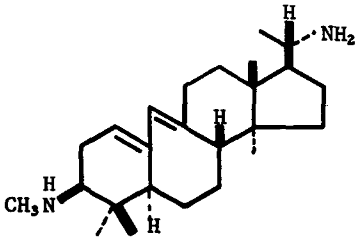
Two alternative diene structures, I and II, have been proposed (1-4) for buxenine-G, a cytotoxic (5) alkaloid isolated from Buxus sempervirens L. However, no definitive proof of the novel skeletal structure, configuration, or location of the diene system has been advanced. We now report a single-crystal X-ray analysis of buxenine-G dihydroiodide (6) which establishes unambiguously that I is correct.



I



II

Buxenine-G dihydroiodide, m.p. 298-300° dec., crystallizes from ethanol-ethyl acetate in the orthorhombic system, space group $\underline{P}2_1 2_1 2_1$, with four molecules of $C_{25}H_{44}N_2I_2$ in a cell of dimensions $\underline{a}$ = 13.32, $\underline{b}$ = 30.65, $\underline{c}$ = 6.96 Å. The crystal structure was elucidated by the heavy atom method and the atomic parameters were refined by Fourier and least-squares methods. The value of $\underline{R}$ is now 13.5% for 1405 independent reflections. The absolute configuration was determined by Bijvoet's anomalous-dispersion method (7,8).

At atoms 9 and 10 the carbon-carbon bonds are directed in a planar manner (average CCC valency angles of 120.0° and 119.9°, respectively) whereas at atoms 5 and 8 they are directed pyramidally (average CCC valency angles of 115.4° and 111.0°, respectively). Ring C exhibits the half-chair conformation typical of a cyclohexene; atoms 8, 9, 11, 12, and 19 are closely coplanar (see Table), consistent with the presence of a double bond between atoms 9 and 11, and atoms 13 and 14 are displaced from the plane by 0.35 and -0.51 Å, respectively. Ring A, on the other hand, exhibits the chair conformation typical of a cyclohexane; atoms 1, 2, 5, 10, and 19 do not constitute a good plane (see Table) and there is clearly no ethylenic bond between atoms 1 and 10. Moreover, atom 2 is displaced by 1.09 Å from the mean plane through atoms 1, 5, 9, 10, and 19, whereas atom 12 does not deviate significantly (0.03 Å) from the mean plane through atoms 8, 9, 10, 11, and 19. The eight atoms 1, 5, 8, 9, 10, 11, 12 and 19 are closely coplanar.

These results, together with detailed consideration of other mean-plane calculations defining the molecular conformation, show that the only acceptable situation for the conjugated diene system is (I).

Table

Deviations (Å) of the atoms from mean planes.

Atom	Displacement
8	0.00
9	0.00
11	0.02
12	-0.01
19	-0.01

Atom	Displacement
8	0.00
9	-0.01
10	0.01
11	0.01
19	0.00

Atom	Displacement
1	0.49
2	-0.31
5	0.01
10	0.03
19	-0.22

Atom	Displacement
1	0.09
5	-0.04
8	0.07
9	-0.01
10	-0.05
11	0.00
12	0.00
19	-0.06

Atom	Displacement
1	0.04
5	0.01
9	0.04
10	-0.05
19	-0.05

(The average standard deviation of position of a carbon atom is about 0.045 Å)

REFERENCES AND FOOTNOTES

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3. D. Stauffacher, *Helv. Chim. Acta*, **47**, 968 (1964); Symposium über Chemie und stereochemie der Steroid und Indolalkaloide, Smolenice, Czechoslovakia, Sept. 14-18, 1965, Abstracts, p. 12.
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5. Buxenine-G acetonimine showed significant inhibitory activity against cells derived from human carcinoma of the nasopharynx (KB); ED_{50}, 0.99, 0.40 μg./ml. Other *Buxus* alkaloids have also shown significant cytotoxicity and *in vivo* inhibitory activity against the Walker 256 intramuscular tumor in rats. Cytotoxicity and *in vivo* inhibitory activity were assayed, under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, by the procedures described in *Cancer Chemotherapy Rept*., **25**, 1 (1962).
6. The stability of buxenine-G toward treatment with mineral acid has been demonstrated earlier (2).
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8. This investigation was supported by grants from the National Science Foundation (GB-2878) and the National Institutes of Health (HE-02275).