N,*N*,5-Trimethyl-1*H*-[1]benzothiopyrano[4,3,2-*cd*]-indazole-1-ethanamine - A Novel Heterocycle

A. Paul Krapcho* and Simon N. Haydar

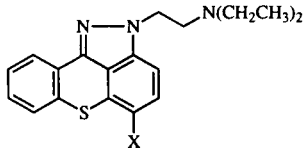
Department of Chemistry, University of Vermont, Burlington VT 05405

Received March 5, 1997
Revised July 11, 1997

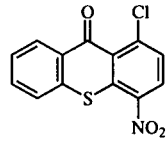
Treatment of thioxanthenone **6** with *N*-(2-dimethylaminoethyl)hydrazine led to the benzothiopyranoindazole **3**, a novel heterocycle, along with the expected compound **8**.

J. Heterocyclic Chem., **34**, 1637 (1997).

Benzothiopyranoindazoles related to **1a** are currently undergoing clinical evaluations as antitumor agents [1,2,3]. Several chemotypes such as **1b** have also been evaluated as antitumor and antischistosomal agents [4,5] (Figure 1).



1a. X = $NH(CH_2)_2NR_1R_2$
b. X = CH_3
c. X = NO_2



2

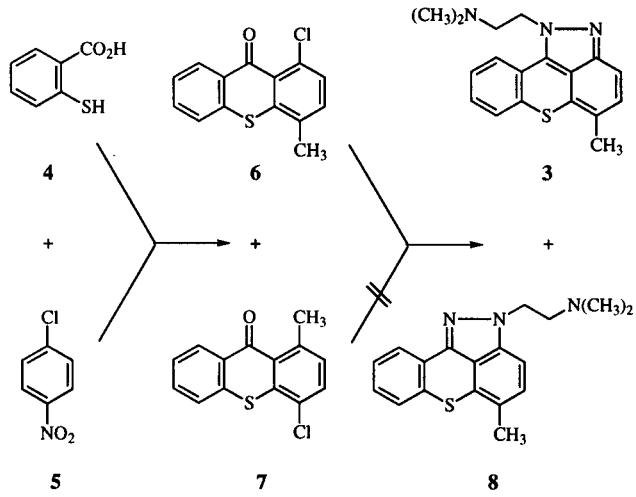
Figure 1.

The synthetic methodology utilized for the construction of the pyrazole moiety involved treatment of thioxanthenone **2** [1] with *N*-2-(diethylaminoethyl)hydrazine to afford **1c**. Functional group elaboration of **1c** subsequently led to chemotypes **1a**. In these displacement reactions, the pyrazole ring arises *via* a S_NAr substitution of the chloride by the nitrogen atom of the hydrazine bearing the substituent followed by cyclodehydration.

We wish to report the isolation and characterization of **3** (Scheme 1), a novel heterocycle in which the unsubstituted nitrogen of the hydrazine displaced the chloride anion.

Treatment of thiosalicylic acid (**4**) with 4-chlorotoluene (**5**) in the presence of concentrated sulfuric acid at room temperature for 18 hours [6,7] led to the regioisomers **6** and **7** (1:1 ratio based on ^1H nmr integration of methyl singlets). Several attempts to separate these regioisomers by crystallization or chromatography proved to be unsuccessful. Since only **6** would undergo a facile S_NAr substitution of the chloride, the regioisomeric mixture of **6** and **7** was heated with *N*-(2-dimethylaminoethyl)hydrazine in an Ace-pressure tube for four hours at 165°. This led to a mixture of products along with the unreactive regioisomer **7**. Column chromatography led to the separation of **7** along with a mixture of two compounds. This mixture

Scheme 1



was separated by chromatography using a chromatotron to yield **3** and **8**. The structure of these products was established using spectroscopic methodology (^1H nmr, ^{13}C nmr, 2D-COSY and 2D-NOESY).

The ^1H nmr of **3** and of **8** exhibited distinctly different chemical shifts. For example, the α-CH_2 protons of **3** and **8** resonated at δ 4.78 and δ 4.38, respectively (Figure 2). The deshielding effect of these protons shown by **3** might be rationalized by the proximity of the pyridine ring.

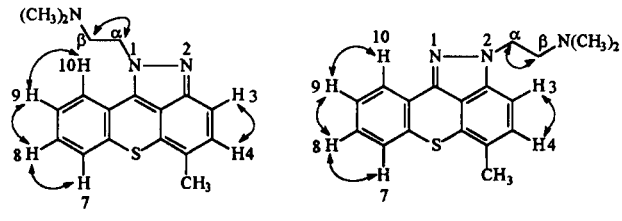


Figure 2. 2D-COSY for compounds **3** and **8**.

The 2D-COSY of **3** and **8** reveal clear interactions between H-9, H-10; H-9, H-8; H-8, H-7; H-3, H-4 and α-CH_2, β-CH_2. The structure of **3** was unequivocally elucidated from the NOESY nmr experiment. The observed NOEs between H-10, α-CH_2 and H-10, β-CH_2 are only consistent with the isomer **3**. In addition, the NOESY nmr spectrum for compound **3** revealed correlations between α-CH_2, β-CH_2; $N(CH_3)_2$, α-CH_2 and H-4, aromatic methyl (Figure 3). The NOESY nmr of **8** revealed NOEs between H-3, α-CH_2; α-CH_2, β-CH_2; H-3, β-CH_2; H-4, aromatic methyl and α-CH_2, $N(CH_3)_2$. The interactions of the *ortho* and *meta* protons in **3** and **8** were poorly resolved.

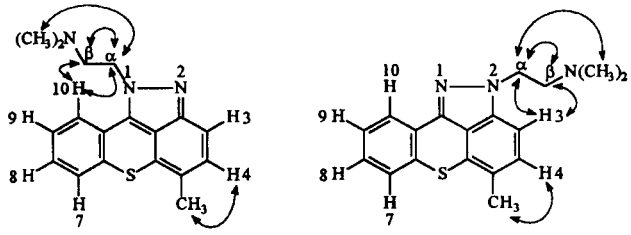


Figure 3. The NOEs detected for compounds **3** and **8**.

EXPERIMENTAL

Melting points were determined on Thomas-Hoover apparatus and are uncorrected. Proton nmr were run on a Bruker ARX-500 pulsed Fourier transform spectrometer. Baker analyzed 230-400 mesh silica gel was used for flash chromatography. Microanalysis were performed by Robertson Microlit Laboratory, Madison, NJ.

1-Chloro-4-methylthioxanthen-9-one (**6**) and 1-Methyl-4-chlorothioxanthen-9-one (**7**).

A mixture of 4-chlorotoluene (1.64 g, 12.96 mmoles), thiosalicylic acid (1.00 g, 6.48 mmoles) and concentrated sulfuric acid (18 ml) was stirred at room temperature for 18 hours and poured onto ice (200 ml). The yellow solid which separated was collected by filtration and suspended in 7% ammonium hydroxide. Steam was bubbled through the mixture for 0.5 hour and the product was collected by filtration. The solid was washed with cold water and air dried to give 1.30 g (77%) as a mixture of **6** and **7** (1:1 ratio as calculated from the methyl absorption areas at δ = 2.49 and 2.88 in the ^{1}H nmr spectrum), mp 147-150°.

N,N,5-Trimethyl-1*H*-[2]benzothiopyrano[4,3,2-*cd*]indazole-2-ethanamine (**8**) and *N,N*,5-Trimethyl-1*H*-[1]benzothiopyrano-[4,3,2-*cd*]indazole-1-ethanamine (**3**).

A mixture of **6** and **7** (0.50 g, 0.96 mmole of each of the regioisomers) and *N*-2-(dimethylaminoethyl)hydrazine (1.18 g, 11.5 mmoles) was heated at 165° for 5 hours. Upon cooling the red solution, a yellow suspension was formed which was diluted with crushed ice (20 ml) containing potassium hydroxide (50%) (2 ml). The latter aqueous mixture was extracted with chloroform (20 ml, 3 times). The organic layer was separated, washed with brine, dried with magnesium sulfate and concentrated to a yellow oil. The residue was flash chromatographed over silica gel eluting first with methanol:dichloromethane (0.5:99.5) with a gradual change to methanol:dichloromethane (3:97) which eluted the products. The solvents were removed to yield a residue, 0.28 g (quantitative yield based on the composition of the starting material). From the ^{1}H nmr integration areas of the aromatic protons, this product consisted of two compounds in a ratio of 9:1. This mixture was then separated, using a chromatotron on a silica gel plate thickness of 2 mm, eluting with methanol:dichloromethane (4:96), to give initially **3**, 0.025 g, mp 100-101°; ^{1}H nmr (deuteriochloroform): δ 7.75 (d, J_{HH} = 7.7 Hz, 1H); 7.35 (d, J_{HH} = 7.6 Hz, 1H); 7.22 (m, 1H); 7.16 (m, 1H); 7.09 (d, J_{HH} = 8.6 Hz,1H); 6.96 (d, J_{HH} = 8.6 Hz, 1H), 4.78 (t, J_{HH} = 7.7 Hz, 2H); 2.89 (t, J_{HH} = 7.7 Hz, 2H); 2.37 (s, 6H); 2.14 (s, 3H). ^{13}C nmr (deuteriochloroform): δ 145.9, 135.7, 131.1, 131.0, 127.9, 127.5, 126.6, 124.5, 124.4, 123.2, 121.4, 119.3, 111.0, 58.5, 52.0, 45.9 [$N(CH_3)_2$], 17.6.

Anal. Calcd. for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.59. Found: C, 69.63; H, 6.31; N, 13.65.

Further elution led to **8**, 0.23 g, mp 75-76°; ^{1}H nmr (deuteriochloroform): δ 8.06 (d, J_{HH} = 6.5 Hz, 1H), 7.31 (d, J_{HH} = 7.06 Hz, 1H), 7.24-7.19 (m, 2H), 7.05 (d, J_{HH} = 8.3 Hz, 1H), 6.85 (d, J_{HH} = 8.3 Hz, 1H), 4.38 (t, J_{HH} = 7.0 Hz, 2H), 2.82 (t, J_{HH} = 7.0 Hz, 2H), 2.31 (s, 6H), 2.22 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 140.7, 139.1, 133.8, 130.4, 126.8, 126.6, 126.5, 126.1, 123.8, 121.0, 120.5, 103.8, 58.3, 47.6, 45.6 [$N(CH_3)_2$], 17.3.

Anal. Calcd. for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.59. Found: C, 69.86; H, 6.17; N, 13.82.

Acknowledgment.

We wish to thank Boehringer Mannheim Italia, Monza, Italy, for financial support.

REFERENCES AND NOTES

[1] H. D. H. Showalter, M. M. Angelo, E. M. Berman, G. D. Kanter, D. F. Ortwine, S. G. Ross-Kesten, A. D. Sercel, W. R. Turner, L. M. Werbel, D. F. Worth, E. F. Elslager, W. R. Leopold and J. L. Shillis, *J. Med. Chem.*, **31**, 1527 (1988).

[2] V. G. Beylin, N. L. Colbry, A. B. Giordani, O. P. Goel, D. R. Johnson, R. L. Leeds, B. Leja, E. P. Lewis, D. M. Lustgarten, H. D. H. Showalter, A. D. Sercel, M. D. Reily, S. E. Uhlendorf and K. A. Zisek, *J. Heterocyclic Chem.*, **28**, 517 (1991).

[3] D. W. Fry and J. A. Besserer, *Mol. Pharmacol.*, **33**, 84 (1988).

[4] C. Bailly and M. J. Waring, *Biochemistry*, **32**, 5985 (1993).

[5] M. Jahangir, P. B. Hulbert and J. A. Grundy, *J. Pharm. Pharmacol.*, **29** 78P (1977); (Suppl., Br. Pharm. Conf. 1977).

[6] H. Mauss, *Chem. Ber.*, **81**, 19 (1948).

[7] S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4296 (1952).