Tetrahedron Letters No.23, pp. 2219-2222, 1967. Pergamon Press Ltd. Printed in Great Britain.

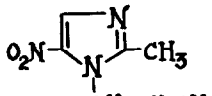
UNEXPECTED FORMATION OF 2-NITRO- AND 2,2'-AZOBENZIMIDAZOLES.

A.F. Pozharskii, E.A. Zvezdina, A.M. Simonov.

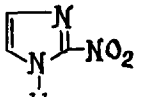
Rostov-on-Don State University, USSR.

(Received 22 December 1966)

Recently it has been shown that nitroimidazoles possess high antimicrobical and antibiotic activity. "Metronidazole" (I)[1] and "azomycine" (II)[2] are two important members belonging to this class of imidazole derivatives. The synthesis of azomycine and its derivatives has been carried out Lancini et al[3,4] and Beaman et al.[5]

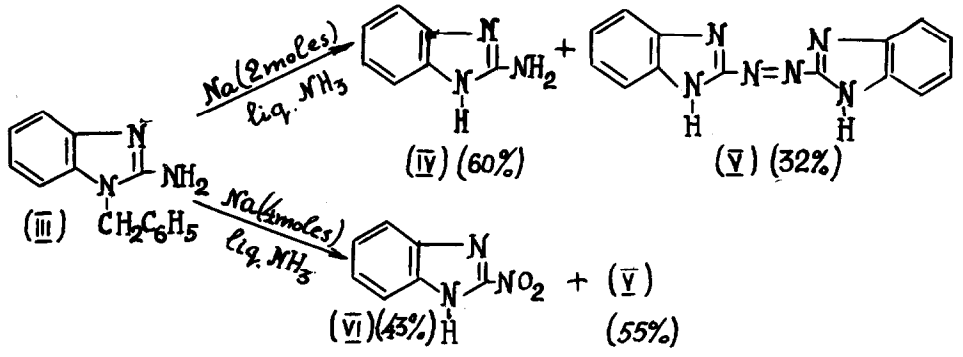


(I)



(II)

2-Nitrobenzimidazole, close analogues of azomycine, however, are unknown. A synthesis of 2-nitrobenzimidazole has been developed in this laboratory. By the interaction of readily accessible I-benzyl-2-aminobenzimidazole (III)[6] with 2 moles of sodium in liquid ammonia in addition to the expected 2-aminobenzimidazole (IV), 2,2'-azobenzimidazole (V) has been obtained in good yield. However, with 4 moles of sodium 2-nitrobenzimidazole (VI) resulted in addition to (V).



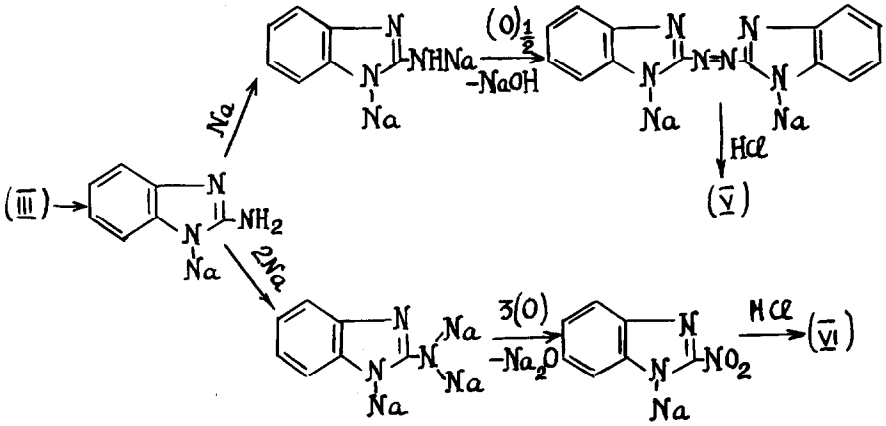
The structure of (V) and (VI) is followed by this reduction by tin and hydrochloric acid to (IV). This is further supported by elemental analysis, molecular weight determination and spectroscopic data.

2,2'-Azobenzimidazole, $C_{14}H_{10}N_6$, orange-red crystals (from dimethylformamide with water), m.p.$>350^{\circ}$; λ max: (in 0,1 M NaOH) 420 mμ (lg ε 4,31); (in 8,25 M H_2SO_4) 505 mμ (lg ε 4,53).

2-Nitrobenzimidazole, $C_7H_5N_3O_2$, yellow crystals purified by recrystallisation from benzene or methanol, reprecipitation from alkaline solution, sublimation (190-195°, 3mm) or chromatography over alumina (acetone-chloroform, 1:1). M.p. 258° (decomp.); λ max: (in methanol) 342 mμ (lg ε 4,00); (in 0,1 M NaOH) 365 mμ (lgε 3,93); (in 8,25 M H_2SO_4) 346 mμ (lg ε 4,01).

2-Nitrobenzimidazole is strongly acidic, soluble in alkali and ammonia solutions, forms stable sodium salt (m.p.$>350^{\circ}$), which can be readily alkylated forming 1-alkyl-2-nitrobenzimidazoles in good yields. 2,2'-Azobenzimidazole is less acidic than 2-nitrobenzimidazole and the advantage is taken of this property in their separation.

The reaction of 1-benzyl-2-aminobenzimidazole with sodium in liquid ammonia is believed to involve the following mechanism:



Debenzylation of (III) followed by the formation of disodio (VII) and trisodio (VIII) derivatives of 2-aminobenzimidazole and their oxidation by oxigen of air to (V) and (VI). This mechanism is confirmed by the formation

of 2-nitrobenzimidazole when four moles of sodium is used. Further it has been observed that the reaction of I-benzyl-2-aminobenzimidazole with 4 moles of reagent in the current of dry nitrogen results in the formation of only 2-aminobenzimidazole in 78% yield. The results of reaction of some 2-aminobenzimidazoles with 4 moles of sodium in liquid ammonia are given in Table I:

TABLE I

Benzimidazole	Yield, %	
	2,2'-Azoderivative	2-Nitroderivative
2-amino-	2	I,6
I-benzyl-2-amino-	55	43
I-methyl-2-amino-	I,5*	-
I-ethyl-2-amino-	0,7**	-

*M.p. 289-290° (from ethanol);

**M.p. I97° (from ethylacetate).

From these results benzylsodium seems to play an important role in the formation sodio derivatives (VII) and (VIII). Another important factor seems to be the smaller ease of oxidation anions of I-substituted 2-aminobenzimidazoles. In fact sodio derivatives from I-alkyl-2-aminobenzimidazoles give corresponding azoproducts only on long contact with air. These azocompounds have been found to be identical with those obtained by us by the oxidation of 2-aminobenzimidazole with sodium hypochlorite[7].

A detailed study of the reaction mechanism and preparation of various 2-nitrobenzimidazoles and attempts to extend the reaction to 2-aminoderivatives of other heterocyclic compounds is in progress.

REFERENCES

I. G.N.Pershin, P.M.Kochergin, A.M.Ziganova et al., J. Medical Industry, USSR, I964, 12.

2. S.Nakamura, Pharm. Bull., 3, 379-83 (I955)., C.A. 50, I5897g (I956).

3. G.Lancini, N.Maggi, P.Sensi, Farmaco (Pavia), Ed. Sci., I8, 390 (I963); C.A., 59, I0032 (I963).

4. G.Lancini, E.Lazzari, Experientia, 2I, 83 (I965).

5. A.Beaman, W.Fautz, T.Gabriel, R.Duschinsky, J. Amer. Chem. Soc., 87, 389 (I965).

6. A.M.Simonov, N.D.Vitkevitch, B.K.Marzocha, J.Gen. Chem, USSR, 30, 3062 (I960).

7. A.F.Posharskii, E.A.Zvezdina, A.M.Simonov, J. Chemistry of Heterocyclic Compounds, USSR, I966, in press.