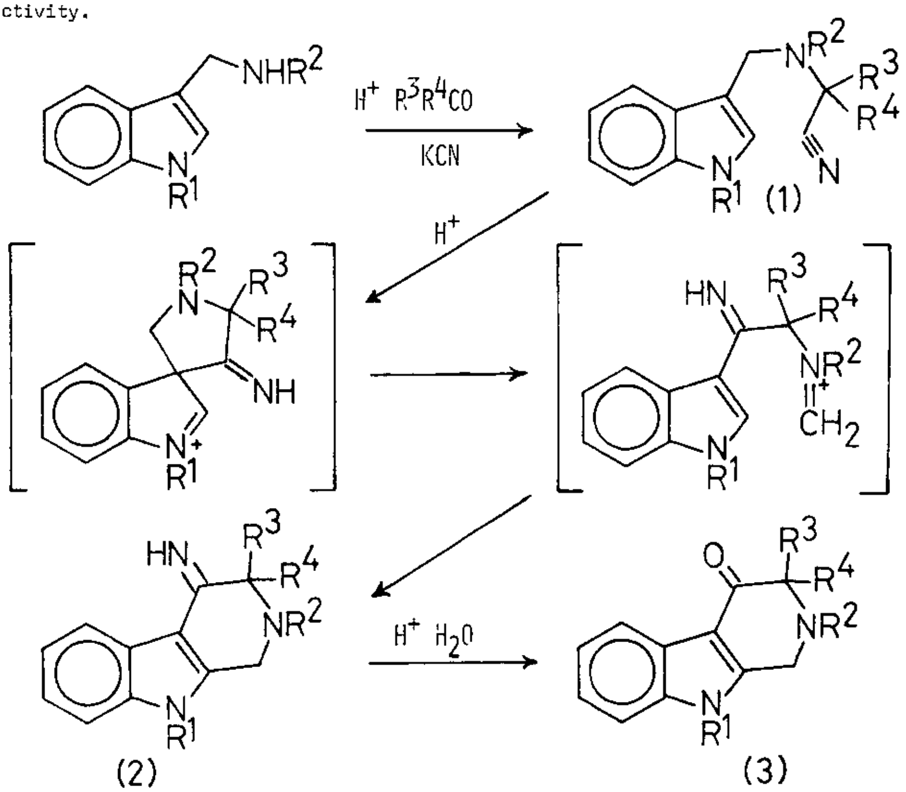
A NEW SYNTHESIS OF 1,2-DIHYDRO-β-CARBOLIN-4(3H)-ONES

Charles Mackay and Roger D. Waigh*

Department of Pharmacy, University of Manchester, Manchester M13 9PL, U.K.

Abstract - Aminonitriles derived from 3-aminomethylindoles are rearranged by treatment with polyphosphoric acid at 80°C or sulphuric acid at 0°C, to give 1,2-dihydro-β-carbolin-4(3H)-ones.

It has been well established that cyclisation of benzylaminonitriles to isoquinolinones[1-5] and other products[6] involves the rearrangement of a spiro intermediate. Rearrangement of spiro intermediates derived from 3-substituted indoles in the formation of tetrahydrocarbazoles has been the subject of intensive study by Jackson[7-11] and co-workers. Since 3-aminomethylindoles (skatylamines) are readily available, rearrangement of a skatylaminoacetonitrile (Scheme) offers an attractive route to new β-carbolines, currently of considerable interest for their C.N.S. activity.



SCHEME

Aminonitriles (1) were prepared by Strecker reactions on 3-aminomethylindoles obtained via the Vilsmeier-Haack formylation of indole and reduction of the corresponding oxime or imine. Cyclohexanone and acetone were chosen for the Strecker reactions, since these had given good yields in the isoquinolinone syntheses[1]. No identifiable product was obtained when formaldehyde was used as the carbonyl component of the mixture.

Table 1 describes the yields, melting points and substitution patterns of the aminonitriles prepared. Structures were confirmed by IR, NMR and MS, and for solids by C,H,N analysis.

Table 1 Aminonitriles (1)

	R^1	R^2	R^3	R^4	Yield (%)	M.pt (°C)
a	H	H	$-(CH_2)_5-$		88	104-5
b	H	H	CH_3	CH_3	75	72-4
c	CH_3	H	$-(CH_2)_5-$		74	57-8
d	CH_3	H	CH_3	CH_3	97	92-3
e	CH_3	CH_3	$-(CH_2)_5-$		88	116-7

As cyclising agent we initially tried sulphuric acid under the conditions used to rearrange benzylaminoacetonitriles[1-6] but observed extensive polymerisation and/or sulphonation; no identifiable products were isolated. Polyphosphoric acid (80°C, 1h) was more successful, as described in Table 2, but reaction conditions were critical; yields decreased rapidly at temperatures above 80°C. Sulphuric acid at lower temperatures (0°C for 15 min) was a considerable improvement (Table 2), in the five instances for which we have data.

Table 2 β-Carbolinones (3)

Product	Yield (%)†	Melting Point (°C)	>C=O (cm^{-1})
a	25 (88)*	189	1610
b	20 (50)	196-8	1630
c	24 (41)	184-6	1630
d	34 (65)	184-6	1630
e	17 (53)	120-2	1605

* Isolated as imine (2), mp 206-8°, after allowing the reaction mixture to stand for only 4 h at room temperature.

† Figures in brackets are yields from reactions in cold sulphuric acid (see text).

Both with polyphosphoric acid and sulphuric acid, the reaction mixture was cooled if necessary, diluted, and allowed to stand, filtered to remove polymeric by-products, and basified. The product was filtered off or extracted with chloroform or ethyl acetate. It was found that hydrolysis of the imines (2) to the ketones (3) was slow compared with iminotetrahydroisoquinolines[1]; work-up before 24h after dilution tended to give (2) rather than (3), or mixtures. The imines that were isolated were also converted with aqueous acid to the ketones as confirmation of structure.

All the products have been characterised by IR, NMR, MS and most by C,H,N analysis. The only question concerning the carbolines was the position of attachment of the carbonyl group, at C_2 or C_3 of the indole i.e. whether rearrangement had in fact occurred. In this respect the work of Neukomm and Hesse[12] was particularly helpful, allowing a comparison with directly analogous oxocarbazoles. Of major significance are (a) the carbonyl stretching frequency, which for 3-acyl indoles is < 1630 cm^{-1}, whereas for 2-acyl indoles it is 30-50 cm^{-1} higher (b) the downfield shift in the ^1H NMR spectrum of the benzene-ring proton near to the carbonyl group; in 2-acyl indoles there is no such proton (c) the UV spectra, which show three bands of similar wavelength and intensity to the 4-oxocarbazoles.

The authors gratefully acknowledge the receipt of an S.E.R.C. C.A.S.E. award (to C.M.) in collaboration with ICI Pharmaceuticals Division, and the interest and assistance of Dr. C.W. Thornber.

REFERENCES

1. D.N. Harcourt and R.D. Waigh, J. Chem. Soc. (C), 1971, 967.
2. D.N. Harcourt, N. Taylor and R.D. Waigh, J.C.S. Perkin 1, 1978, 722.
3. D.N. Harcourt, N. Taylor and R.D. Waigh, J.C.S. Perkin 1, 1978, 1330.
4. D.N. Harcourt, N. Taylor and R.D. Waigh, J. Chem. Research (M), 1978, 1954.
5. D.N. Harcourt, N. Taylor and R.D. Waigh, J.C.S. Chem. Comm., 1972, 644.
6. R.D. Waigh, J.C.S. Chem. Comm., 1980, 1164.
7. A.H. Jackson, B. Naidoo and P. Smith, Tetrahedron, 1968, **24**, 6119.
8. K.M. Biswas and A.H. Jackson, Tetrahedron, 1969, **25**, 227.
9. R. Iyer, A.H. Jackson, B. Naidoo and P.V.R. Shannon, J.C.S. Perkin 2, 1973, 872.
10. R. Iyer, A.H. Jackson and P.V.R. Shannon, J.C.S. Perkin 2, 1979, 878.
11. J.S.L. Ibaceta-Lizana, R. Iyer, A.H. Jackson and P.V.R. Shannon, J.C.S. Perkin 2, 1978, 733.
12. G. Neukomm and M. Hesse, Helv. Chim. Acta, 1977, **60**, 2431.

Received, 28th November, 1983