Acta Cryst. (1976). B**32**, 936

The Bisindole Alkaloid Catharine

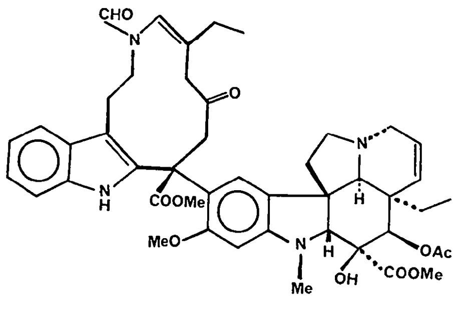
By J. Guilhem, A. Ducruix, C. Riche and C. Pascard

Institut de Chimie des Substances Naturelles, CNRS, 91190-Gif sur Yvette, France

(*Received* 8 *September* 1975; *accepted* 23 *October* 1975)

Abstract. $C_{46}H_{54}N_4O_{10}.CO(CH_3)_2$. Orthorhombic, $P2_12_12_1$, $a=9{\cdot}709$ (2), $b=17{\cdot}258$ (3), $c=27{\cdot}547$ (4) Å. $M=823$ (+58), $Z=4$, $D_x=1{\cdot}27$ g cm^{-3}. The title compound was extracted from *Catharanthus roseus* (Svoboda, Gorman, Neuss & Barnes, 1961) and *C. longifolius* (Rasoanaivo *et al.*, 1974). Though catharine shows no pharmacological activity, it was important to know its structure, in view of the anti-tumoural activity of several bisindole alkaloids isolated from various species of *Catharanthus*: vincaleucoblastine (VLB), leurocristine (LCR) (Moncrief & Lipscomb, 1966).

Introduction. When this crystal structure investigation was begun, one part of the molecule was known (Abraham, Farnsworth, Blomster & Rhodes, 1967) to be identical to one half (vindoline) of VLB, but there were no chemical or spectral means of characterizing the other part, except for the chemical functions, indole, N–CHO, CO_2CH_2 and CH_2CH_3. The data were collected with a 4-circle Philips diffractometer, using Cu $K\alpha$ radiation. Of 4752 recorded intensities (up to $\theta=68°$), 3784 were significantly above background $[I>2\sigma(I)]$. The crystal was cut to approximately $0{\cdot}5\times0{\cdot}5\times0{\cdot}5$ mm, and the quality of the reflexions was rather bad. Lorentz and polarization corrections were applied (but none for absorption).



The structure was solved using the phase function (Riche, 1973) with the symbolic-addition procedure (Karle & Karle, 1966). Six symbolic phases were used (5 general, 1 equatorial) and the computation of the phase function with the program *DEVIN* (Riche, 1973) gave 16 maxima, corresponding to the most probable values of the symbols. The 16 tangent refinements, using the subprogram *FASTAN* from *MULTAN* (Germain, Main & Woolfson, 1971), allowed discrimination of the solutions. The best figure of merit (which was also the highest maximum of the phase function) gave an *E*-map in which a six-membered ring was recognized. Ten peaks (including 2 spurious ones) were introduced in the recycling procedure of Karle

Table 1. *Fractional atomic coordinates* (× 10⁴) *and isotropic temperature factors*

C*A*(1), C*A*(2), C*A*(3) and O*A*(4) correspond to the acetone molecule.

	x	y	z	B (Å^2)
N(1)	8694 (8)	4337 (4)	8416 (3)	3·08 (13)
C(2)	7642 (8)	3842 (4)	8641 (2)	2·41 (13)
C(3)	4125 (11)	3538 (6)	9667 (4)	4·13 (19)
N(4)	4989 (7)	3623 (4)	9244 (2)	2·73 (12)
C(5)	4219 (10)	3544 (6)	8769 (3)	3·70 (17)
C(6)	5082 (10)	3996 (5)	8410 (3)	3·26 (16)
C(7)	6316 (8)	4345 (5)	8692 (3)	2·48 (13)
C(8)	6782 (8)	5116 (5)	8477 (3)	2·45 (13)
C(9)	6036 (9)	5787 (5)	8389 (3)	2·53 (13)
C(10)	6614 (9)	6409 (5)	8135 (3)	2·69 (14)
C(11)	7981 (9)	6328 (5)	7983 (3)	3·11 (15)
C(12)	8729 (9)	5653 (5)	8063 (3)	3·00 (15)
C(13)	8101 (9)	5064 (5)	8313 (3)	2·86 (14)
C(14)	4953 (11)	3702 (6)	10105 (4)	4·23 (19)
C(15)	6124 (10)	4082 (6)	10091 (3)	3·59 (17)
C(16)	8179 (9)	3476 (5)	9127 (3)	2·69 (14)
C(17)	8184 (9)	4128 (4)	9515 (3)	2·72 (14)
C(18)	5710 (15)	5762 (8)	9945 (5)	6·06 (27)
C(19)	6953 (10)	5342 (5)	9741 (3)	3·41 (17)
C(20)	6746 (9)	4467 (5)	9639 (3)	2·66 (14)
C(21)	5730 (9)	4366 (5)	9215 (3)	2·82 (14)
C(22)	9638 (9)	3188 (5)	9054 (3)	2·95 (15)
O(23)	9678 (7)	2492 (4)	8832 (2)	3·85 (12)
C(24)	11052 (13)	2180 (7)	8741 (4)	5·11 (23)
O(25)	10667 (8)	3526 (4)	9179 (3)	4·51 (14)
O(26)	7350 (6)	2836 (4)	9261 (2)	3·28 (11)
O(27)	8824 (7)	3795 (4)	9941 (2)	3·59 (11)
C(28)	9857 (11)	4182 (6)	10159 (4)	4·12 (19)
C(29)	10608 (15)	3692 (8)	10529 (5)	5·97 (27)
O(30)	10163 (9)	4850 (5)	10056 (3)	5·76 (18)
C(31)	9668 (13)	4004 (7)	8066 (4)	5·06 (23)
O(32)	8510 (8)	6939 (4)	7726 (3)	4·54 (14)
C(33)	9893 (17)	7005 (9)	7673 (6)	7·00 (33)
N′(1)	6862 (9)	8463 (4)	7839 (3)	3·60 (14)
C′(2)	6554 (9)	7865 (5)	8159 (3)	2·69 (14)
C′(3)	3284 (18)	7879 (10)	9507 (6)	7·28 (34)
N′(4)	4438 (10)	8224 (5)	9295 (3)	4·56 (17)
C′(5)	5870 (13)	8058 (7)	9457 (4)	4·92 (22)
C′(6)	6728 (11)	7643 (6)	9094 (4)	3·91 (18)
C′(7)	6950 (10)	8070 (5)	8623 (3)	3·35 (16)
C′(8)	7607 (12)	8811 (7)	8590 (4)	4·61 (21)
C′(9)	8194 (17)	9307 (9)	8928 (6)	6·99 (33)
C′(10)	8702 (20)	10002 (11)	8731 (7)	8·58 (41)
C′(11)	8556 (18)	10215 (10)	8286 (6)	7·59 (37)
C′(12)	8005 (14)	9754 (8)	7928 (5)	5·55 (26)
C′(13)	7475 (12)	9063 (6)	8094 (4)	4·52 (20)
C′(14)	3430 (11)	7808 (6)	8023 (4)	4·12 (19)
C′(15)	2568 (12)	8231 (6)	8394 (4)	4·35 (20)

Table 1 (*cont.*)

C′(16)	5829 (9)	7136 (5)	7994 (3)	2·88 (14)
C′(17)	4332 (10)	7149 (6)	8212 (3)	3·46 (16)
C′(18)	2300 (37)	10075 (21)	8378 (11)	15·22 (94)
C′(19)	3391 (31)	9651 (16)	8238 (9)	12·39 (72)
C′(20)	3374 (14)	8893 (8)	8600 (5)	5·80 (26)
C′(21)	4216 (13)	8858 (7)	8986 (4)	5·30 (24)
C′(22)	5663 (10)	7094 (6)	7435 (3)	3·63 (17)
O′(23)	4790 (8)	6513 (4)	7320 (3)	4·53 (14)
C′(24)	4436 (16)	6451 (8)	6790 (5)	6·27 (29)
O′(25)	6221 (8)	7482 (4)	7133 (2)	4·39 (14)
O′(26)	3381 (14)	7343 (8)	9783 (4)	9·36 (31)
O′(27)	3421 (9)	7985 (5)	7602 (3)	5·45 (17)
C*A*(1)	1369 (14)	6097 (8)	8949 (5)	5·51 (25)
C*A*(2)	180 (19)	6493 (10)	9187 (6)	8·27 (40)
C*A*(3)	2050 (24)	5430 (13)	9186 (8)	10·53 (57)
O*A*(4)	1754 (15)	6285 (8)	8545 (5)	10·24 (34)

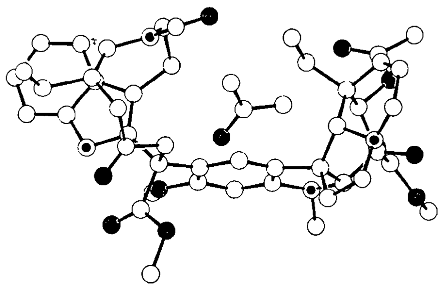
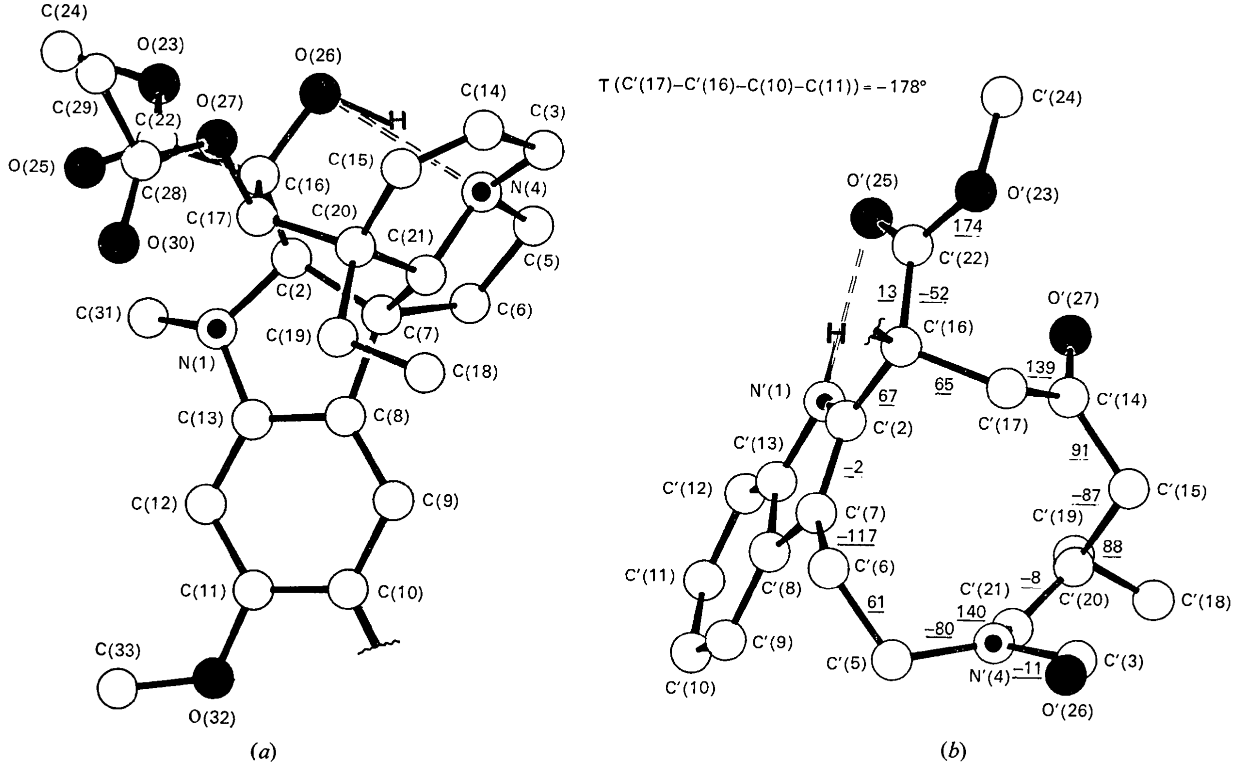


Fig. 1. The catharine molecule. Full black circles: O atoms; circles with a black spot: N atoms.

(1968) and all the atoms of the molecule were located in 4 steps. A difference synthesis showed one molecule of crystallization solvent (acetone). The coordinates and the isotropic temperature factors were refined (full-matrix) to a conventional R value of 11·6%.* In the final cycles of refinement, the weighting scheme used was $w=(2{\cdot}5+0{\cdot}3\ F_o)^{-1}$; scattering factors were those of Doyle & Turner (1968). H atoms were not located, but those whose positions could be calculated (32 of the 60) were included in structure-factor computations. Atomic parameters are given in Table 1, the whole molecule (projected along the a axis) is shown in Fig. 1, and its two moieties (with the labelling of the atoms) in Fig. 2(*a*) and (*b*) (*ORTEP* drawings, Johnson, 1965).†

Discussion. The vindoline part [Fig. 2(*a*)] of the molecule shows an intramolecular hydrogen bond [2·69 (1) Å] between N(4) and O(26), as observed by Mon-



(*a*) (*b*)

Fig. 2. (*a*) The vindoline moiety of the molecule. (*b*) The other part of the molecule. Some torsion angles are given ('+' sign clockwise)

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* A list of structure factors and interatomic distances and angles has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31491 (34 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

† The drawings depict the absolute configuration, which was established (Rasoanaivo, 1974) by correlation between the rotatory power of the vindoline part of catharine and an authentic sample of vindoline.

crief & Lipscomb (1966) in the LCR methiodide structure. The chemical formula of the other part is in agreement with the latest ^{13}C n.m.r. studies (Rasoanaivo *et al.*, 1974), except for the position of the *cis* double bond included in the 11-membered ring: C′(20)–C′(21) = 1·34 (2) Å. Another intramolecular hydrogen bond links the indole nitrogen N′(1) to the carbonyl oxygen O′(25) [2·65 (1) Å], stabilizing the conformation of the $COOCH_3$ group which is substituted at C′(16) (one end of the C(10)–C′(16) bridge between the two halves of the molecule). As frequently observed, the terminal methyl of the ethyl chain is disordered [C′(18)–C′(19) = 1·34 (5) Å], but the shortening effect seems to be enhanced by the misplacing of C′(19): C′(19)–C′(20) = 1·64 (3) Å. All the other distances are in good agreement with standard values within experimental r.m.s. deviation (0·03 Å). Table 2 gives the mean values of the bond lengths, classified schematically according to the hybridization of the carbon atoms. The end of the other ethyl chain, C(18), is not far from the aldehyde oxygen O′(26): 3·57 (2) Å, so that the general conformation of the catharine molecule is rather compact. The acetone molecule is inserted into the hollow formed by the catharine molecule: C′(17)–O*A*(4) = 3·05 (2) Å. No intermolecular hydrogen bond was found.

Table 2. *Mean values of the bond lengths* (Å), *with the corresponding root mean square deviations, calculated with respect to those mean values*

N is the number of distances.

Bond type	Mean	σ	*N*
C_{ar}–C_{ar}	1·39	4	14
C_{sp3}–C_{sp3}	1·54	3	12*
C_{sp3}–N	1·47	2	6
C_{sp2}–N	1·40	1	5
C_{sp3}–C_{sp2}	1·51	2	14†
C_{sp2}–C_{sp2}	1·33	2	2
C=O	1·21	1	6
C_{sp3}–O	1·44	5	5
C_{sp2}–O	1·36	1	4

* Excluding C′(18)–C′(19).
† Excluding C′(19)–C′(20).

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Acta Cryst. (1976). B**32**, 938

(—)-3(*a*)-Trimethylammonio-2(*a*)-acetoxy-*trans*-decalin Iodide

By Byungkook Lee and George M. Henry

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045, *U.S.A.*

(*Received* 30 *June* 1975; *accepted* 30 *October* 1975)

Abstract. $C_{15}H_{28}NO_2I$, M.W. 381·3, orthorhombic, $P2_12_12_1$, $Z=4$, $a=16·079$ (3), $b=14·373$ (3), $c=7·585$ (1) Å, $D_x=1·44$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, μ(Mo $K\alpha$) = 18·5 cm^{-1}, $R=0·031$ for 2030 observed reflections. This acetylcholine analog is the biologically inactive isomer. Its absolute configuration was determined using the anomalous dispersion effect of iodine. It has the 2(*R*)-3(*R*) configuration. The biologically active dextrorotatory isomer must, therefore, have the 2(*S*)-3(*S*) configuration.

Introduction. The title compound was synthesized, purified, and crystallized by Smissman, Schowen, Paske & Magarian (manuscript in preparation). The X-ray photographs of the needle-shaped crystals showed orthorhombic symmetry and systematic absences consistent with the space group $P2_12_12_1$ (*h*00 reflections absent when *h* odd, 0*k*0 absent when *k* odd, and 00*l* absent when *l* odd). Three-dimensional data were collected using a specimen 0·15 × 0·15 × 0·20 mm, a Syntex $P\bar{1}$ diffractometer, graphite-monochromated Mo $K\alpha$ radiation, and a θ–2θ scan procedure, the details of which have been reported (Seccombe, Lee & Henry, 1975). Intensities were measured for all 2314 independent reflections with $2\theta \leq 55°$. Of these, 2030 reflections had $I > 3\sigma(I)$ and were used for the structure analysis. The intensity data were reduced to the structure factors by the application of Lorentz and polarization corrections. No absorption or extinction correction was applied. The neglect of the absorption effect could