

CYCLISATION OF DINITRILES BY SODIUM ALKOXIDES

A NEW SYNTHESIS OF NAPHTHYRIDINES

\*

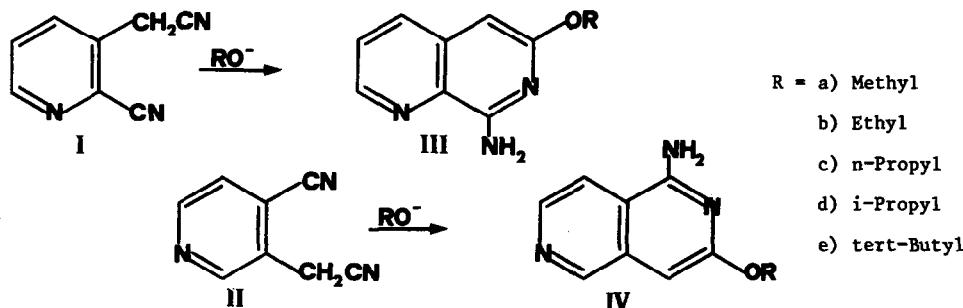
F. Alhaique, F.M. Riccieri, E. Santucci

Istituto di Chimica Farmaceutica - Università di Roma

(Received in UK 28 November 1974; accepted for publication 5 December 1974)

Damerow (1), Albahary (2) and more recently Johnson and Nasutavicus (3) have reported that the reaction of 2-cyanobenzyl cyanide with sodium ethoxide led always to the formation of dimers. We have now found that a completely different behaviour is shown by the analogous pyridine derivatives I or II, which, when treated with sodium alkoxides, yielded amino alkoxy naphthyridines, according to scheme I:

SCHEME I



In a typical experiment 0.012 moles of sodium were added to 150 ml of anhydrous ethanol and after dissolution 0.010 moles of the dicyano derivative were added. The solution was then refluxed for 3 hrs, kept overnight at room temperature and the solvent removed by distillation. The residue was crystallised from methylene chloride - petroleum ether or was purified by sublimation in vacuo.

The structures of compounds III and IV were confirmed by NMR spectra and by comparison with those of the corresponding isomers bearing  $-\text{OR}$  and  $-\text{NH}_2$  groups in the reversed positions. These isomers were synthesized by addition of the appropriate sodium alkoxide 6-amino-8-bromo-1,7-naphthyridine and 1-bromo-3-amino-2,6-naphthyridine respectively, which were obtained by cyclisation of dinitriles I and II by means of dry hydrogen bromide (4,5).

It must be noted that the overall yield of the obtained naphthyridines decreases rapidly going from methoxide to tert-butyrate, as shown in table I.

TABLE I

Compound	Yield	m.p.	Compound	Yield	m.p.
IIIa	77%	125-126°	IVa	75%	122° dec.
IIIb	70%	123-124°	IVb	72%	134-135°
IIIc	21%	99-101°	IVc	26%	108-109°
IIId	10%	84-85°	IVd	12%	177-178°
IIIE	--	---	IVe	--	---

(Melting points are uncorrected. All analytical samples gave appropriate IR spectra and combustion analysis for C, H and N within 0.4% of theory)

Sometimes small amounts (never more than 7%) of the isomeric 8-alkoxy-6-amino-1,7-naphthyridine and 1-alkoxy-3-amino-2,6-naphthyridine were obtained together with III and IV. In these cases the isomers were separated by preparative TLC.

The different behaviour of 2-cyanobenzyl cyanide and our pyridine derivatives I and II can be ascribed to the presence of the aza group. This heteroatom behaves as an electron withdrawing group and therefore promotes the formation of the imide, which is probably the first intermediate of this reaction (6).

This new dinitrile cyclisation represents a direct and simple method for the synthesis of some naphthyridine derivatives and attempts are being made for the further application of this reaction to, e.g. the preparation of isoquinoline derivatives.

#### REFERENCES

- 1) F. Damerow, Ber. 27, 2232 (1894).
- 2) J.M. Albahary, ibid. 29, 2392 (1896).
- 3) F. Johnson, W.A. Nasutavicus, J. Org. Chem. 27, 3953 (1962).
- 4) R. Tan, A. Taurins, Tetrah. Letters 31, 2737 (1965).
- 5) F. Alhaique, F.M. Riccieri, Ann. Chim. 60, 791 (1970).
- 6) F.C. Schaefer in "The chemistry of the cyano group", Zvi Rappoport Ed., Interscience Publishers, New York (1970) p. 267.

This work was supported by a C.N.R. Research Grant.