The Rearrangement of a Dihydropyridine

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IN connection with our studies of the acid (1),[1] we have investigated the effect of heat upon the acid (2), prepared from β-aminocrotonic nitrile and glyoxylic acid.[2] Changes are observed at *ca.* 150°; and after 5 min. at 250°, several very polar and highly coloured materials are produced, together with four isolable pyridine derivatives (3) (10%) (ref. 3), (7) (23%), (9) (14%), and (10) (5%).

The structure of the lactone (10) was determined by its synthesis from the acid (2). The methyl ester of (2) was reduced by lithium borohydride in tetrahydrofuran to (11), which was oxidized by sodium nitrite in acetic acid to give the pyridine (4); in 7% methanolic trifluoroacetic acid at room temperature, the pyridine (4) is converted into the lactone (10). In some of the oxidations of (11) the lactone (10) was isolated directly, without treatment by stronger acid. The lactam (9), which is very similar in spectral properties to the lactone (10), has not yet been synthesized.

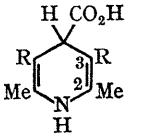
Compound (7) shows the chemical properties of an imide oil, its sodium salt forms the corresponding *N*-methyl derivative on treatment with methyl iodide. The synthesis of the imide (7) was effected by oxidizing the methyl ester of the acid (2) to give the pyridine ester (5), which, on treatment with ammonia in methanol, gave the amide (6). Treatment by trifluoroacetic acid at room temperature produced the imide (7).

These rearrangements of the acid (2) also occur in various solvents at reflux temperature: acetic acid, 5 hr: 48% (7) and 24% (9); diglyme, 18 hr: 30% (2), 10% (3), 30% (7), and 25% (9). The reaction occurs very slowly in boiling pyridine, 60% of the acid (2) being recoverable after 5 days with the production of 27% (3), 2% (7), and 4% (9). Acid conditions are evidently favourable for the rearrangement.

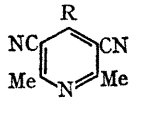
We suggest the following mechanism for the rearrangement of the acid (2): interaction of the neighbouring carboxy- and nitrile groups produces first (12), then the imide (13),‡ which is either oxidized to the pyridine imide (7), or is reduced by the dihydropyridine nucleus to compound (14). Finally, disproportionation of (14) leads to the pyridine imide (7), the lactam (9), and to the lactone (10).

The participation of the carboxy-, amide, and alcohol groups in the saponification of a nitrile, exemplified here, parallels the ready hydrolysis of the nitrile group in *o*-cyanobenzoic acid, which is converted into phthalic acid upon being heated under reflux in water.[4] Of particular interest in the conversion of (13) into (14) is the reduction of an imide group by the dihydropyridine nucleus, as this is the first instance in which such a nucleus has effected the reduction of a derivative of an acid.[5]

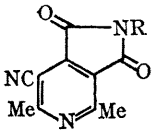
The reactions of the acid (2) are different from those of (1), although the coloured products which accompany the pyridines produced from (2) may well be condensation products of the same type (*e.g.* pyrroles) as those produced from (1). The different behaviour of (1) and (2) may well result from the neighbouring-group participation between the nitrile and carboxy-group, possible in the case of (2) because of the lesser steric requirements of the nitrile group.



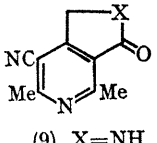
(1) R=CO_2Et
(2) R=CN



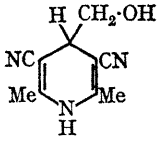
(3) R=H
(4) R=CH_2·OH
(5) R=CO_2Me
(6) R=$CONH_2$



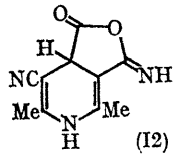
(7) R=H
(8) R=Me



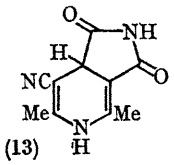
(9) X=NH
(10) X=O



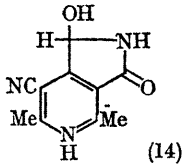
(11)



(12)



(13)



(14)

It is interesting to contrast the course of the rearrangements of the dihydropyridines (1) and (2). Steric interaction of the adjacent methyl and ethoxycarbonyl groups in (1) probably forces the carbonyl groups out of the plane of the dihydropyridine nucleus, and thus reduces their electron attracting effect.[6] As a result, the electron density at C-3 is higher in (1) than in (2). Rearrangement of (1) may therefore be initiated by protonation at C-3, while that of (2) commences with the interaction of the C-4 carboxy-group with the nitrile.

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‡ With the homologue of (2) bearing a 4-methyl group, the corresponding imide may be isolated.

[1] J. F. Biellmann and H. J. Callot, preceeding Communication.
[2] D. Hoffmann, E. M. Kosower and K. Wallenfels, *J. Amer. Chem. Soc.*, 1961, **83**, 3314.
[3] E. V. Meyer, *J. prakt. Chem.*, 1908, **78**, 508.
[4] S. Hoogewerff and W. A. Van Dorp, *Rec. Trav. chim.*, 1892, **11**, 91; See also: S. Fallab and H. Erlenmeyer, *Helv. Chim. Acta*, 1951, **34**, 488; A. Hantzsch, *Ber.*, 1928, **61**, 1776; S. L. Ruskin and M. Pfalz, *J. Amer. Chem. Soc.*, 1938, **60**, 1471; D. E. Ames, R. E. Bowman, and T. F. Grey, *J. Chem. Soc.*, 1953, 3011; K. Hoffmann, J. Kebrle, and H. J. Schmid, *Helv. Chim. Acta*, 1957, **40**, 387; C. M. Hendry, *J. Amer. Chem. Soc.*, 1958, **80**, 973; A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, 1962, **27**, 1760; A. Roedig, K. Grohe, and W. Mayer, *Tetrahedron*, 1968, **24**, 1853.
[5] For examples of reduction of other groups, see T. C. Bruice and S. J. Benkovic, "Bio-organic Mechanism," Vol. 2, W. A. Benjamin, 1966, New York, p. 343.
[6] A similar effect has been observed; J. F. Biellmann and H. J. Callot, *Bull. Soc. chim. France*, 1968, 1159.