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SYNTHESES BASED ON NORFLUOROCURARINE. 6. REACTION WITH PHENYLHYDRAZINE

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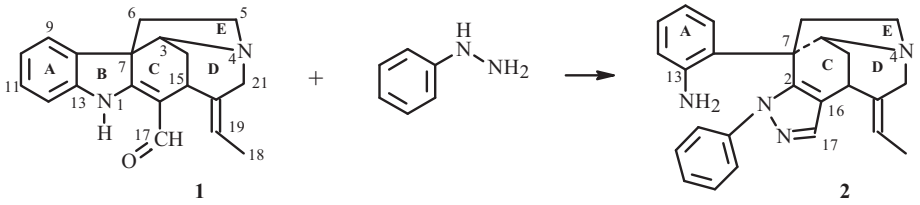
The indole alkaloid norfluorocurarine was reacted with phenylhydrazine. An x-ray crystal structure analysis found that the phenylhydrazine was bonded through its N atoms to C2 and C17 and that the N1–C2 bond of the indole core was cleaved to form an NH_2 group and a water molecule was released.

Keywords: indole alkaloid, norfluorocurarine, x-ray crystal structure analysis.

In continuation of our research [1] on the discovery of new biologically active compounds through transformation of the indole alkaloid norfluorocurarine (**1**) isolated from *Vinca erecta*, we reacted it with phenylhydrazine. The α-methyleneindoline alkaloids contain a reactive aldehyde that characteristically reacts with hydrazines to form hydrazones. However, the aldehyde in **1** is conjugated to a double bond (–HN1–C2=C16–C17H=O). Therefore, it did not form the expected phenylhydrazone. Instead, an unusual C–N bond cleavage in the indole core occurred and the new heterocyclic compound **2** was formed.



1 **2**

The reaction was carried out with the hydrated form of norfluorocurarine hydrochloride and phenylhydrazine sulfate and chloride. In both instances a single product was obtained. The phenylhydrazine N atoms were bonded to the C2 and C17 positions of **1** to form an imidazole ring. The N1–C2 bond of the indole ring of **1** was cleaved and a water molecule was released to form an exocyclic NH_2 group.

The cleavage of the N1–C2 bond in the indole ring of **1** was somewhat unusual. Not one example of a reaction destroying an indole ring has been reported in the literature on derivatives of alkaloids of this type [2–5].

Thus, we carried out for the first time a reaction that destroyed an indole ring and established the structure of the product.

Product **2** gave a methyliodide **3** in which the methyl was located on N4.

As noted above, the molecular structure of reaction product **2** was established unambiguously by an x-ray crystal structure analysis (XSA). The structure of its methyliodide (**3**) was also determined (Fig. 1). The IR and UV spectral properties of the products agreed well with the XSA data (see Experimental).

The Flack parameter [0.02(2)] found for **3** showed that asymmetric atoms C3, C7, and C15 of **1** retained their absolute configurations 3*S*, 7*R*, and 15*S* after the reaction with phenylhydrazine. As expected, the transformation did not affect these asymmetric centers.

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TABLE 1. Principal Crystallographic Parameters and X-ray Structure Characteristics for **2** and **3**

Parameter	**2**	**3**
Molecular formula	$C_{25}H_{26}N_4$	$C_{26}H_{29}N_4I$
MW, g/mol	382.50	524.43
System	Orthorhombic	Orthorhombic
Space group	P $2_12_12_1$	P $2_12_12_1$
Z	4	4
a, Å	8.0764 (2)	11.463 (5)
b, Å	9.9777 (2)	13.355 (6)
c, Å	25.4336 (5)	15.297 (6)
α	90.00	90.00
β	90.00	90.00
γ	90.00	90.00
V, Å^3	2049.54 (6)	2341.8 (17)
ρ, g/cm^3	1.240	1.487
Crystal size, mm	0.8 × 0.5 × 0.4	0.4 × 0.2 × 0.2
Scan range	4.76 ≤θ ≤ 75.69°	4.44 ≤ θ ≤ 59.96°
μ_{exp}, cm^{-1}	0.577	10.889
Number of reflections	3724	1986
Number of reflections with $I > 2\sigma(I)$	3363	1777
R_1 [$I > 2\sigma(I)$ and total]	0.0408 (0.0448)	0.0812 (0.0915)
WR_2	0.1168 (0.1227)	0.2018 (0.2190)
GOOF	1.044	1.091
Electron-density difference peaks, eÅ^{-3}	0.19 and –0.15	1.23 and –2.66
CCDC	861019	861020

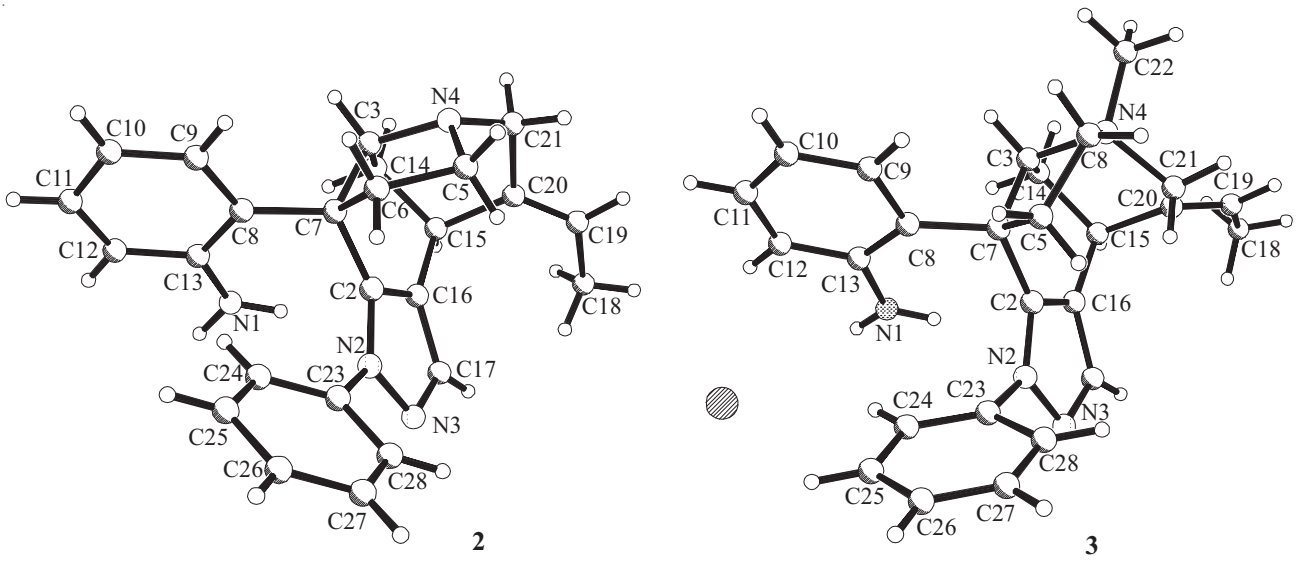

Fig. 1. Molecular structures of **2** and **3**.

The XSA results, in particular the bond lengths and angles and the experimental determination of the H atoms in **2**, enabled the structure of the reaction product to be established unambiguously. The unusual cleavage of the indole ring to form an NH_2 group and a new imidazole ring occurred because the C2=C16 [1.377(3) Å], C19=C20 [1.330(3) Å], and the hetero double bond (aldehyde O replaced by N) C17=N3 [1.316(3) Å] were retained. Furthermore, the bonds of atoms C2, C16, C17, and N3 of the newly formed ring had a planar configuration. The formation of a planar pseudo-aromatic system was also confirmed by the average lengths of the other N2–N3 [1.365(2) Å] and N2–C2 [1.375(2) Å] bonds in the ring. The planar (within ±0.014 Å) benzene ring joined through a C23–N2 bond to the pseudo-aromatic system (±0.003 Å) was twisted relative to its plane by 41.8°. This did not favor conjugation of the aromatic π-electron cloud with the pseudo-aromatic system.

Benzene ring A in **2** and the exocyclic NH_2 group were in the same plane (±0.018 Å). Ring C adopted a half-chair conformation (±0.042 Å) with C14 deviating from the plane of the remaining atoms by ±0.710 Å. Ring D formed a slightly

distorted boat (±0.076 Å) with C14 and C21 deviating from the plane of the remaining four atoms. Ring E took the 6α-envelope shape (±0.016 Å) with C6 deviating from the plane of the remaining atoms by 0.665 Å.

The geometry of **3** in the salt form (methylated at N4) was distorted from that observed in base **2** (Fig. 1). The bond lengths and angles of **3** could not be compared with those observed in **2** because of poor statistics (large uncertainties). However, conformational changes in **3** could be noticed. For example, ring D in **3** adopted a slightly distorted chair conformation although in **2** and in all previously examined fluorocurarine frameworks it typically adopted the boat conformation [1, 6–8]. The placement of the benzene ring (±0.004 Å) joined through the C23–N2 bond to the pseudo-aromatic system (±0.006 Å) also differed from that observed in **2**. It was situated at an angle of 75.9° relative to the heteroaromatic system. Ring E in **3** had the Nβ-envelope shape (±0.017 Å) with N4 deviating from the plane of the remaining atoms by 0.630 Å, which differed from that observed in **2**. However, ring C retained its half-chair conformation with C14 deviating by 0.680 Å from the plane of the other five atoms (±0.001 Å).

In conclusion, we note that the conformation change of five-membered ring E after methylation of N4 in the salt caused a change from the 6α-envelope (**2**) to the N4β-envelope (**3**). This changed the mutual position of the C5 and C6 protons, which explained easily the anomalous locations of the resonances for these protons in the PMR spectra [9].

The packing of **2** in the crystal exhibited a weak intermolecular interaction between N4 of the initial molecule and an NH_2 H atom of the molecule translated along the *a* axis [–1 + *x*, *y*, *z*] with parameters N4…N1 3.153(2), N4…H 2.34 Å, and N4…H–N1 152°. The iodide atom in **3** also approached an NH_2 H atom, forming a H-bond with parameters 4.01(2), 3.18, and 163, respectively.

EXPERIMENTAL

IR spectra were recorded in KBr pellets on a PerkinElmer Model 2000 Fourier IR spectrometer. UV spectra were measured on a PerkinElmer Lambda-16 spectrophotometer.

Compound 2. Norfluorocurarine hydrochloride (2.94 g) with one water of crystallization was dissolved in hot water (100 mL), treated with an aqueous solution (30 mL) of phenylhydrazine hydrochloride (1.7 g), heated on a water bath for 1 h, cooled, made basic with aqueous NaOH (10%), and extracted with Et_2O. The Et_2O extract was dried over anhydrous Na_2SO_4 and condensed. The resulting crystals (1.08 g) were separated and recrystallized from Me_2CO, mp 177–178°C, $C_{25}H_{26}N_4$, $[\alpha]_D^{20}$ –192.3° (*c* 1.258, MeOH). TLC R_f 0.60 ($CHCl_3$:MeOH, 1:1). UV spectrum (λ_{max}, nm, log ε): 240.7 (4.02), 294.07 (3.22). IR spectrum (ν_{max}, cm^{-1}): 3452, 3315, 3195 (NH_2), 1956 (NH_2), 1634 (C=N), 1310 (=N–).

Compound 2 Hydrochloride. Norfluorocurarine hydrochloride (1 g) with one water of crystallization was dissolved in H_2O (100 mL), treated with phenylhydrazine sulfate (0.9 g) dissolved in H_2O (20 mL), heated on a boiling-water bath for 1 h, and evaporated in vacuo after adding EtOH (100 mL). The solid was stirred with hot water (20 mL). The crystals were separated. Yield 1.61 g, mp 285–286°C (aqueous EtOH), $C_{25}H_{27}N_4Cl$, $[\alpha]_D^{20}$ –142.29° (*c* 1.962, MeOH). The base was obtained by the usual method from the hydrochloride (1.61 g). Under analogous conditions, anhydrous norfluorocurarine hydrochloride (3 g, mp 220–221°C) and phenylhydrazine hydrochloride (1.5 g) afforded **2** (1.87 g).

Methyliodide of 2. Compound **2** (640 mg) was dissolved in MeOH (3 mL), treated with methyliodide (0.5 mL), heated on a boiling-water bath for 30 min, and condensed. Crystals of **3** (700 mg) formed, mp 292–293°C, $C_{26}H_{29}H_4I$.

X-ray Crystal Structure Analyses (XSA). Single crystals of **2** and **3** for the XSA were grown by slow evaporation from aqueous alcohol at room temperature. Unit-cell constants for crystals of **2** were determined and refined on an Xcalibur Ruby CCD diffractometer (Oxford Diffraction) using Cu Kα-radiation (300 K, graphite monochromator) [10]. A three-dimensional dataset of reflections was obtained on the same diffractometer. The XSA of a crystal of **3** was performed on a STOE Stadi-4 four-circle diffractometer using Cu Kα-radiation (300 K, graphite monochromator, θ/2θ-scanning). Absorption corrections were applied in both instances by a semi-empirical methods using the SADABS program [11]. Table 1 presents the principal parameters of the XSA and refinement calculations for **2** and **3**.

The structures were solved by direct methods using the SHELXS-97 software. The structures were refined using the SHELXL-97 program. Graphics were plotted using the SHELXTL program [12]. All non-hydrogen atoms were refined by a full-matrix anisotropic least-squares method (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 atom. H atoms of the NH_2 group in **2** were found in a difference electron-density synthesis.

The XSA data were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC).

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