THE X-RAY STRUCTURAL INVESTIGATION OF ALKALOIDS

I. MOLECULAR STRUCTURE AND ABSOLUTE CONFIGURATION OF (+)-COCCULINE

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The role of x-ray structural analysis in the objective establishment of the molecular structures of natural compounds is generally known. One of the features of this method is the possibility of a direct determination of the absolute configuration relative to all the asymmetric centers, regardless of their number.

We have performed a systematic investigation of the molecular structure and absolute configuration of alkaloids, mainly those isolated and studied in the Institute of the Chemistry of Plant Substances of the Academy of Sciences of the Uzbek SSR (for example, cocculine). The present paper is the first of a series of communications on this subject.

Cocculine was first isolated by S. Yu. Yunusov [1] from Cocculus laurifolius D. C. The results of detailed chemical and physicochemical investigations permitted cocculine to be assigned to the cis- series of $\Delta^{1(6)}$-erythrine alkaloids and its configuration to be established as 3R,5S.

For an independent determination of the details of the molecular structure and the absolute configuration we have performed an x-ray structural study of (+)-cocculine in the form of the hydrobromide $C_{17}H_{21}NO_2 \cdot HBr$ [2]. The absolute configuration of the molecule is shown in Fig. 1, which also gives the bond lengths and the valence and torsional angles.

These investigations have confirmed the position established previously (15) for the substituent (hydroxy group) in the aromatic nucleus, the position (1-6) of the double bond, and the cis (equatorial) position of the substituent at C(3) in relation to the C(5)–N bond. In the Cahn–Ingold–Prelog system of symbols [3], the absolute configuration of cocculine of 3R,5S agrees with the previous results. We may note that in the majority of stereochemical investigations the nitrogen atoms are not considered as asymmetric centers. However, in this case the N(9) atom, which is tetrahedral (since the hydrobromide was investigated), is such a center and has the R-configuration. Nevertheless, in the free base, as well, because of the absence of inversion in view of the rigidity of the polycyclic structure, the pyramidal N(9) atom remains asymmetric with the some configuration. Here, according to the literature [3], the junior substituent is considered to be the unshared pair of electrons.

In spite of the limited accuracy of the determination of bond lengths and valence angles, their means (over groups of monotypical values) are the usual ones [4]: C–C 1.52(3), C^{ar}–C 1.39(2), C–O 1.39(2), N–C 1.52(3), C=C 1.31(4) Å, C–C–C at saturated atoms in the six-membered rings 114(3)°, in the five-membered ring 106(4)°, C–C=C at double bonds and in the benzene ring 120(3)°, C–O–C 114(3)°. The somewhat greater value of the length of the $\overset{+}{N}$–C bond of the ammonium nitrogen as compared with the standard length of an ordinary N–C bond of pyramidal nitrogen (1.47 Å [10]) may be noted; this is characteristic for the salts of other alkaloids, as well [5].

As can be seen from Fig. 1, rings A and B, and also B and C, have the cis type of linkage. The conformations of the rings can be judged reliably from the values of the torsional angles (see Fig. 1) and by the deviations from the atoms from the mean square planes (Table 1). The benzene ring D is planar with

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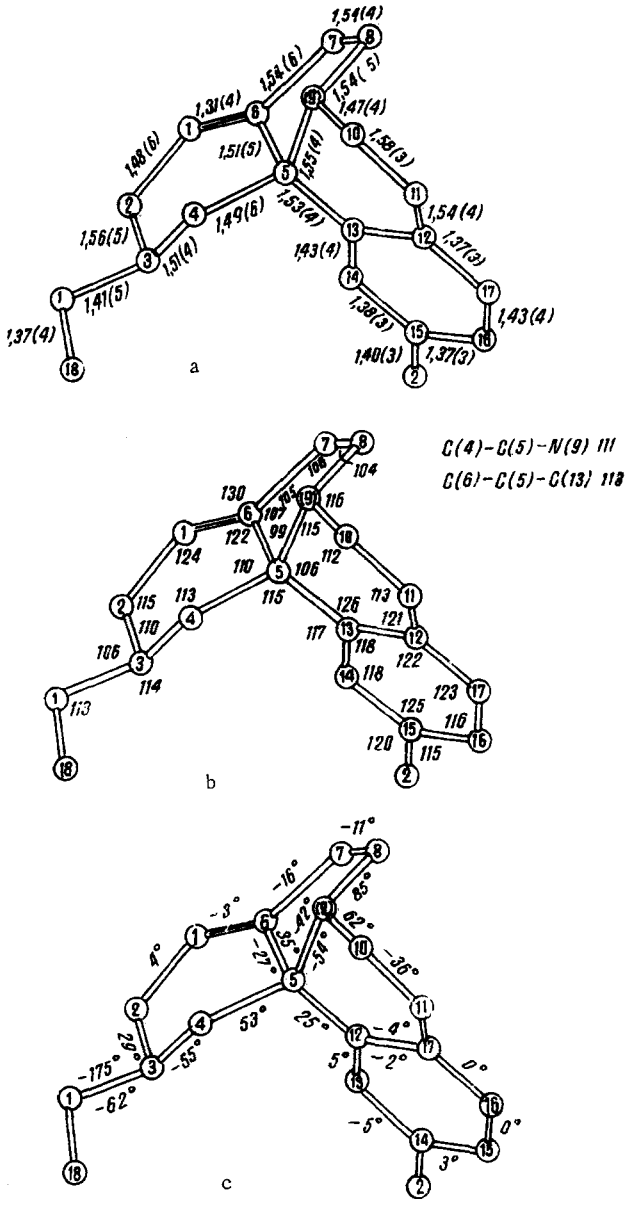

Fig. 1. Configuration of the molecule: a) bond lengths; b) valence angles (errors 2-3°); c) torsional angles.

TABLE 1. Mean Square Planes of the Fragments of the Molecule

Ring	Deviations of the atoms, Å							A	B	C	D
I	C(1)	C(2)	C(3)	C(5)	C(6)	C(4)	—	3,898	3,814	−0,424	0,204
(A)	0,017	−0,023	0,015	−0,009	0,000	−0,620					
II	C(6)	C(7)	C(8)	N (9)*	C(5)*	—	—	−3,912	−4,646	2,410	1,036
(B)	0,000	0,000	0,000	+0,283	−0,397						
III	C(11)	C(12)	C(13)	C(5)	N (9)*	C(10)*	—	7,625	−5,627	−3,476	4,199
(C)	0,008	−0,017	0,018	−0,008	−0,558	−0,127					
IV	C(12)	C(13)	C(14)	C(15)	C(16)	C(17)	O(2)*	7,730	−5,610	−3,243	3,962
(D)	0,001	−0,016	0,026	−0,020	0,003	0,006	0,019				

*Atoms not included in the calculation of the equations of the planes.

an accuracy of ± 0.01 Å, while the "substituents" C(5), C(11) and O(2) are coplanar with the ring. The six-membered ring A with one double bond possesses not the half-chair conformation (which is typical for cyclohexene derivatives) but the envelope conformation with a departure from the plane of the other atoms of

the fifth carbon atom C(4) by −0.62 Å, i.e., in Schwärz's nomenclature [6] this ring has the ^4E conformation. The other six-membered ring, C, has a similar conformation: the N(9) departs appreciably from the plane of four of the atoms (by +0.56 Å) and C(10) less considerably and in the opposite direction (by −0.13 Å).

If we neglect the deviation of C(10), the conformation of the ring is envelope ^9E; if this is not neglected, it is an unsymmetrical (because of the linkage with the five-membered ring) half-chair $^{10}H_9$. It is just such a conformation that was to be expected in the linkage of this ring with the benzene ring at the C(12)−C(13) bond. Finally, in the five-membered ring B the neighboring atoms C(5) and N(9) depart from the plane of the other three atoms in opposite directions (by −0.40 Å and by +0.28 Å, respectively), i.e., this has the twist or half-chair conformation $^9T_5$.

In the structure investigated, both active hydrogen atoms participate in two interionic hydrogen bonds $\overset{+}{N}$−H... Br^- with a length of 3.21 Å and O(1)−H... Br with a length of 3.18 Å, forming an infinite chain ...H−K^+−H...Br^-... along the [010] direction. Only van der Waals forces exist between the chains. Judging from their lengths, both hydrogen bonds are very strong [7].

EXPERIMENTAL METHOD

Triclinic crystals were investigated. The parameters of the cell were refined on a Hilger-Watts four-circle automatic diffractometer, and the density was determined by hydrostatic weighing:

$a = 8,839\,(9)\,Å$	$V = 406\,Å^3$
$b = 7,400\,(8)$	$M = 352,3$
$c = 7,115\,(8)$	$d_{meas} = 1,45$ g/cm^3
$\alpha = 80,98\,(5)°$	$d_{calc} = 1,45$
$\beta = 109,44\,(6)$	$Z = 1$
$\gamma = 112,23\,(6)$	Space group P1

The intensities of ~3000 reflections in the spherical region of reciprocal space up to $\nu = 23°$ were measured on the above-mentioned diffractometer (λMoK_α, graphite monochromator, ω-scanning, ordinate analysis) by the method of Bokii et al. [8]. After the averaging of the reflections of the Friedel pairs hk$l$ and hk$l$ a set of 1395 reflections with $|F|^2 \geq 3\sigma(|F|^2)$ was obtained; extinction was not taken into account.

Since the choice of origin in the space group P_1 is arbitrary, it was made to coincide with the heavy bromine atom. The difference $\Delta\rho(xyz)_{Br^-}$ synthesis with the deduction of the bromine atom revealed 10 light atoms. Several successive approximations of the $\Delta\rho(xyz)_{Br^-}$ synthesis taking into account the contribution of the light atoms in the calculations of the phases enabled all the nonhydrogen atoms to be localized; at this stage, R = 0.22 at $B_{tot} = 3.0$ Å^2. Refinement by the method of least squares in the isotropic approximation lowered the residual factor to R = 0.15. The definitive positions and the thermal parameters are given in Table 2.

TABLE 2. Coordinates of the Atoms and Their Individual Thermal Factors

Atom	x	y	z	B, Å^2
Br	0	0	0	3,19(4)
C(1)	0,028(4)	−0,360(4)	−0,342(4)	2,8(4)
C(2)	0,164(4)	−0,445(5)	−0,305(4)	2,5(5)
C(3)	0,129(4)	−0,593(5)	−0,460(5)	2,2(4)
C(4)	0,022(4)	−0,542(4)	−0,662(4)	2,3(4)
C(5)	−0,141(4)	−0,530(5)	−0,657(5)	2,1(4)
C(6)	−0,106(4)	−0,392(5)	−0,500(5)	2,8(5)
C(7)	−0,251(4)	−0,306(4)	−0,566(4)	3,1(5)
C(8)	−0,337(4)	−0,347(4)	−0,785(4)	3,2(5)
C(10)	−0,292(3)	−0,526(4)	−1,030(4)	3,0(5)
C(11)	−0,447(4)	−0,720(4)	−1,016(4)	3,4(5)
C(12)	−0,419(3)	−0,818(4)	−0,806(4)	2,2(4)
C(13)	−0,283(3)	−0,726(4)	−0,647(4)	1,9(3)
C(14)	−0,275(3)	−0,819(4)	−0,454(4)	1,8(3)
C(15)	−0,396(3)	−1,001(4)	−0,440(4)	2,4(4)
C(16)	−0,532(3)	−1,093(4)	−0,596(4)	2,9(5)
C(17)	−0,540(4)	−0,995(4)	−0,786(4)	2,9(5)
C(18)	0,287(3)	−0,740(4)	−0,531(4)	4,7(7)
N(9)	−0,217(3)	−0,418(3)	−0,845(3)	2,6(3)
O(1)	0,292(2)	−0,585(3)	−0,457(3)	3,0(3)
O(2)	−0,392(2)	−1,099(2)	−0,254(3)	2,8(3)

TABLE 3. Comparison of r_{meas} and r_{calc}

hkl	r_{meas}	r_{calc}	hkl	r_{meas}	r_{calc}
100	−0,22	−0,24	$\bar{3}50$	0,19	0,22
200	0,28	0,27	050	0,12	0,16
$\bar{5}10$	−0,18	−0,14	$\bar{3}60$	−0,07	−0,14
310	0,19	0,23	$05\bar{1}$	0,16	0,14
$\bar{1}20$	0,13	0,14	$3\bar{5}1$	0,23	0,14
$\bar{5}20$	−0,15	−0,10	$\bar{2}\bar{4}1$	0,11	0,13
520	0,19	0,11	$\bar{1}\bar{3}1$	−0,05	−0,10
$\bar{6}30$	0,20	0,17	331	−0,19	−0,19
030	−0,15	−0,13	$\bar{5}\bar{2}1$	0,06	0,11
$\bar{5}30$	−0,18	−0,15	$\bar{4}\bar{2}1$	0,11	0,15
340	−0,22	−0,19	$\bar{1}\bar{2}1$	0,32	0,36
040	−0,21	−0,21	001	0,62	0,61
$\bar{6}50$	0,21	0,15			

The absolute configuration was established from the anomaly of the scattering of the Mo radiation by the Br atoms ($\Delta F''_{Br}$ = 2.456 [9]) by Bijvoet's method [10]. For this purpose, 120 Friedel pairs of $hkl-\bar{h}\bar{k}\bar{l}$ reflections the intensities of which differed most strongly were selected. The signs of r_{meas} and r^*_{calc} for all the selected reclections coincided, and their absolute values were similar (Table 3 gives these values for some of the reflections). Consequently, the coordinates of the atoms in Table 2 and the molecular model constructed from them (see Fig. 1) correspond to the absolute configuration of the molecule.

All the calculations in the interpretation and refinement of the structure were performed by programs due to B. L. Tarnopol'skii, V. I. Andrianov, and Z. Sh. Safina (OIKhF AN SSSR) and the calculations to determine the absolute configuration by the ABKONF program.

SUMMARY

An x-ray structural investigation of the alkaloid (+)-cocculine in the form of the hydrobromide has been performed. The bond lengths and valence angles are the usual ones. The conformations of the rings are: A – envelope ^4E; B – half-chair $^9T_5$; C – half-chair $^{10}H_5$. The absolute configuration 3R,5S has been established.

LITERATURE CITED

1. S. Yu. Yunusov, Zh. Obshch. Khim., 20, 368 (1950).
2. R. Razakov, S. Yu. Yunusov, S.-M. Nasirov, V. G. Andrianov, and Yu. T. Struchkov, Izv. Akad. Nauk SSSR, 218 (1974).
3. R. S. Cahn, C. K. Ingold, and V. Prelog, Angew. Chem., Int. Ed., 5, 385 (1966).
4. Tables of Interatomic Distances and Configurations in Molecules and Ions, Chemical Society, London (1955).
5. T. Sato and H. Koyama, J. Chem. Soc., B 1070 (1971).
6. J. C. P. Schwarz, Chem. Comm., 505 (1973).
7. W. C. Hamilton and J. A. Ibers, Hydrogen Bonding in Solids, W. A. Benjamin, New York (1968)
8. N. G. Bokii, Yu. T. Struchkov, D. N. Kravtsov, and E. M. Rokhlina, Zh. Strukt. Khim., 14, 291 (1973).
9. C. H. Dauben and D. H. Templeton, Acta Crystallogr., 8, 841 (1955).
10. J. M. Bijvoet, A. F. Peerdeman, and A. I. van Bommel, Nature (London), 168, 271 (1951).
11. A. N. Chekhlov, Yu. T. Struchkov, and A. I. Kitaigorodskii, Dokl. Akad. Nauk SSSR, 215, 122 (1974).

* $r = 2\{|F(hkl)|^2 - |F(\bar{h}\,\bar{k}\,\bar{l})|^2\} / \{|F(hkl)|^2 + |F(\bar{h}\,\bar{k}\,\bar{l})|^2\}$