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A CONVENIENT SYNTHESIS OF 2,4-DIAMINOQUINOLINE DERIVATIVES

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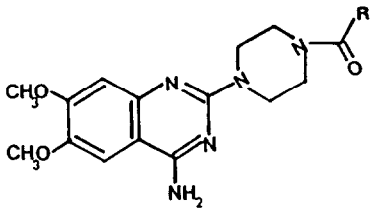
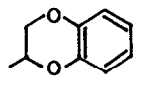
Summary: Base or Lewis acid induced cyclisation of the o-amidinobenzonitriles (III) provides 2,4-diaminoquinoline derivatives (IV) in high yield.

As part of a programme to clarify structural requirements for α_1-adrenoceptor antagonist activity, the corresponding quinoline analogues of the clinically effective antihypertensive agents prazosin[1] and doxazosin[2] were required.

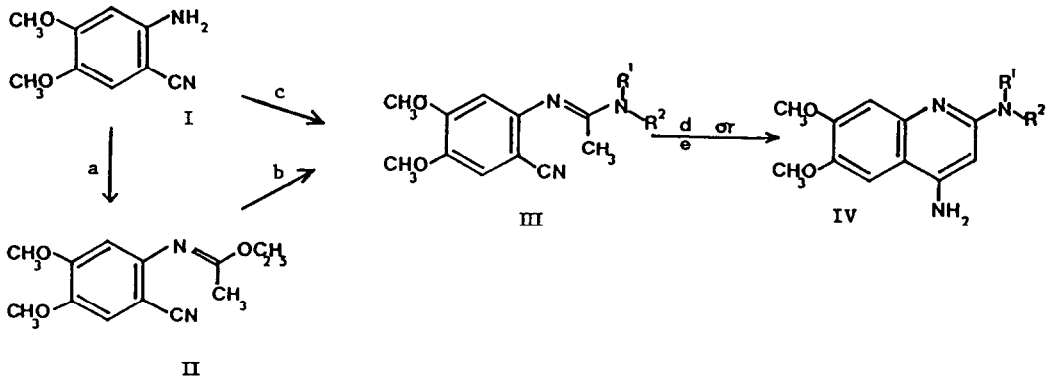


prazosin, R =

doxazosin, R =

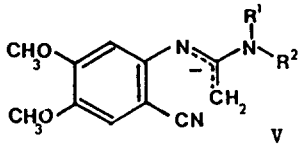


However, few diaminoquinolines of this type have been reported and no general syntheses appear to be documented. For example, although aminolysis of 2,4-dihaloquinolines has been described[3], harsh conditions are required, regiocontrol is poor and rearrangements can occur[4]. We now report a convenient synthesis of 2,4-diaminoquinoline derivatives based on a novel, intramolecular cyclisation[5,6] of an o-(N,N-disubstituted)amidinobenzonitrile. In this case, ring closure is initiated via the central alkyl residue in the amidine moiety since conventional[7], N-induced, cyclisation to a quinazoline system is not possible.

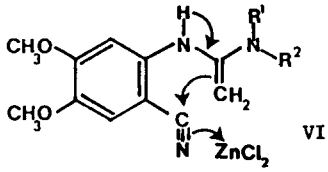


Reagents: (a) $CH_3C(OC_2H_5)_3$, H^+, 150°; (b) HNR^1R^2, H^+, 150°; (c) $CH_3CONR^1R^2/POCl_3/CHCl_3$; (d) LDA/THF -70° to room temp.; (e) $ZnCl_2$/DMA, reflux.

Thus, reaction of the anthranilonitrile (I) with triethylorthoacetate gave, in quantitative yield, the crude imidate (II) which, on treatment with a secondary amine, furnished the key acetamidinonitriles[8] (III). Alternatively, these intermediates were obtained by direct reaction of (I) with an imidinium chloride, conveniently prepared by brief exposure of an N,N-disubstituted acetamide to phosphorous oxychloride. When a solution (THF) of the amidine (III) was treated with LDA at -70° and then allowed to reach room temperature, intramolecular cyclisation of the anion (V) gave a 2,4-diaminoquinoline derivative (IV) as the sole product.[9,10]



V



VI

In cases where the $-NR_1R_2$ residue contained a benzylic proton (Table I, entries 4,5) base-induced cyclisation did not proceed. However, ring closure could be effected by treatment of the amidine (III) with zinc chloride[5,9,10], presumably via the enamine tautomer (VI).

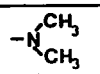
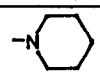
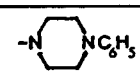
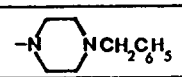
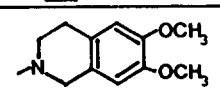
Entry	$-NR^1R^2$	cyclisation method	yield[9] (%)	m.p. (°C)
1		d	76	294-5 [f]
2		d	98	279-80[f]
3		d	77	288-9 [g]
4		e	63	211-13[h]
5		e	48	229-30[h]

Table I, Cyclisation method and yields (analysed material) for the preparation of (IV). M.p. refers to the salt form characterised, (f) hydrochloride, (g) dihydrochloride, (h) free base.

Although this report is confined to our studies on 2,4-diamino-6,7-dimethoxyquinolines, many other aromatic substituents can be accommodated, additional functionality can be incorporated at the 3-position and reaction scale can be easily varied[11].

Finally, debenzylation (H_2/Pd/C) of the protected 2-piperazinoquinoline (Table I, entry 4) followed by acylation (furoyl chloride or 1,4-benzodioxan-2-carbonyl chloride in chloroform) provided the quinoline analogues[9] of prazosin and doxazosin. Both compounds displayed exceptional α_1 -adrenoceptor binding affinity[12] (Ki, 2×10^{-11}, 1×10^{-10} respectively) and these results support recent proposals concerning the nature of antagonist interactions at α_1-adrenoceptors.[13]

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2. W. Singleton, C.A.P.D. Saxton, J. Hernandez and B.N.C. Prichard, J.Cardiovasc.Pharmacol. 4, S145 (1982).

3. H.J. den Hertog and D.J. Buurman, Rec.Trav.Chim. 91, 841, (1972).

4. H.N.M. van der Lans, H.J. den Hertog and A. van Veldhuizen, Tetrahedron Letters, 1875 (1971).

5. For related approaches to 2-alkyl- and 2-hydroxy-4-aminoquinolines see for example, J.A. Moore and L.D. Kornreich, Tetrahedron Letters, 1277, (1963); H. Schafer, K. Sattler and K. Gewald, J. Prakt.Chem. 321, 695, (1979); H.E. Schroeder and G.W. Rigby, J.Amer.Chem.Soc. 71, 2205, (1949).

6. After this work had been completed, a related cyclisation via an amidine intermediate was reported, M.V. Kormer, I.A. Maretina and A.A. Petrov, Zh.Org.Khim., 19 2455 (1983)

7. Cyclisation of amidines (III, R^1=R^2=H) to give quinazoline derivatives is well documented, for example see E.C. Taylor and A.L. Borror, J.Org.Chem., 26, 4967 (1961).

8. Amidine derivatives gave consistent combustion analyses (C, H, N), i.r. (2,200cm^{-1}, -CN) and n.m.r. [1.9 - 2.0 ppm, 3H singlet (-CH_3)] spectra.

9. Compounds (IV) were fully characterised either as free bases or hydrochloride salts (hygroscopic) and combustion analyses (C, H, N), i.r., mass and n.m.r. spectra were consistent with structure. In particular, formation of the quinoline ring system was confirmed by the appearance of a singlet (6.0-6.2 ppm) for the new aromatic proton.

10. Typical cyclisation procedures are as follows; (i) the amidine III (-NR^1R^2 = 4-phenylpiperazine, 0.5 g; 1.4 mmoles) in THF (10 ml) was added to a stirred solution of LDA (1.6 mmoles, from n-BuLi and diisopropylamine) in THF (5 ml) at -70°. The resulting solution was stirred at -70° for 0.5 hr. followed by a further 1 hr. at room temperature. The reaction was then quenched (ice-water) extracted (chloroform) and purified by chromatography (silica) to give 4-amino-6,7-dimethoxy-2(4-phenylpiperazino)quinoline (0.45 g, 90% yield) characterised[9] as the dihydrochloride salt hemihydrate m.p. 288-9° (77% overall yield from III).

(ii) A solution of the amidine III (-NR^1R^2 = 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 4.2 g, 11 mmole) and anhydrous zinc chloride (1.95 g, 14 mmole) in DMA (25 ml) was stirred under reflux for 2 hr. The mixture was then extracted (ether) and the residual zinc complex destroyed by treatment with sodium hydroxide (2N, 50 ml) at 50°

for 10 min. The solution was extracted (chloroform) then purified by chromatography (silica) followed by crystallisation (IPA/EtOH) to give 4-amino-6,7-dimethoxy-2(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolino)quinoline m.p. 229-30° (2.0 g, 48% yield).[9]

11. J.D. Hardstone, unpublished results.

12. For methods see, P. Greengrass and R. Bremner, Eur.J.Pharmacol. 55, 323, (1979).

13. S.F. Campbell in X-Ray Crystallography and Drug Action, Eds., A.S. Horn and C.J. De Ranter, Clarendon Press, Oxford (1984) Chapter 19.

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