Synthesis of 1,2-Disubstituted Benzimidazoles involving an *N*-Heteroparaffinic Ring Cleavage

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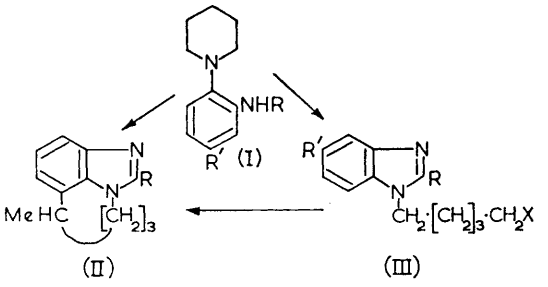
WE have shown[1] that hot polyphosphoric acid converts *N*-acylaminophenyl-heterocycles (*e.g.*, I; R = Ac, R′ = H) into benzimidazoles (II; R = Me) with fission of the *N*-heteroparaffinic ring. We have now found that a similar cleavage can be effected under very mild conditions yielding benzimidazoles with reactive substituents in the 1- and the 2-positions and, if required, also in the benzene ring. For instance, a 0·3M-hydrochloric acid solution of the *o*-aminophenylpiperidine (I; R = H, R′ = H, Cl, or NO_2) when stirred at room temperature in presence of chloral hydrate and hydroxylamine hydrochloride deposited the 1-(5-chloro-n-pentyl)benzimidazole-2-aldoxime (III;



R = CH:NOH; R′ = H, Cl, or NO_2; X = Cl) as hydrochloride which gave the crystalline, free base

TABLE

Chemical shifts (τ-values) of protons in the benzimidazoles (III)

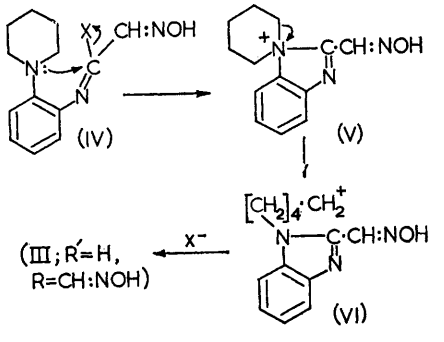
Benzimidazole (III)				Group								
R	R′	X	M.p.	N·CH_2[e]	X·CH_2[e]	$[CH_2]_3$	CH: in R	OH in R	4-H	5-H	6-H	7-H
CH:NOH[a]	H	Br	164°	5·42	6·52	7·9—8·7	1·67	−2·0	2·3		(2·67)	2·5
CH:NOH[a]	H	Cl	163	5·45	6·50	7·9—8·7	1·67	−1·9	2·3		(2·67)	2·5
CH:NOH[a]	NO_2	Cl	191	5·37	6·40	7·9—8·7	1·65	−2·3	1·45[f]	—	1·78	2·20
CH:NOH[a]	Cl	Cl	195	5·44	6·41	7·9—8·7	1·68	−2·1	2·27[g]	—	2·67	2·37
CH:NNH·CO·NH_2[a,c]	H	Cl	194	5·43	6·47	7·9—8·7	1·80	—	2·3		(2·7)	
CN[b]	H	Cl	75	5·60	6·48	7·8—8·6	—	—	2·13		(2·52)	
CO·NH_2[b]	H	Cl	130	5·24	6·46	7·8—8·6	—	—	2·18		(2·56)	
CO·NH_2[b]	H	ONO_2	113	5·26	5·57	7·8—8·6	—	—	2·18		(2·56)	

[a] In $CDCl_3$ + $(CD_3)_2SO$
[b] In $CDCl_3$
[c] NH (τ −0·7), NH_2 (τ 3·93)
[d] 2NH (2·2 and *ca.* τ 4)
[e] Triplets J 6—7 c./sec.
[f] $J_{4,6}$ 2 c./sec., $J_{6,7}$ 8·8 c./sec.
[g] $J_{4,6}$ 2 c./sec., $J_{6,7}$ 8·5 c./sec.

with ammonia solution. Yields were 20, 30, 40, and 60% after 1, 2, 7, and 14 days, respectively. The oxime (III; R = CH:NOH, R′ = H) was of the *anti*-configuration as it was quantitatively converted into the cyanobenzimidazole (III; R = CN, R′ = H) on treatment with hot acetic anhydride followed by aqueous alkali. A possible stereochemical conversion during the reaction with acetic anhydride is unlikely as benzimidazole-2-aldoxime itself, in which the oxime function is introduced by a different route,[2] gave only the *O*-acetyl derivative under similar conditions and must therefore be the *syn*-form.

Instead of hydroxylamine, other carbonyl reagents could be used: semicarbazide or phenylhydrazine gave the corresponding semicarbazone or phenylhydrazone of the benzimidazole aldehyde (III; R = CH:N·NH·CO·NH_2 or CH:N·NHPh, R′ = H, X = Cl) and in the former case also some semicarbazone of the carbamoyl formaldehyde (I; R = CO·CH:N·NH·CO·NH_2, R′ = H) m.p. 198°, identified by analysis and nuclear magnetic resonance spectrum: chemical shifts of τ = 8·33 ($[CH_2]_3$), 7·19 (CH_2·N·CH_2), 2·59 (CH:N), 2·90 (3-, 4-, and 5-H), 1·68 (6-H), 3·85 (NH_2), 0·22 (NH) and −0·97 (=NH).

Our benzimidazole synthesis is analogous to that described by Somin and Petrov[3] who in an attempt to prepare *o*-dimethylaminoisonitrosoacetanilide from *NN*-dimethylaniline, hydroxylamine, and chloral hydrate obtained 1-methylbenzimidazole-2-aldoxime. We found that the use of ammonium sulphate and sulphuric acid instead of hydrochloric acid produces the isonitrosoacetanilide (*e.g.*, I; R = CO·CH:NOH, R′ = H) in good yields rather than the benzimidazole. Since the isonitroso-compound cannot be converted into the benzimidazole under the reaction conditions it is not a



precursor of the heterocycle. When bromal replaces chloral in the reaction and sodium chloride is added to provide an excess of chloride ion, chloropentylbenzimidazole (III; R = CH:NOH, R′ = H, X = Cl) predominates over the bromo-analogue (III; R = CH:NOH, R′ = H, X = Br). This is suggestive of an intermediate possibly (VI; *cf.* below) for which the halogen ions can compete since the product itself (III; R, R′ as before, X = Br) did not exchange its halogen under the conditions of the reaction.

To explain the formation of benzimidazole it is reasonable to postulate that the intermediate (IV; X = Cl) formed from amine and chloral oxime is nucleophilically attacked by the tertiary nitrogen as indicated to give the imidazole (V). This is followed by opening of the heteroparaffinic ring with formation of a carbonium ion (VI) which by combining with a halogen gives the product (*e.g.*, III; R = CH:NOH, R′ = H, X = Cl). The slowness of the reaction is probably due to the small concentration of "unprotonated" nitrogen in the acidic medium. We consider the intermediate (IV; X = halogen) to be common to both the

benzimidazole (III) and the isonitrosoacetanilide (I; R = CO·CH:NOH, R′ = H) routes. In the latter, however, the halogen (X in IV) is hydrolysed when sulphuric acid is used possibly *via* the sulphate (IV; X = O·SO_3H).

This new type of benzimidazole (III) is a versatile synthetic intermediate. For instance, treatment of the oxime (III; R = CH:NOH, R′ = H, X = Cl) or the nitrile (III; R = CN, R′ = H, X = Cl) with hot polyphosphoric acid gave the amide (III; R = $CONH_2$, R′ = H, X = Cl). This one prolonged heating in polyphosphoric acid cyclised on to the benzene ring with elimination of hydrogen chloride and loss of the amide group to give the tricyclic compound (II; R = H), identical with an authentic specimen.[1b] The chlorine in the side chain (III; R = $CONH_2$, R′ = H, X = Cl) was replaceable on treatment with a hot ethanolic solution of silver nitrate to give an ester (III; R = CO·NH_2, R′ = H, X = ONO_2).

All new compounds had the correct analysis, and n.m.r. data relevant to structural assignment are tabulated (*cf.* Table 1). The preparative scope of this reaction is under investigation.

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[1] (a) R. Garner and H. Suschitzky, *J. Chem. Soc.* (*C*), **1966**, **1572**; (b) O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 1964, 2609.
[2] H. R. Hensel, *Chem. Ber.*, 1965, **98**, 1325.
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