ALKYLATING ACTIVITY OF POLYPHOSPHATE ESTER IN THE COURSE OF THE SYNTHESIS OF BENZIMIDAZOLES

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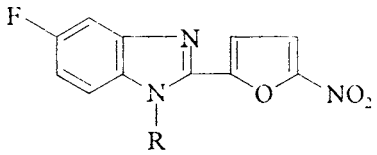
5-Fluoro-2-(5-nitrofuryl)benzimidazole (*I*) was synthesized from 4-fluoro-1,2-diaminobenzene and 5-nitro-2-furoic acid using ethyl polyphosphate as cyclization reagent. N-Ethyl derivative was isolated as by-product in substantial amount.

We have recently synthesized[1] a series of 52 benzimidazoles the majority of which showed important germicidal activity. One of these molecules, 5-fluoro-2-(5-nitrofuryl)benzimidazole (*I*) was remarkably active against such microbial cultures as *Escherichia coli*, *Staphylococcus epidermidis*, *Salmonella typhimurium* and *Staphylococcus aureus*[2,3]. A more detailed study of this compound's microbiological action as well as animal tests requires an efficient method for its preparation in greater quantities. We have previously used the Weidenhagen[4,5] procedure but because of low yields of *I* we turned to the methode of Dunn and coworkers[6], in which lead tetraacetate was used as the oxidant; however, this technique also proved inadequate. Similarly, tentative synthesis of *I* based on cyclization using boric acid in boiling xylene gave insignificant yields; this attempt was inspired by a method described by Terashima and coworkers[7] for the synthesis of the benzoxazole ring.

Finally, we resorted to polyphosphoric acid and its ethyl ester already well-known in this type of synthesis[8-10]. Using polyphosphoric acid at various temperatures no reaction was observed. On the other hand, the use of ethyl polyphosphate was successful; by controlled reaction time and temperature yields of 40% of pure product could be obtained after chromatography. A by-product was also isolated. We propose structure *II* for this compound. This implies that, in addition to the cyclizing action of the ethyl polyphosphate, the reagent also alkylates the N—H group of the imidazole ring. Although this alkylating property of ethyl polyphosphate is well-known in the indole series[11-13], nothing has been reported for benzimidazoles. We have confirmed this proposed structure by ethylating *I* using a classical procedure (diethyl sulfate and sodium hydroxide) giving *II* as the final product.

In order to improve the yield of *I* we tried variations in reaction temperature and time as well as using different quantities of the ethyl polyphosphate. Table I shows the percentage of *I* and *II* (calculated from UV spectra I_{max} 381 nm; II_{max} 378 nm)



I, R = H
II, R = C_2H_5

of the constituents separated by thin layer chromatography as a function of time and temperature. It can be seen that the best total yield (82%) and also the relative yield (55% of *I* and 44% of *II*) are obtained after 2 h at 150°C. Table II confirms that using 4 : 1 ethyl polyphosphate : amine ratio (weight) under the same reaction conditions gives optimal yields of *I*.

TABLE I
Yields of *I* and *II* under various reaction conditions

Time, min	*I*, %	*II*, %	Total yield, %
	At 150°C[a]		
30	84·8	15·2	8·6
60	71·4	28·6	35·7
120	55·6	44·4	81·9
240	50·0	50·0	78·3
	At 170°C		
30	38·2	61·8	19·8
60	19·2	80·8	53·3
120	12·9	87·1	78·8
240	0	100·0	71·0

[a] At 120°C and 30, 60, 120 or 240 min, *I* was the sole product, but the yield was nearly zero.

TABLE II

Relative percentage of *I* and *II* under various ethyl polyphosphate to 4-fluoro-1,2-diaminobenzene weight ratios

Ratio	4	8	16	32
I, %	71·0	38·2	24·1	15·7
II, %	29·0	61·8	75·9	84·3

EXPERIMENTAL

4-Fluoro-1,2-diaminobenzene (0·15 mol) was added to the four times the weight of ethyl polyphosphate (prepared according to ref.[10]). The mixture was heated and after addition of 5-nitro-2-furoic acid (0·1 mol) left for 2 h at 150°C, then cooled and water was added. After neutralization with ammonium hydroxide the mixture was extracted several times with chloroform, the combined extracts were evaporated and the residue was chromatographed on a column of neutral alumina using dichloromethane–hexane 1 : 1 as eluent. Yellow needles of *II* were obtained from first fractions, m.p. 151—152°C, well soluble in organic solvents and showing tendency to be oxidized in the light. IR spectrum shows the absence of the N—H band (appearing at 3 296·5 cm^{-1} in *I*). NMR spectrum (C^2HCl_3, tetramethylsilan, 60 MHz): 4·6 ppm (s, CH_2), 1·6 ppm (s, CH_3). Mass spectrum: *m/e* 275. For $C_{13}H_{10}FN_3O_3$ (275·3) calculated: 56·73% C, 3·66% H, 15·27% N; found: 56·58% C, 3·68% H, 15·08% N. Subsequently, yellow crystals of *I* were obtained from second fraction after crystallization from ethanol, identical with an authentic sample[1], m.p. 225°C.

REFERENCES

1. Allunni Bistocchi G., De Meo G., Pedini M., Ricci A., Pitzurra M., Cavallo R., Sposini T., Jacquignon P.: Il Farmaco Ed. Sci. *37*, 597 (1982).
2. Ricci A., De Meo G., Pedini M., Alunni Bistocchi G., Jacquignon P., Pitzurra M., Tricarico L., Scaringi L., Cavallo R., Sposini T.: Proceeding of the 41st session of the Italian Microbiological Society (Umbria), Sienna, May 29—30, 1981.
3. Alunni Bistocchi G., De Meo G., Pedini M., Ricci A., Cavallo R., De Cataldo F., Sbaraglia G., Sposini T., Pitzurra M., Jacquignon P.: Proceeding of the 44th session of the Italian Microbiological Society (Umbria), Teramo, December 3—5, 1982.
4. Weidenhagen R.: Ber. Deut. Chem. Ges. *69*, 2263 (1936).
5. Buu Hoi N., Jacquignon P., Hoeffinger J. P.: Arzneim.-Forsch. *1963*, 865.
6. Dunn G. L., Actor P., Di Pasquo V. J.: J. Med. Chem. *9*, 751 (1966).
7. Terashima M., Ishii M., Kanaoka Y.: Synthesis *1982*, 484.
8. Hein D. W., Alheim R. J., Leavitt J. J.: J. Amer. Chem. Soc. *79*, 427 (1957).
9. Kanaoka Y., Yonemitsu O., Tanizawa K., Ban Y.: Chem. Pharm. Bull. *12*, 773 (1964).
10. Kanaoka Y., Hamada T., Yonemitsu O.: Chem. Pharm. Bull. *18*, 587 (1970).
11. Yonemitsu O., Miyashita K., Ban Y., Kanaoka Y.: Tetrahedron *25*, 99 (1969).
12. Kanaoka Y., Miyashita K., Yonemitsu O.: Tetrahedron *25*, 2757 (1969).
13. Fieser L. F., Fieser M.: *Reagents for Organic Synthesis*, Vol. 1, p. 892. Wiley–Interscience, New York 1967.