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A VERSATILE NEW SYNTHESIS OF QUINOLINES AND RELATED FUSED PYRIDINES. PART 10[1]. ROUTES TO QUINOLINES WITH FUSED AZACYCLES.

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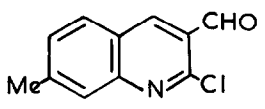
Summary: Three efficient routes to the title systems have been elaborated utilising 2-chloroquinoline-3-aldehyde acetals, 2-chloroquinoline-3-ketones or 2-aminoquinoline-3-aldehydes.

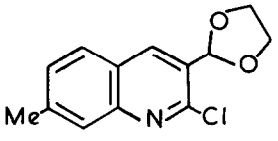
2-Chloroquinoline-3-aldehydes (e.g.1) have been rendered readily available as described in earlier papers[2] and have been shown to be versatile intermediates for functional group interconversions and for the synthesis of fused quinolines[1]. However, except for one or two special cases[1,3], we have been frustrated in our attempts to fuse nitrogen heterocycles to the quinoline nucleus in this way. Thus hydrazones and oximes of these aldehydes exist in the E-form and resist cyclisation even under the most rigorous conditions.[1] We now describe three simple approaches which render such target molecules readily accessible and are generally the method of choice for their synthesis.

Method 1. Use of 2-Chloroquinoline-3-aldehyde acetals (e.g. 2). -

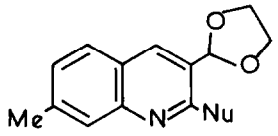
Whereas the aldehydes (e.g.1) are attacked first at the aldehyde function



(1)



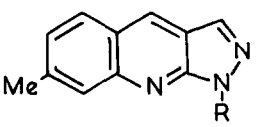
(2)



(3)

by nitrogen nucleophiles, the corresponding acetals[1] undergo initial substitution at chlorine and the products (3) undergo spontaneous cyclisation on de-acetalisation with hot aqueous alcoholic mineral acid. By this means we have

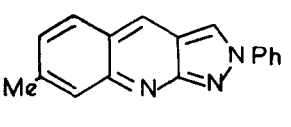
prepared in excellent yields the fused pyrazoles (4) and (5) and the diazepine (6) by use of hydrazine, methylhydrazine, phenylhydrazine and ethylenediamine



(4)

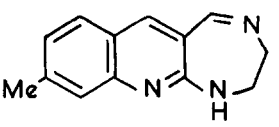
a; R=H, m.p. 144-5°

b; R=Me, m.p. 225-7°



(5)

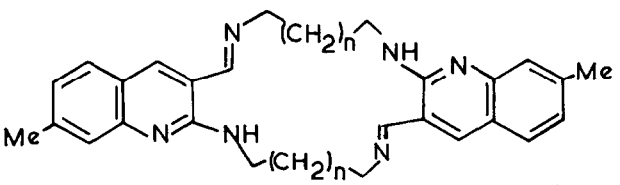
m.p. 235-6° (d)



(6)

m.p. 169-72°

respectively. Other routes to the pyrazoles (4 and 5) are multistage and give only complex substituted analogues[4]. The di-azepinoquinoline (6) is a new system. Interestingly, the fused quinoline (6) on standing in chloroform solution was slowly transformed into the insoluble dimer (7a), a process which could be followed by Fourier transform ^{1}H n.m.r. and involved hydration at the C=N to a carbinolamine followed by ring-opening of the monomer. The similar action of 1,3-diaminopropane led to the 16-membered dimer (7) rather than the



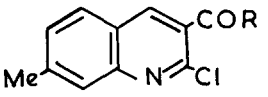
(7)

a; n=o, m.p. > 360° (d)

b; n=1, m.p. > 360° (d)

expected diazocine, as evidenced by mass spectrometry.

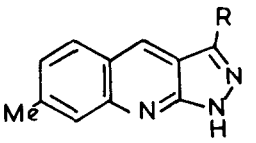
Method 2. Use of 2-Chloroquinoline-3-ketones (8). - The action of a Grignard reagent on the aldehyde (1) followed by dichromate oxidation of the resulting secondary alcohols gave the ketones (8) in high yield. These with hydrazine cyclised rapidly and in good yield indicating that the substituent R favoured formation of the Z-hydrazone. Indeed small amounts of the uncyclised



(8)

a; R=Me, m.p. 81-2°

b; R=Ph, m.p. 115-7°

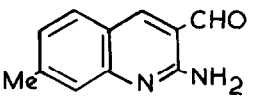


(9)

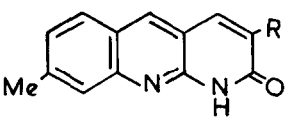
R=Ph, m.p. 258-60°

E-hydrazones could also be isolated in these cases.

Method 3. Use of 2-Aminoquinoline-3-aldehydes (e.g. 10). -



(10)



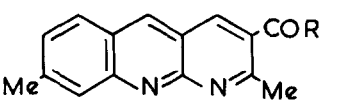
(11)

a; R=CO_2H, m.p. > 300° (d)

b; R=CO_2Et, m.p. 206-8°

c; R=CN, m.p. > 330°

d; R=Ac, m.p. 270° (d)



(12)

a; R=Me, m.p. 157-9° (d)

b; R=OEt, m.p. 154-6° (d)

The acetal (2) on treatment with liquid ammonia and sodium iodide at 120° for 19 h efficiently yielded the corresponding 2-amino derivative (92%, m.p. 161-2°) which easily hydrolysed to the 2-amino-3-aldehyde (10) with acid (100%, m.p. 194-6°). This stable versatile intermediate readily produced such systems as (11a, 85%), with malonic acid, (11b, 100%) with diethyl malonate and (11c, 95%) with ethyl cyanoacetate. With acetylacetone (12a, 99%) was obtained while ethyl acetoacetate gave a mixture of (11b, 30%) and (12b, 13%).

The full potential of these approaches is under active study.

References

1. Part 9. O.Meth-Cohn, B.Narine, B.Tarnowski, R.Hayes, A.Keyzad, S.Rhouati and A.Robinson, *J.Chem.Soc., Perkin Trans.I*, 1981, 2509.

2. see especially O.Meth-Cohn, B.Narine, and B.Tarnowski, *J.Chem.Soc. Perkin Trans.I*, 1981, 1520.

3. O.Meth-Cohn and B.Tarnowski, *Tetrahedron Letters*, 1980, 3721.

4. e.g. see G.Wolfrum, R.Pütter, and H.Hanke, U.S.Patent, 1966, 3234142 and 3257410; R.G.Stein, J.H.Biel, and T.Singh, *J.Med.Chem.*, 1970, 13, 153; R.Y.Ning, J.F.Blount, P.B.Madan. and R.I.Fryer, *J.Org.Chem.*, 1977, 42, 1791; A.Brack, *Ann.*, 1965, 681, 105; V.Purnaprajna and S.Seshadri, *Ind.J.Chem.*, 1976, 14B, 971.

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