Synthesis of Indazole Derivatives from a *N,N*-Disubstituted 2-Halobenzoic Hydrazide. Crystal Structure of 1,2-Pentamethylene-5-nitro-1,2-dihydro-3*H*-indazol-3-one

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Thermal cyclization of the *N,N*-disubstituted 2-chlorobenzoic hydrazide **1** yields the 1,2-pentamethylene indazolone **5**, which structure is confirmed by X-ray crystallography. We suggest that the reaction proceeds through an *N,N*-alkyl shift in an initially formed indazolinium salt **2**. An intermediate 1-(5-chloropentyl)indazolol **4** has been isolated.

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The synthesis of indazole derivatives from 2-halobenzoic hydrazides is well documented [1,2]. Nevertheless, the cyclization of *N,N*-disubstituted hydrazides such as **1** has not been reported. We are now interested in this reaction that could produce, through an intermediate salt **2**, the 1,1-disubstituted indazolium betaine **3**.

In the past years some syntheses of related pyrazolium 3-oxides from aminoisocyanates and acetylenes [3], or from *N,N*-disubstituted hydrazines and electrophilic acetylenic compounds [4a,b], have been described. Several syntheses of the isomeric pyrazolium 5-oxides, from the tautomeric mixture of *N,N*-disubstituted hydrazones of β-ketoesters and β-*N,N*-hydrazinopropenoic esters [5a-e], have also been reported. We have found that thermal cyclization of **1** at 200° for 20 minutes affords a 1:9 mixture of the indazolol **4** and the indazolodiazepine **5** in 85% yield. Since compound **4** forms a red-orange sodium salt solution with diluted sodium carbonate, it can be easily extracted from the reaction mixture. When pure compound **4** is heated at 200° for 25 minutes, hydrogen chloride is evolved yielding **5** in 90% yield.

1-(5-Chloropentyl)-5-nitro-1*H*-indazol-3-ol (**4**).

This compound had mp 184-186°, toluene; ^{1}H nmr (deuteriochloroform, tetramethylsilane): δ 1.2-2.1 (m, 6H, $C(CH_2)_3C$), 3.52 (t, 2H, CH_2Cl), 4.25 (t, 2H, CH_2N); ^{13}C nmr (DMSO-d_6, tetramethylsilane): δ 45.46 (t, CH_2Cl), 48.70 (t, CH_2N), 157.57 (s, C-3); ir (Nujol): 3300-2100 br, 1620, 1600, 1568 cm^{-1}; ms: (75 eV) 283 (M^+, 17%), 248 (15%), 193 (13%), 192 (100%), 146 (33%).

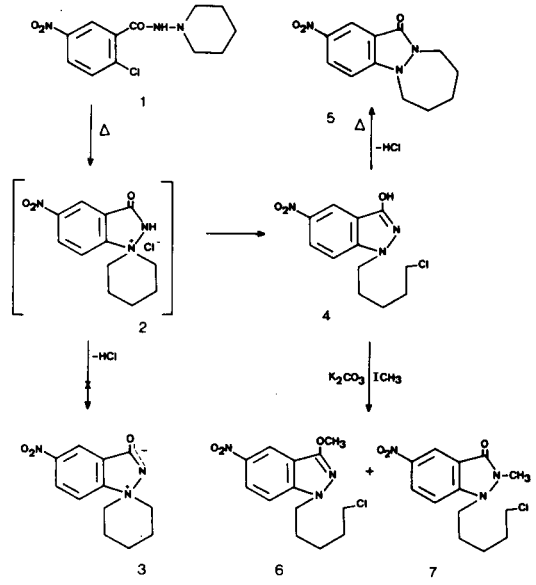
Anal. Calcd. for $C_{12}H_{14}ClN_3O_3$: C, 50.80; H, 4.97; N, 14.81; Cl, 12.50. Found: C, 50.96; H, 5.23; N, 14.86; Cl, 12.59.

1,2-Pentamethylene-5-nitro-1,2-dihydro-3*H*-indazol-3-one (**5**).

This compound had mp 157-159°, 1-propanol; ^{1}H nmr (deuteriochloroform, tetramethylsilane): δ 1.86 (br, 6H, $C(CH_2)_3C$), 4.15 (br, 4H, CH_2Cl + CH_2N); ir (Nujol): 1670 (CO), 1630 cm^{-1}; ms: (75 eV) 248 (15%), 247 (M^+, 100%), 218 (13%), 201 (15%), 192 (24%), 191 (21%), 146 (10%), 89 (11%).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.58; H, 5.42; N, 16.94.

Scheme 1



We assumed that the reaction takes place through a non isolated salt **2** as shown in Scheme 1. Similar piperidine ring opening followed by ring expansion to a diazepine has been observed in some 1,1-pentamethylenepyrazolinium salts [4a,b]. Other cases of N-N, or N-C alkyl shifts (Stevens or Wawzoneck rearrangement) in pyrazolinium betaines [6] or in spiropiperidinium salts [7a,b] have also been reported.

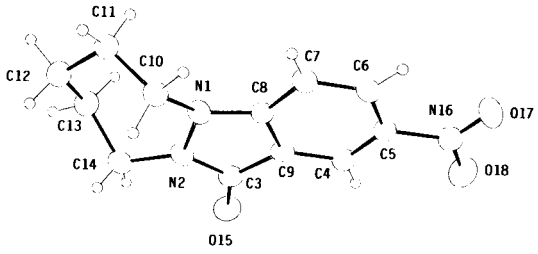


Figure 1. A view of the molecular structure of **5** with the atomic numbering. Selected torsional angles (°):

C(10)—(N(1)—N(2)—C(14)	27.6(4)
N(1)—N(2)—C(14)—C(13)	44.9(4)
C(12)—C(13)—C(14)—N(2)	−81.4(4)
C(11)—C(12)—C(13)—C(14)	69.0(4)
C(10)—C(11)—C(12)—C(13)	−57.5(5)
N(1)—C(10)—C(11)—C(12)	71.8(4)
N(2)—N(1)—C(10)—C(11)	−78.6(4)
N(2)—N(1)—C(8)—C(9)	4.1(3)
N(1)—C(8)—C(9)—C(3)	−1.3(4)
N(2)—C(3)—C(9)—C(8)	−2.1(3)
N(1)—N(2)—C(3)—C(9)	4.7(3)
C(8)—N(1)—N(2)—C(3)	−5.7(3)

Methylation of compound **4** with methyl iodide/potassium carbonate in boiling acetone yields a 3:2 mixture of *O*- and *N*-methylated products **6** and **7**, which can be easily separated by column chromatography over silica gel using a 95:5 chloroform/ethanol mixture as eluent.

1-(5-Chloropentyl)-3-methoxy-5-nitro-1*H*-indazole (**6**).

This compound had mp 55-57°, 2-propanol; ^{1}H nmr (deuteriochloroform, tetramethylsilane): δ 1.1-2.1 (m, 6H, $C(CH_2)_3C$), 3.49 (t, 2H, CH_2Cl), 4.12 (s, 3H, CH_3O), 4.18 (t, 2H, CH_2N); ir (Nujol): 1620, 1595, 1550 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}ClN_3O_3$: C, 52.44; H, 5.42; N, 14.11; Cl, 11.91. Found: C, 52.31; H, 5.56; N, 14.28; Cl, 12.13.

1-(5-Chloropentyl)-2-methyl-5-nitro-1,2-dihydro-3*H*-indazol-3-one (**7**).

This compound was purified by preparative tlc on silica-gel plates; it is a thick orange oil which solidifies on standing, mp 83-85°; ^{1}H nmr (deuteriochloroform, tetramethylsilane): δ 1.2-1.9 (m, 6H, $C(CH_2)_3C$), 3.46 (t, 2H, CH_2Cl), 3.50 (s, 3H, CH_3N), 3.92 (t, 2H, CH_2N); ir (Nujol): 1670 (CO), 1625 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}ClN_3O_3$: C, 52.44; H, 5.42; N, 14.11; Cl, 11.91. Found; C, 52.54; H, 5.63; N, 14.03; Cl, 11.75.

The structure of **4**, **6**, and **7** was deduced from analytical, spectral [1,4b], and chemical evidences. Since little information was available from the spectral data of **5**, X-ray diffraction measurements were done in order to establish unambiguously the indazolodiazepine structure of this compound [8].

The final X-ray model of **5** is shown in Figure 1 together with several torsional angles. All bond distances have normal values. The geometry around N(1) deviates from planarity, the sum of bond angles being 354.9(3)°, while that around N(2) is 359.2(3)°. Bond angles C(9)-C(3)-O(15) = 131.2(3)° and N(2)-C(3)-O(15) = 124.2(3)° are significatively different, probably due to the approach O(15)...H(4) of 3.05(3)Å and O(15)...H(7)^i in 2.43(3) Å [9], O(15)...C(7)^i = 3.252(4)Å, < O(15)...H(7)^i-C(7)^i = 151(3)° (i = 1 + x,y,z). The NO_2 group makes an angle of 1.7(3)° with the phenyl ring. The five membered ring conforms as a twist with the binary axis through N(1)-N(2), distorted to an envelope at N(2) [10]. The seven membered ring shows a "chair" (C_1) with a quasi mirror plane through N(1)-N(2), distorted towards a "twist chair" (TC_1) [11] with a quasi binary axis through N(2).

Work in this area is currently being done in order to extend the reaction to other *N,N*-disubstituted 2-halobenzoic hydrazides. Attempts to isolate the intermediate indazolinium salt **2** are also in progress.

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[8] Crystal data of compound **5**: $C_{12}H_{13}N_3O_3$; M = 247.25; monoclinic, space group $P2_1/c$, a = 7.2465(1), b = 20.0005(13), c = 8.3068(2) Å, β = 105.543(2)°, U = 1159.91(8)Å^3, Z = 4, Dc = 1.416 g cm^{-3}, F(000) = 520, CuKα radiation, crystal dimensions 0.3 × 0.3 × 0.2 mm^3; no absorption correction was applied. 1969 independent reflections were collected up to θ = 65°, on a PW 1100 diffractometer, of which 1350

($I > 3\sigma(I)$) were used in the refinement (215 variables) to give R = 0.053 and Rw = 0.059, maximum ratio shift/error 0.06, highest peak in final $\Delta\varrho$ map 0.17 e Å^{-3}. The hydrogen atoms were placed at their expected position, but they were checked in a Fourier difference map and were included as fixed isotropic contributors in the refinement; [a] "International Tables for X-Ray Crystallography", Vol 4, Kynoch Press, Birmingham, England, 1974; [b] P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, "Multan 80 System", University of York, England, 1980; [c] J. M. Stewart, P. A. Machin, C. W. Dickinson, H. L. Ammon, H. Heck and H. Flack, "The X-Ray System", Technical Report TR-446, Computer Science Center, University of Maryland, USA, 1976.

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