A Simple Synthesis of 1-Imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole—A Novel Heterocyclic System

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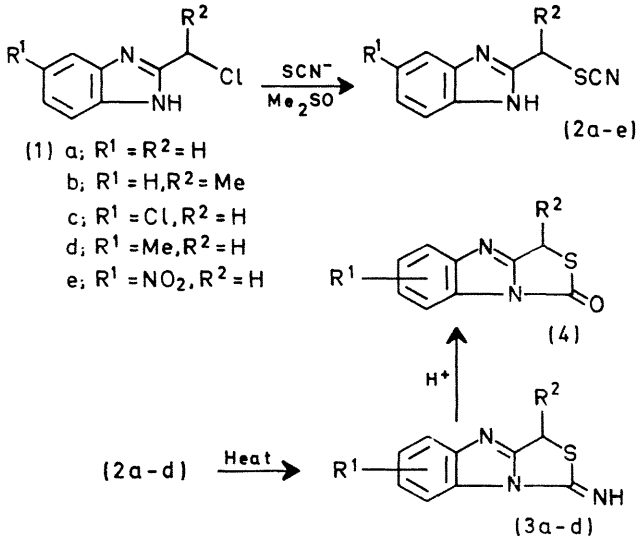
Summary Intramolecular cyclization of 2-thiocyanatoalkylbenzimidazoles under mild conditions gives the novel 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles in good yields.

SEVERAL instances of biological activity of benzimidazole derivatives have been reported.[1] We report here the synthesis of the 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole ring system (**3**).

2-Chloromethylbenzimidazole[2] was prepared from *o*-phenylenediamine and chloroacetic acid, and treated with NH_4SCN in refluxing MeOH to give, instead of the expected thiocyanato-derivative (**2a**), a crystalline isomer of (**2a**) (84%), m.p. 169—170°†; *m/e* 189 (M^+). Its n.m.r.‡ τ 5·30 (s, CH_2S), 2·07—2·70 (3H, m, ArH), 1·76—2·00 (m, 8-H), and 0·26br (s, NH); i.r. (Nujol) 3310 (NH), no band at 2160 cm^{-1} (SCN); and u.v. ν_{max} (EtOH) 226 (ϵ 23,400), 275 (2590), and 285 (5380) nm spectra were compatible with the tricyclic structure (**3a**). This structure was confirmed by mild acid hydrolysis of (**3a**) to the cyclic thiocarbamate (**4**), independently synthesized from 2-mercaptomethylbenzimidazole and phosgene in the presence of pyridine at 0°; m.p. 212—214°, *m/e*/ 190 (M^+); τ 5·18 (s, CH_2S) and 2·00—2·47 (4H, m, Ar*H*). The intermediate (**2a**) in the formation of (**3a**) could be isolated when the reaction was carried out in Me_2SO at room temperature, m.p. 153—154°; τ 5·38 (s, CH_2) and 2·33—2·91 (4H, m, Ar*H*). Refluxing of a methanolic solution of (**2a**) for a short period gave (**3a**).

This simple, high-yield, one-step synthesis has been extended to derivatives (**3b—d**). Attempts to cyclize the nitro-derivative (**2e**) failed, even under forcing conditions (100°; DMF; several hours). This inertness could be



attributed to the decreased nucleophilicity of the secondary nitrogen atom. In the synthesis of (**3b**), the methanolysis

product, 2-(1-methoxyethyl)benzimidazole, was also isolated by chromatography (10%) m.p. 195—196°, τ ($CDCl_3$), 8·40 (d, J 6 Hz, Me), 6·58 (s, OMe), 2·27 (d, J 6 Hz, CH), and 2·34—2·86 (4H, m, Ar*H*).

As expected,[3] ring-closure of (**2c**) furnished a 1 : 1 mixture of 6- and 7-isomers, separable by fractional crystallization from ether, which showed identical chemical shifts in their n.m.r. spectra. Coupling constants, however, allowed unambiguous assignment. The 6-isomer, as expected, showed *ortho*-coupling (J 6—10Hz) for the 8-H, whereas this proton in the 7-isomer, as predicted, exhibited only *meta*-coupling (J 1—3 Hz). Furthermore, 8-H was consistently the most downfield signal, owing to the deshielding effect of the NH group. Thus, the isomer of m.p. 158—159°, [τ 5·32 (s, CH_2S), 2·62 (q, J 8·5 and 2·0 Hz, 7-H), 2·25 (d, J 2·0 Hz, 5-H), 1·96 (d, J 8·5 Hz, 8-H), and 0·26 (s, NH)] was identified as the 6-isomer, and the less soluble compound, m.p. 161—162°, as the 7-isomer [τ 5·32 (s, CH_2S), 2·62 (q, J 8·5 Hz, 6-H), 2·29 (d, J 8·5 Hz, 5-H), 1·96 (d, J 2 Hz, 8-H), and 0·29 (s, NH). A similar isomeric mixture was obtained in the cyclization of (**2d**), as shown by n.m.r. spectroscopy.

In view of the observed stability of this ring system, we are currently investigating the nucleophilic character of the thioimino-carbamate group.

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† Satisfactory analytical data were obtained for all new compounds where m.p.'s are specified.

‡ If not stated otherwise, the spectra (60 MHz) were determined in $(CD_3)_2SO$.

[1] *E.g.* (a) cholesterol-lowering: M. L. Black, G. Rodney, and D. B. Capps, *Biochem. Pharmacol.*, 1968, **17**, 1083; (b) antiviral: I. Tamm, H. J. Eggers, R. Bablaninan, A. F. Wagner, and K. Folkers, *Nature*, 1969, **223**, 785; (c) anthelmintic: H. D. Brown, A. R. Matzuk, I. R. Ilves, L. H. Peterson, S. A. Harris, L. H. Sarett, J. R. Egerton, J. J. Yakstis, W. C. Campbell, and A. C. Cuckler, *J. Amer. Chem. Soc.*, 1961, **83**, 1764.

[2] A Bloom and A. R. Day, *J. Org. Chem.*, 1939, **4**, 14.

[3] K. Hofmann, 'The Chemistry of Heterocyclic Compounds, Imidazole and Its Derivatives, Part I, Interscience, New York, 1953, p. 225.