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SYNTHESES BASED ON NORFLUOROCURARINE. 2. REDUCTION AND DEHYDROGENATION PRODUCTS

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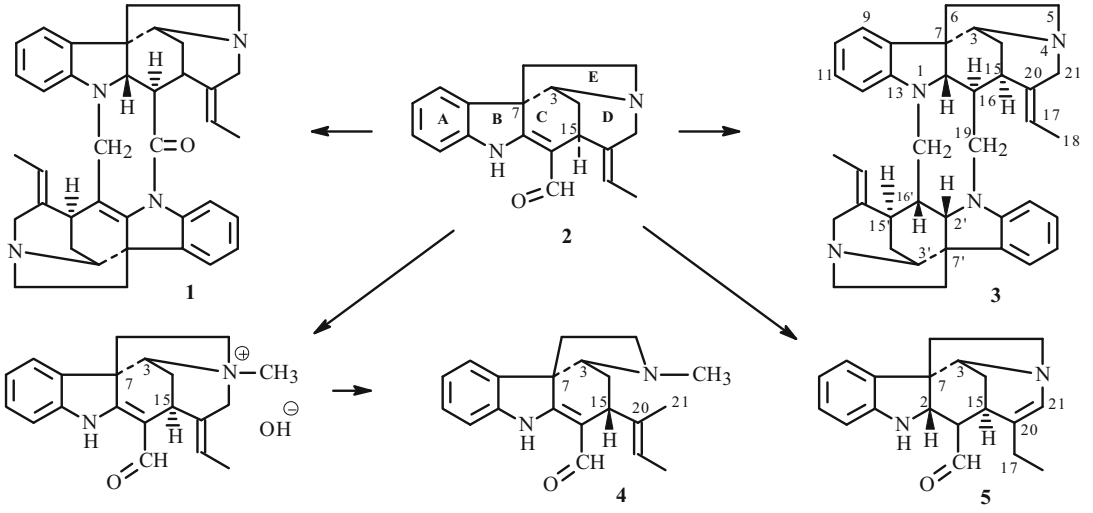
*The bisindole compound 2β,16α,2′β,16′β(*H*)-tetrahydronordihydrotoxiferine consisting of two diastereoisomeric deoxytetrahydronorfluorocurarine moieties was isolated from the reduction mixture of the alkaloid norfluorocurarine. 16-Deformyl-2,16,17,20-tetrahydro-20,21-dehydronorfluorocurarine was produced by dehydrogenation of norfluorocurarine;* N*(β)-methyldihydrodefluorocurarine, by hydrogenation of fluorocurarine. The structures of the synthesized compounds were established by x-ray structure analyses. The configurations of the asymmetric centers in 2β,16α,2′β,16′β(*H*)-tetrahydronordihydrotoxiferine were determined as 2*S*,3*S*,7*R*,15*S*,16*R*,2′*S*,3′*S*,7′*R*,15′*S*,16′*S*. Inversion to the* R*-configuration at the C15 center was observed in* N*(β)-methyldihydrodefluorocurarine whereas the configurations 3*S *and 7*R *were retained. Atom C2 adopted the* S*-configuration in 16-deformyl-2,16,17,20-tetrahydro-20,21-dehydronorfluorocurarine.*

Keywords: indoline alkaloids, norfluorocurarine derivatives, absolute configuration, x-ray structure analysis.

Indoline alkaloids of the norfluorocurarine type exhibit a broad spectra of biological activity and are used in medical practice as valuable drugs [1–3]. They were previously reduced (hydrogenated) under various conditions in order to discover new physiologically active compounds in this series. Deoxytetrahydronorfluorocurarine, tetrahydronorfluorocurarine, deoxydihydronorfluorocurarine, and a bisindoline (2,16-dihydro-19-oxonordihydrotoxiferine, **1**) were isolated from the reaction mixture [4]. The structures of the last two compounds were established by x-ray structure analyses (XSAs).

In continuation of the separation of products from hydrogenation of norfluorocurarine (**2**) by zinc in H_2SO_4 on a sand bath, we isolated a bisindoline base of formula $C_{38}H_{44}N_4$ that consisted of two moieties (reduced at the C2–C16 bond) of the alkaloid deoxytetrahydronorfluorocurarine. We called the bimolecular base 2,16,2′,16′-tetrahydronordihydrotoxiferine (**3**) in analogy with bisindoline **1**.



Scheme 1. Transformations of norfluorocurarine (**2**).

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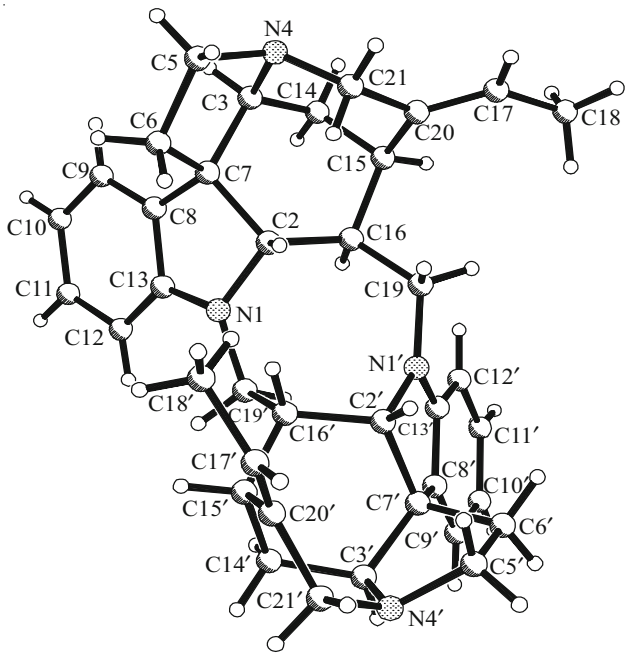

Fig. 1. Molecular structure and atomic numbering of **3**.

A structure with an opened ring E was proposed earlier for *N*(β)-methyldihydrodefluorocurarine (**4**), which was prepared by hydrogenation of fluorocurarine [*N*(β)-methylnorfluorocurarine] under an H_2 atmosphere in the presence of a Pt catalyst. It was assumed that the N4–C5 bond was cleaved during the reaction [5]. However, our structural studies showed that tertiary base **4** is formed by opening of ring D and cleavage of the N4–C21 bond. The other rings, which contain a more labile chromophore (π-bond system), did not undergo structural changes. This can also be noticed in the UV spectra because the absorption bands of starting **2** (containing the chromophore system NH–C2=C16–CH=O with absorption bands at 245, 300, and 365 nm) and **4** are practically identical (see Experimental).

N(β)-Methyldihydrodefluorocurarine is a weak base so that its methyliodide salt $C_{26}H_{27}ON_2I$ forms with difficulty.

Norfluorocurarine was also dehydrogenated by selenium at 400°C. In this instance, structural changes occurred with retention of the alkaloid heterocyclic framework. The formyl substituent was lost from C16. The C2–C16 double bond was reduced. The formal C20=C17 double bond shifted to C20=C21. The reaction product had the structure 16-deformyl-2,16,17,20-tetrahydro-20,21-dehydronorfluorocurarine (**5**). Its 20,21-dihydro analog has been reported, was also prepared synthetically, and was called (–)-tubifolidine [6].

The structures of the prepared norfluorocurarine derivatives were established by x-ray crystal structure analyses. Herein the XSA results are reported and structural data are discussed for norfluorocurarine hydrogenation products **3** and **4** and dehydrogenation product **5**.

Questions about the stereochemistry of this type of alkaloids were addressed earlier. The absolute configuration of the asymmetric centers in the norfluorocurarine heterocyclic framework is considered to be known [4]. For bisindoline **3** (resulting from reduction and dimerization), 16 diasteroisomeric compounds differing in the absolute configurations of the four asymmetric centers C2, C16, C2′, and C16′ can theoretically be formed. If the indole monomers of **3** are considered to be structurally identical (the molecular has an intrinsic second-order symmetry axis), then the number of diastereoisomers decreases to 8. This reaction did not affect the 3*S* and 7*R* centers in the norfluorocurarine framework. Therefore, the XSA data enabled the configuration of all asymmetric centers in **3** to be determined relative to the known ones. Figure 1 shows the three-dimensional molecular structure of bimolecular alkaloid **3**. The indole monomers in **3** are diastereoisomers and differ in the configuration of asymmetric C16. One of the indole monomers of **3** has the same configuration as the reduced part of bimolecular **1** (Scheme 1). According to the presented structure, the asymmetric centers of **3** were determined as 2*S*,3*S*,7*R*,15*S*,16*R*,2′*S*, 3′*S*,7′*R*,15′*S*, and 16′*S*. Thus, the alkaloid is properly called 2β,16α,2′β,16′β(*H*)-tetrahydronordihydrotoxiferine.

N(β)-Methyldihydrodefluorocurarine (**4**), which was obtained by hydrogenation of fluorocurarine, also had C3 and C7 asymmetric centers that were unaffected. They retained the *S*- and *R*-configurations, respectively. However, the opening of ring D in fluorocurarine was accompanied by a sign change of the C15 asymmetric center so that **4** adopted the 15*R*-configuration. This is somewhat unusual and unexplained. Figure 2 shows the three-dimensional structure from an XSA of one of the four (configurationally identical) molecules of **4** situated in the asymmetric unit of the cell.

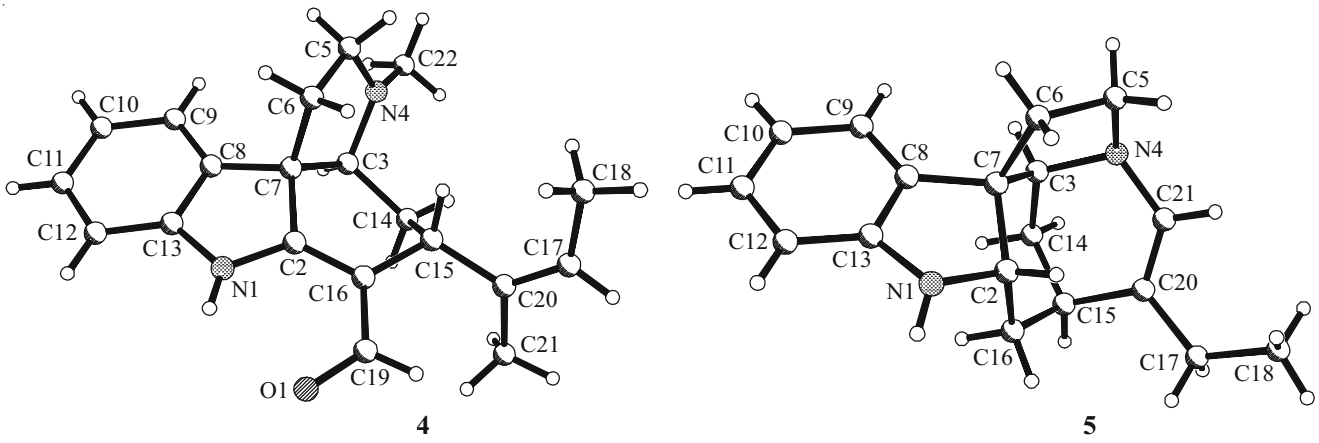

Fig. 2. Molecular structures and atomic numbering of **4** and **5** (one of the four molecules of **4** and one of the two molecules of **5** in the asymmetric unit are shown).

It can be seen that the C15 H atom has the β-axial orientation whereas it had the α-orientation in norfluorocurarine and its known derivatives. The configuration change of this asymmetric center suggests that this is possible if one of the neighboring double bonds (C2=C16 or C17=C20) migrated temporarily to C15 during the opening of ring D. Of course, this hypothesis requires additional experimental verification. Thus, compound **4** can properly be called 15β(*H*),*N*(β)-methyldihydrodefluorocurarine.

Dehydrogenation removed the C16 substituent and reduced the C2–C16 double bond to produce **5**. The asymmetric centers adopted the 3*S*, 7*S*, and 15*S*-configurations as a result of these changes in the heterocyclic framework. Figure 2 shows (one of the two molecules of **5** in the asymmetric unit of the crystal cell) that asymmetric C2 adopted the *S*-configuration whereas C16 lost its asymmetry because of the removal of the formyl group. Thus, the dehydrogenation product can properly be called 2β(*H*),16-deformyl-2,16,17,20-tetrahydro-20,21-dehydronorfluorocurarine.

Five-membered rings B and B′ in the indoline core of dimer **3** assumed a highly flattened envelope conformation with C2 and C2′ deviating from the plane of the other atoms by 0.380 and 0.140 Å, respectively. Rings C and C′ had identical slightly distorted chair (twist-chair) conformations. However, rings D and D′ had different conformations, chair and slightly asymmetric boat (flattened toward C21′), respectively. The conformations of five-membered heterocycles E and E′ were intermediate between envelope and twist. Despite the reduction of the C2–C16 [1.544(4) Å] and C2′–C16′ [1.553(4) Å] bonds in **3**, the conformations of the rings in general were the same as those observed in the other bisindoline compound (**1**) [4]. The ring fusions in the monomers did not differ (B/C-, C/E- and E/D-*cis*).

The asymmetric unit in the crystal of *N*(β)-methyldihydrodefluorocurarine (**4**) included parts of four alkaloid molecules (a, b, c, d) with approximately the same geometries for rings A, B, C, and E and the same arrangement of the planar but fluxional part with C15, C20, C21, C17, and C18. The indoline cores (rings A and B) in these four molecules (a, b, c, d) were practically planar within ±0.028, ±0.046, ±0.031, and ±0.052 Å, respectively. Ring C in all four molecules adopted a distorted boat conformation (twist-boat) with a C2 symmetry axis passing through the middle of the C2–C7 and C14–C15 bonds. However, five-membered ring E had C6- and C5-envelope conformations in rings a and b, respectively, whereas it had a twist conformation in rings c and d with C5 and C6 deviating to different sides of the plane of the other ring atoms. The conformationally fluxional planar part (C15, C20, C21, C17, C18) in the four molecules was situated practically the same relative to ring E. The C14–C15–C20–C21 torsion angle that characterized its position was –54.2°, –66.4°, –49.9°, and –42.2°, respectively. Rings C and E were *cis*-fused in the four molecules. An intramolecular H-bond between the carbonyl O atom and the N1H H atom was observed in these molecules and formed a six-membered ring. The parameters of the H-bonds (N1...O1 and H...O distances in Å and N1–H...O angles in degrees) in the four molecules were 2.723(4), 221, and 118 for a; 2.750(4), 2.24, and 117 for b; 2.800(3), 2.29, and 118 for c; and 2.751(4), 2.24, and 118 for d.

The indoline core in the two asymmetric molecules of **5** was similar in shape to that observed in bisindoline **3**. Ring B in both molecules adopted a strongly flattened envelope conformation with C2 deviating from the plane of the other atoms by 0.473 and 0.362 Å, respectively. Ring C in both molecules had a slightly distorted chair conformation; ring D, a chair with C14 deviating from the plane (within ±0.037 and ±0.036 Å) of the remaining atoms by 0.683 and 0.692 Å, respectively. This was possibly due to the presence of the C20=C21 double bond [1.334(3) and 1.317(4) Å]. Five-membered heterocycle E had an envelope conformation with C3 deviating from the plane (within ±0.025 and ±0.030 Å) of the other four atoms by 0.588 and 0.572 Å, respectively. The ring fusions in the two molecules were B/C-, C/E- and E/D-*cis*.

TABLE 1. Intermolecular H-bonds in the Crystal of **4**

Atom	H…O (Å)	N…O (Å)	N-H<O (°)	Transformation
N1–H (d) … O1 (b)	2.21	2.970 (3)	148	–
N1–H (b) … O1 (d)	2.30	3.004 (3)	139	–
N1–H (c) … O1 (a)	2.17	2.898 (3)	142	*1-x, -1/2+y, 1-z*
N1–H (a) … O1 (c)	2.57	3.381 (4)	158	*1-x, -1/2+y, 1-z*

TABLE 2. Principal Crystallographic Data and Characteristics of the X-ray Structure Analysis for **3**, **4**, and **5**

Structure	**3**	**4**	**5**
Molecular formula	$C_{38}H_{44}N_4 \cdot C_3H_6O$	$C_{20}H_{24}N_2O$	$C_{18}H_{22}N_2$
MW/g·mol^{-1}	614.85	308.41	266.38
System	Orthorhombic	Monoclinic	Monoclinic
Space group	P $2_12_12_1$	P 2_1	P 2_1
Z	4	4	4
a, Å	7.7043 (6)	12.899 (3)	12.143 (1)
b, Å	18.9053 (15)	18.013 (4)	7.2288 (6)
c, Å	23.5675 (16)	14.970 (3)	17.949 (2)
α	90.00	90	90
β	90.00	90.80 (3)	108.78 (1)
γ	90.00	90	90
V, Å^3	3432.7 (4)	3477.8 (12)	1491.6 (2)
ρ, g/cm^3	1.190	1.178	1.186
Crystal size, mm	0.2 × 0.3 × 0.4	0.3 × 0.4 × 0.4	0.15 × 0.15 × 0.3
2θ scan range	3.75 ≤ θ ≤ 76.21°	3.43 ≤ 75.98°	3.84 ≤ θ ≤ 71.01°
μ_{exp}, cm^{-1}	0.550	0.567	0.531
Number of reflections	5854	10524	4394
Number of reflections with $I > 2\sigma$ (I)	3475	7226	3630
R_1 ($I > 2\sigma$ (I) and total)	0.0525 (0.0904)	0.0463 (0.0686)	0.0408 (0.0505)
WR_2	0.1229 (0.1404)	0.1113 (0.1249)	0.1082 (0.1147)
GOOF	0.898	0.930	0.887
Electron-density difference peaks (e·Å^{-3})	0.23 and –0.21	0.20 and –0.16	0.15 and –0.14
CCDC	775350	775351	775352

The molecules in the crystal of **3** were situated at van-der-Waals distances. No anomalously short intermolecular contacts were observed.

The crystal structure of **4** contained bifurcated intermolecular N–H...O H-bonds. The H atom of N1 was involved simultaneously in intra- and intermolecular H-bonds. The intermolecular H-bond formed between four separate molecules situated in the asymmetric unit of the crystal lattice. As a result, two bimolecular clusters bonded through two opposing H-bonds and consisting of two pairs of b,d and a,c molecules were formed. These clusters were situated at van-der-Waals distances in the crystal. Table 1 presents the parameters of the intermolecular H-bonds formed in the clusters. Their values indicate that these H-bonds were non-equivalent, especially the weak N1–H(a)...O1(c) bond.

The crystal of **5** exhibited alternating N1–H..N4′ and N1′–H...N4 H-bonds between separate molecules in the assymetric unit of the crystal cell. The parameters of these H-bonds were 3.103(3), 2.22 Å, and 171° and 3.140(3), 2.32 Å, and 169°, respectively. These formed infinite chains of alternating separate molecules along the crystallographic *a* axis.

EXPERIMENTAL

UV spectra were recorded on a Lambda-16 spectrophotometer (Perkin—Elmer). Melting points were determined in a Boetius heating stage.

2,16,2′,16′-Tetrahydronordihydrotoxiferine (3). The Al_2O_3 column that was eluted to isolate 2,16-dihydro-19-oxonordihydrotoxiferine (**1**) and deoxydihydronorfluorocurarine was eluted further using $CHCl_3$:C_6H_6. The solvent was

distilled off. The solid was dissolved in MeOH:CH_3COCH_3. The dimer crystallized slowly as rosettes from the solution standing at room temperature, mp 287–291°C (dec.), $C_{38}H_{44}N_4$. UV spectrum (λ_{max}, nm): 261, 311.

Fluorocurarine. Norfluorocurarine (**2**, 1 g) was dissolved in MeOH (50 mL) and treated with methyliodide (1 mL). Fluorocurarine iodide precipitated upon standing, yield 1.24 g, mp 280–282°C (dec.), $C_{20}H_{23}ON_2I$. Then fluorocurarine iodide (1 g) was dissolved with heating in aqueous KOH (20 mL, 2%). Fluffy yellow needle-like crystals of fluorocurarine formed upon cooling, mp 255–256°C (dec.) (H_2O), $C_{20}H_{23}ON_2OH$. UV spectrum (λ_{max}, nm, log ε): 244 (3.96), 300 (3.56), 362 (4.16).

***N*(*β*)-Methyldihydrodefluorocurarine (4).** Fluorocurarine (0.52 g) was dissolved in aqueous MeOH (20 mL) and hydrogenated under an H_2 atmosphere in the presence of Pt catalyst for 5 h. The MeOH was evaporated to dryness. The solid was recrystallized from acetone, mp 166–167°C, $C_{20}H_{24}ON_2$, $[\alpha]_D^{20}$ +433.6° (*c* 2.61, MeOH). UV spectrum (λ_{max}, nm, log ε): 245 (4.01), 300 (3.61), 365 (4.26).

***N*(*β*)-Methyldihdyrodefluorocurarine methyliodide.** *N*(*β*)-Methyldihydrodefluorocurarine (1 g) was dissolved in MeOH (20 mL), treated with MeI (1 mL), and heated on a water bath for 6 h. The MeOH was distilled off. The solid (1.26 g) was recrystallized from acetone, mp 217–218°C, $C_{21}H_{27}ON_2I$.

16-Deformyl-2,16-dihydronorfluorocurarine (5). Norfluorocurarine (1 g) was mixed in a mortar with gray selenium (5 g) and asbestos powder (10 g). The mixture was placed into a quartz tube, heated in a tube furnace at 400°C for 1 h, mixed with sand, and extracted with benzene in a Soxhlet apparatus. The benzene extract was evaporated to dryness. The solid was dissolved in $CHCl_3$ and washed with soda solution (10%) and HCl (2%). The acidic solution was made basic with ammonia. The base was extracted with ether. The ether extract was dried over anhydrous ammonium sulfate and evaporated to dryness. The solid was recrystallized from acetone, mp 142–143°C, $C_{18}H_{22}N_2$. UV spectrum (λ_{max}, nm, log ε): 235 (3.28), 297 (3.42).

X-ray Structure Analysis. Single crystals for XSA were grown by slow evaporation of the appropriate solvents at room temperature. Unit-cell constants of crystals of **3**, **4**, and **5** were determined and refined on a CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα-radiation (300 K, graphite monochromator).

A three-dimensional data set of reflections was obtained on the same diffractometer. Absorption corrections were applied using the SADABS program [7]. Table 2 lists the principal parameters of the XSAs and refinement calculations for the structures of **3**, **4**, and **5**.

The structures were solved by direct methods using the SHELXS-97 programs and were refined using the SHELXL-97 program [8]. All nonhydrogen atoms were refined using full-matrix anisotropic least-squares methods (over F_2). Positions of H atoms were found 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} is the equivalent isotropic thermal parameter of the corresponding C atoms.

Data for the XSAs were deposited as CIF-files in the Cambridge Crystallographic Data Centre (CCDC).

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