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# SYNTHESES BASED ON NORFLUOROCURARINE. 3. STRUCTURES OF (–)-NORFLUOROCURARINE, (±)-NORFLUOROCURARINE, AND FLUOROCURARINE

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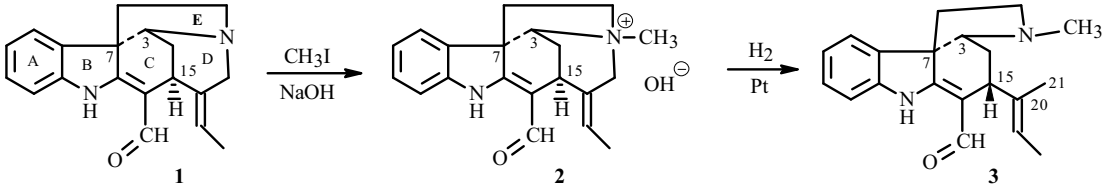
*Structures of the alkaloids* (–)-*norfluorocurarine, its racemate* (±)-*norfluorocurarine from* Vinca erecta*, and fluorocurarine obtained by* N(β)-*methylation of* (–)-*norfluorocurarine were established by x-ray crystal structure analyses. The alkaloid crystallized with two molecules in the asymmetric unit for the first two crystals. The asymmetric unit of* (±)-*norfluorocurarine crystal consisted of two antipods. The asymmetric unit in the crystal of the last compound consisted of the* N(β)-*methylated cation and a hydroxide anion. The formation of bimolecular associates through intermolecular N–H…O H-bonds was typical of these crystalline structures. An associate in the crystal structure of fluorocurarine involved two hydroxide anions.*

**Keywords:** indoline alkaloids, fluorocurarine, norfluorocurarine, XSA.

We previously reduced and dehydrated (–)-norfluorocurarine under various conditions and determined the structures of the reaction products during a search for new biologically active compounds among derivatives of the indoline alkaloid norfluorocurarine [1–3]. Determination of their x-ray crystal structures showed that the configuration of asymmetric C15 changed in the reaction product formed via opening of fluorocurarine ring D [3]. This unusual phenomenon could not be explained [3]. Therefore, we decided to elucidate the structures of the starting compounds themselves, i.e., (–)-norfluorocurarine (**1**) and fluorocurarine (**2**). This would explain the aforementioned assertion because x-ray structure analyses (XSA) of the starting compounds were not performed, in contrast with transformation product **3**.




**1** **2** **3**

Furthermore, the reasons for the separation over a chromatographic column of (–)-norfluorocurarine and its natural racemate (±)-norfluorocurarine (**1′**), which was isolated under the name vinervidine [4], have not yet been found. It is well known that optical antipods are not usually separated over extraction (chromatographic) columns. Therefore, (–)-norfluorocurarine, (+)-norfluorocurarine, and (or) their racemate should be separated simultaneously upon extraction. Such an unusual separation of components is evidently due to differences in the nature of intermolecular interactions. This also stimulated the elucidation of the structures of the starting compounds.

For the aforementioned reasons, we selected XSA for the determination of the structures of **1** and **1′** isolated from *Vinca erecta* [5, 6] and **2** obtained by *N*(*β*)-methylation of **1** [3].

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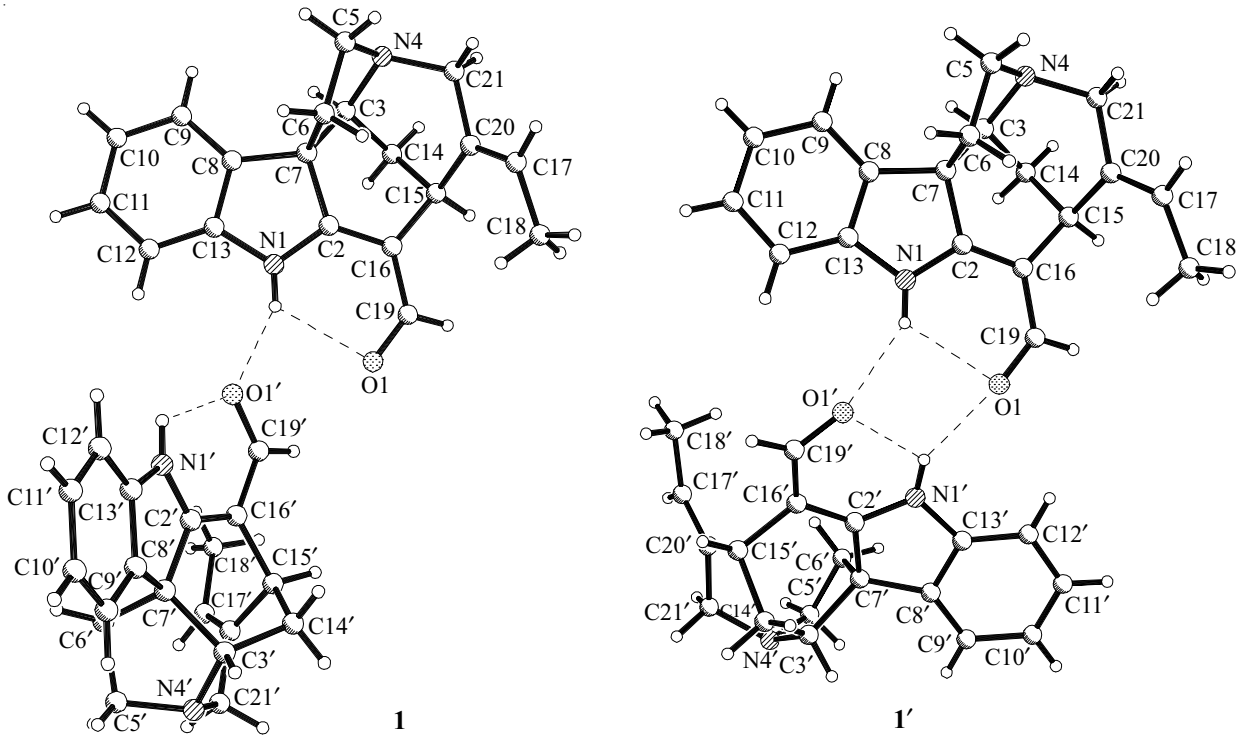


Fig. 1. Molecular structures and formation of associates in crystals of **1** and **1′** (dashed lines show inter- and intramolecular H-bonds).

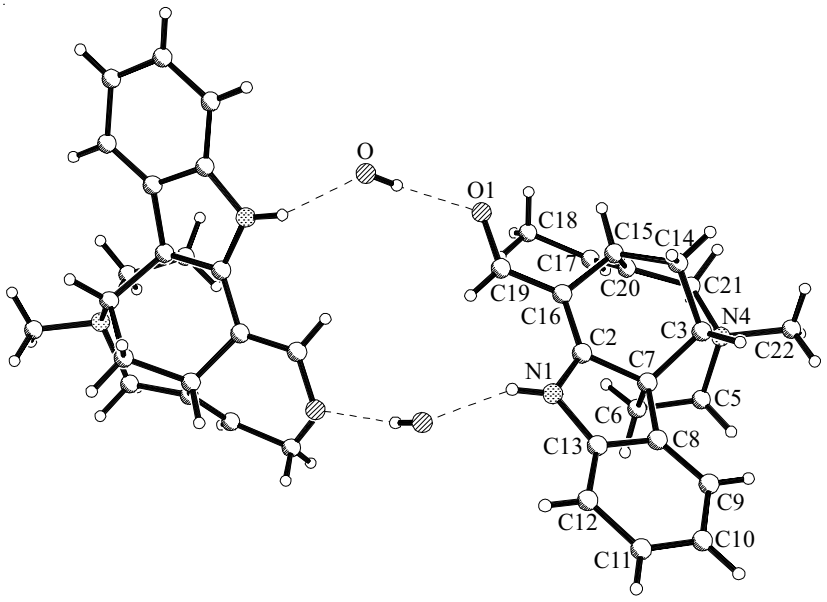


Fig. 2. Molecular structure of **2** (the asymmetric unit is numbered) and formation of an associate in the crystal (dashed lines shown intermolecular H-bonds).

Figures 1 and 2 show the molecular structures of **1**, **1′**, and **2**. The absolute configuration of **1** is considered established [2] whereas **2** is the *N*($\beta$)-methyl derivative of **1**. Therefore, the absolute configurations of the molecules correspond to the illustrated structure, i.e., 3*S*, 7*R*, and 15*S*. Atom N4 in **2** was methylated, as a result of which it also became an asymmetric center with the 4*S*-configuration. The illustrated structures of **1** and **2** suggest that asymmetric C15 in both starting molecules retains the *S* absolute configuration. Therefore, the question about the reason for the configuration change of C15 to *R* in **3** remains unanswered. It may be related to the formation of an intermediate transition compound (or state) upon opening ring D.

TABLE 1. Hydrogen Bonds in Crystals of **1**, **1′**, and **2**

| Atom | H…A (Å) | D…A (Å) | D-H < A (°) |
|---|---|---|---|
| | Crystal of **1** | | |
| N1-H… O1 | 2.30 | 2.777 (7) | 115 |
| N1′-H… O1′ | 2.23 | 2.741 (8) | 118 |
| N1-H… O1′ | 2.11 | 2.899 (8) | 153 |
| | Crystal of **1′** | | |
| N1-H… O1 | 2.33 | 2.809 (2) | 116 |
| N1′-H… O1′ | 2.25 | 2.750 (2) | 117 |
| N1-H… O1′ | 2.13 | 2.869 (3) | 143 |
| N1′-H… O1 | 2.25 | 3.029 (2) | 150 |
| | Crystal of **2** | | |
| N1-H… O | 1.96 | 2.762 (6) | 155 |
| O-H… O1 | 1.91 | 2.709 (6) | 156 |

TABLE 2. Principal Crystallographic Data and Parameters of the X-ray Crystal Structure for **1**, **1′**, and **2**

| Parameters | **1** | **1′** | **2** |
|---|---|---|---|
| Molecular formula | $C_{19}H_{20}N_2O$ | $C_{19}H_{20}N_2O$ | $C_{20}H_{23}N_2O^+ \cdot OH^-$ |
| MW/g mol$^{-1}$ | 292.37 | 292.37 | 324.41 |
| System | Monoclinic | Orthorhombic | Tetragonal |
| Space group | P $2_1$ | Pbcn | $P4_32_12$ |
| *Z* | 4 | 16 | 8 |
| *a*, Å | 14.711 (2) | 22.2109 (3) | 9.8276 (5) |
| *b*, Å | 7.1599 (7) | 10.7536 (2) | 9.8276 (5) |
| *c*, Å | 16.088 (2) | 25.3861 (4) | 34.395 (4) |
| $\alpha$ | 90.00 | 90 | 90 |
| $\beta$ | 116.115 (15) | 90 | 90 |
| $\gamma$ | 90.00 | 90 | 90 |
| V, Å$^3$ | 1521.5 (3) | 6063.4 (2) | 3321.9 (5) |
| ρ, g/cm$^3$ | 1.276 | 1.281 | 1.297 |
| Crystal size, mm | 0.2 × 0.2 × 0.4 | 0.3 × 0.4 × 0.4 | 0.2 × 0.2 × 0.03 |
| Scan region θ | 3.35 ≤ θ ≤ 66.84° | 3.48 ≤ 70.88° | 4.68 ≤ 67.08° |
| $\mu_{exp}$, cm$^{-1}$ | 0.623 | 0.626 | 0.667 |
| Number of reflections | 3506 | 5579 | 2483 |
| Number of reflections with $I > 2\sigma(I)$ | 2632 | 3746 | 1005 |
| $R_1$ ($I > 2\sigma(I)$ and total) | 0.0664 (0.0980) | 0.0463 (0.0666) | 0.0604 (0.1772) |
| W$R_2$ | 0.1731 (0.2408) | 0.1151 (0.1232) | 0.1053 (0.1395) |
| GOOF | 1.093 | 0.805 | 0.882 |
| Electron-density difference peaks, e Å$^{-3}$ | 0.32 and –0.30 | 0.24 and –0.24 | –0.16 and 0.15 |
| CCDC | 818744 | 818743 | 818745 |

Compounds **1** and **1′** crystallized with two molecules in the asymmetric unit. The asymmetric unit in the structure of **1′** consisted of the two molecules of the alkaloid antipods. Bimolecular associates were typically present in the crystal for these structures. Figure 1 shows their molecular structures and associates formed through N1–H…O1 intermolecular H-bonds. These atoms were involved simultaneously in the formation of an intramolecular H-bond. Table 1 presents the parameters for these inter- and intramolecular H-bonds. Table 1 and Fig. 1 show that an intramolecular N1–H–O1 H-bond occurred in both instances. However, the nature of the intermolecular H-bond was different in these crystalline associates. Whereas the associate in the crystal of **1′** was formed through two N1–H…O1′ and N1′–H…O1 H-bonds (the molecules were related by a pseudo-center of symmetry), the two molecules of the associate in **1** were bonded through a single N1–H…O1′ H-bond. This indicated that the mutual location of the two independent molecules interacting through H-bonds differed considerably in crystals of **1** and **1′**.

In contrast with the two structures examined above, the asymmetric unit in the crystal structure of **2** consisted of a cation, norfluorocurarine methylated on N4 of the alkaloid, and a hydroxide anion. Furthermore, the orientation of the C19=O1 carbonyl also differed in **2**. Torsion angle C2–C16–C19=O1 in **2** was 155.6° (they were –10.2, –11.4° and 6.9, –9.2° in **1** and **1′**). As a result, the intramolecular C19=O1…H–N1 H-bond that was characteristic of **1** and **1′** was missing in **2**. Despite this difference for the structure of **2**, bimolecular associates were also characteristic of it. However, the associate in this instance was formed through two hydroxide anions with the halves of the associate related by a two-fold symmetry axis (Fig. 2).

The bimolecular associates in crystals of **1**, **1′**, and **2** were situated at van-der-Waals distances from each other. Anomalously short intermolecular contacts were not observed in the packing.

The chemically equivalent norfluorocurarine frameworks in the four independent molecules of **1** and **1′** had the same conformations. The indoline cores in the two independent molecules in the crystal of **1** were planar to within ±0.040 and ±0.055 Å , respectively. They were situated at an angle of 71.1° to each other. The indoline cores in the crystal of **1′** were also planar in the two molecules (±0.042 and ±0.055 Å). However, they were situated at an angle of 32.8° to each other. Ring C in all instances adopted a distorted boat (twist-boat) conformation with $C_2$ symmetry passing through the middle of the two opposing bonds C2–C7 and C14–C15; ring D, a slightly distorted boat; ring E, a C5-envelope in all molecules.

The geometry of the cation in **2** was practically the same as that observed in **1** and **1′**. The indoline core was planar within ±0.038 Å. Ring C adopted a twist-boat conformation; ring D, a slightly distorted boat; and ring E, a C5-envelope. This meant that a change in the nature of the intra- and intermolecular H-bonds did not cause a change or deformation of the ring conformations in the norfluorocurarine framework.

Thus, the XSA obtained for the starting compounds (although they did not reveal the reasons for the configuration change of C15 in **3**) enabled the reason for the separation over a chromatographic column of **1** and its racemate **1′** during their isolation from total alkaloids of *V. erecta* to be understood. According to the literature [6], the main component **1** is eluted first during elution of total alkaloids successively by benzene and then ether. Then, the alkaloids reserpinine and isoreserpinine are eluted followed by small quantities of the racemic mixture (±)-norfluorocurarine (**1′**). Such a dramatic separation over a chromatography column of **1** and **1′** indicated that (+)-norfluorocurarine, which occurred in small quantities in the plant, was located in the mother liquor as a stable bimolecular associate with (–)-norfluorocurarine, as observed in the crystalline state.

## EXPERIMENTAL

**X-ray Crystal Structures.** Single crystals of **1** and **1′** for the XSA were grown by slow evaporation from the appropriate solvents at room temperature. However, single crystals suitable for the XSA could not be grown from the yellow silky powder of **2** using the traditional organic solvents. Crystals were produced after several collections from acetone–alcohol mixtures. Slow evaporation formed fine yellow plate-like crystals on the crystallizer walls. Chips of these were used for the XSA.

Unit cell constants of crystals of **1**, **1′**, and **2** were determined and defined on an Xcalibur Ruby CCD diffractometer (Oxford Diffraction) using Cu $K_\alpha$-radiation (300 K, graphite monochromator) [7]. A three-dimensional dataset of reflections was obtained on the same diffractometer. A dataset with satisfactory statistics [$I > 2\sigma(I)$] could not be collected for **2** because of the small crystal size and low quality of the single crystal. Absorption corrections were made for all crystals using the semi-empirical method in the program SADABS [8]. Table 2 presents the principal parameters of the XSA and the refinement of the structures of **1**, **1′**, and **2**.

The structures were solved by direct methods using the SHELXS-97 programs. The structures were refined using the SHELXL-97 programs [9]. All nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods (over $F^2$). Positions of H atoms were set geometrically and refined with fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and $U_{eq}$ were the equivalent isotropic thermal parameter of the corresponding C atoms. The position of the H atom in the anion in **2** was determined from a difference electron-density synthesis and refined isotropically despite the poor statistics (Table 2).

Data from the XSA were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC) (Table 2).

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