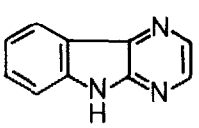
Tetrahedron Letters No. 40, pp 3611 - 3614, 1976. Pergamon Press. Printed in Great Britain.

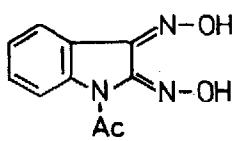
THE REACTION OF *N*-ACETYLISATIN WITH HYDROXYLAMINE

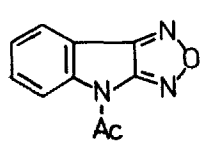
Jan Bergman,* René Carlsson and Jan-Olof Lindström
Department of Organic Chemistry, Royal Institute of Technology,
S-100 44 Stockholm 70, Sweden

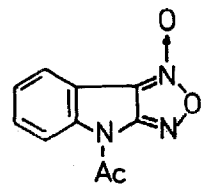
(Received in UK 15 June 1976; accepted for publication 16 August 1976)

We are interested in azacarbazoles and related compounds and for the synthesis of 1,4-diazacarbazole (1) we have considered several possibilities. For one approach we needed *N*-acetylisatin-2,3-dioxime (2) or related compounds such as (3) or (4) as starting materials for cycloadditions. Although a compound readily prepared from *N*-acetylisatin and hydroxylamine with the purported structure (2), has been known for several years,[2-5] we had our doubts in advance about its structure as it is known that *N*-acetylisatin is readily ring-opened by ammonia[6] and amines[7] and even by alcohols.[8]

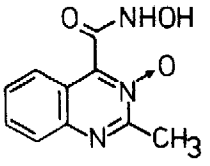

1


2

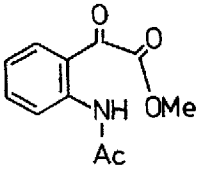

3


4

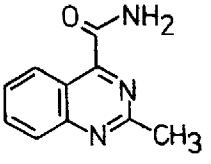
This anticipation was strengthened when it was found that the product gave a stable hydrochloride and failed to give a cycloaddition addition product with dimethyl acetylene-dicarboxylate.[9] Furthermore, no stable complex was formed with Ni^{2+} ions. After considering the MS[10] (which indicated the presence of an *N*-oxide function) and UV spectra and comparison with spectra of known[11,12] quinazoline-*N*-oxides, it appeared likely that the product actually was the hydroxamic acid (5) formed by nucleophilic ring-opening of *N*-acetylisatin by hydroxylamine followed by recyclization. In keeping with this formulation it was found that the ester (6) when treated with hydroxylamine also gave 5. Conversion (Raney nickel in dioxan at reflux) of 5 to the known[6] compound 2-methylquinazoline-4-carboxamide (7) corroborated the structure. Reduction of 5 with tributylphosphine in hot (95°/2 h) dioxan or catalytic hydrogenation (Pd/C) of an aqueous solution (25°)[13] of the anion of 5, gave 2-methylquinazoline-4-hydroxamic acid (8). Similar reduction of 10 (prepared by treating 9 with hydroxylamine) gave 7.



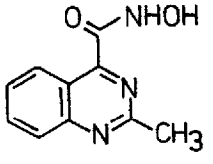
5



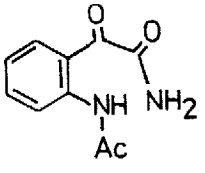
6



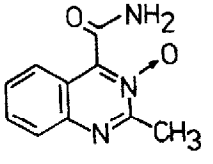
7



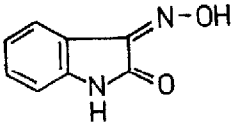
8



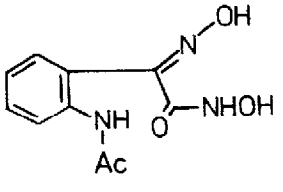
9



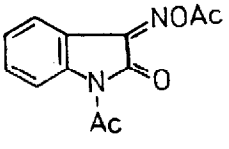
10



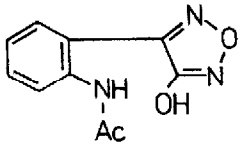
11



12



13



14

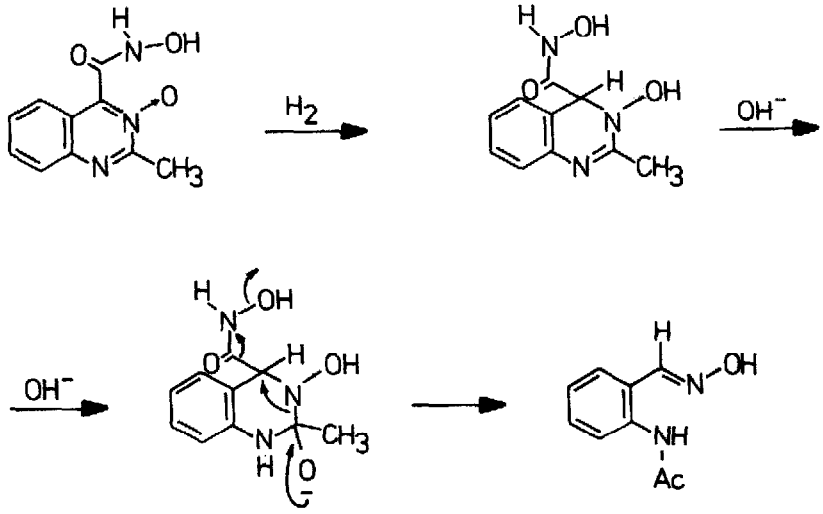
Although hydrolysis of 5 with boiling aqueous 2n NaOH for 1 h gave isatin-3-oxime (11), action of the same reagent for 1 h at 25° gave 12 (*cf.* ref. 14). Hydrolysis of 12 with boiling aqueous 2n NaOH gave 11, showing that 12 is one of necessarily several intermediates in the conversion 5 ⟶ 11. In earlier literature[2-5] this same conversion was considered as the strongest structure proof for the now rejected structure 2.

Attempted ring-closure of 12 to 5 or 14[15] with Ac_2O gave a product for which the structure 13 is suggested. The same product was prepared in excellent yield by refluxing 11 with Ac_2O (*cf.* ref. 16). These results are in contrast with the reported[4] inertness of 11 towards Ac_2O.

REFERENCES AND NOTES

1. (a) 1,4-Diazacarbazole has recently been prepared.[1b]
   (b) A.J. Clark, R.J. Dorgan and J. Parrick, *Chem. and Ind.* 215 (1975).
2. E. Schunck and L. Marchlewski, *Berichte* 29, 194 (1896).
3. J. Kozak, *Anzeiger Akad. Wiss. Krakau* 628 (1909).
4. E. Beckman and E. Bark, *J. Prakt. Chem.* (2) 105, 227 (1923).
5. A. Etienne, *Bull. Soc. Chim. France* 651 (1948).
6. F.J. Meyer, *Chem. Ber.* 99, 3060 (1966).
7. F.D. Popp, R.M. Piccirilli, *J. Heterocyclic Chem.* 8, 473 (1971).
8. P. de Mayo and J.J. Ryan, *Can. J. Chem.* 45, 2177 (1967).
9. At this point we reasoned that 4 should be more prone for cycloadditions. In our efforts to synthesize 4 *via* 3 we treated the alleged dioxime with dicyclohexylcarbodiimide. The structure elucidation of this rearranged product is reported in the following paper.
10. MS of 5 219 (76), 203 (3), 160 (8), 159 (7), 144 (19), 143 (100), 142 (14), 129 (9), 118 (8), 102 (39). Only peaks above *m/e* 100 and stronger than 2 % of the base peak are listed.
11. M. Uchida, T. Higashino and E. Hayashi, *Shitsuryo Bunseki* 21, 245 (1973).
12. W.L.F. Armarego, *"Fused Pyrimidines, Part I. Quinazolines"*. (Edited by D.J. Brown), Interscience Publishers, London (1967).

13. Catalytic hydrogenation at 65° gave *o*-*N*-acetylaminobenzaldehyde oxime. The following mechanism is suggested:



14. (a) The parent compound α-hydroxyiminophenylacethydroxamic acid is known.[14b] Compound 12 gave the following mass spectrum:

237 (8), 219 (15), 205 (8), 204 (10), 177 (37), 163 (43), 162 (100), 161 (19), 160 (9), 146 (15), 145 (67), 144 (18), 143 (15), 134 (14), 133 (11), 132 (13), 119 (52), 118 (99), 117 (32), 102 (16). Only peaks above *m/e* 100 and stronger than 6 % of the base peak are listed.

(b) J.V. Burakevich, R.S. Butler and G.P. Volpp, *J. Org. Chem.* 37, 593 (1972).

15. (a) The parent compound 4-phenyl-3-hydroxyfurazane is known.[15b]

(b) B.W. Nash, R.A. Newberry, R. Pickles and W.K. Warburton, *J. Chem. Soc. (C)* 2794 (1969).

16. W. Borsche and W. Sander, *Berichte* 47, 2815 (1914).