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INTERNUCLEAR CYCLISATIONS IN SOME s-TRIAZOLES

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THE isolation[1] of small quantities of 3:4-disubstituted-5-hydroxy-1:2:4-triazoles (I, X = OH, shown[2] to exist predominantly in the triazolone form in the solid state) during the alkaline ferricyanide oxidation of 4-substituted thiosemicarbazones - a reaction mainly giving rise to 2-substituted-5-substitutedimino- Δ^4-1:3:4-thiadiazolines[3,4] - led to the development, in these laboratories, of a facile method[1,2] for the synthesis of such s-triazoles from 4-substituted semicarbazones through alkaline ferricyanide oxidation. The functional group in these hydroxy-triazoles is replaceable[5] by others (e.g., -Cl, $-NH_2$, -SH, -H etc.) through reactions well in vogue for nitrogen heterocycles and such derivatives strategically o-substituted in the aryl residues at the 3- and 4-positions, suggested themselves as suitable framework for further ring closure. These structures (II) reveal four sites, arbitrarily termed A, B, C and D, for further cyclisation and all these ring closures, except at site D, would result in s-triazoles

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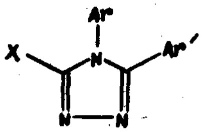
[1] G. Ramachander and V.R. Srinivasan, Curr. Sci. **28**, 368 (1959).
[2] V.R. Srinivasan, G. Ramachander and S. Naqui, Arch. Pharm., **295**, 405 (1962)
[3] K.C. Das and M.K. Rout, J. Sci. Industr. Res. **14B**, 98 (1955).
[4] G. Ramachander and V.R. Srinivasan, J. Sci. Industr. Res. **21C**, 44 (1962).
[5] S. Naqui and V.R. Srinivasan, J. Sci. Industr. Res. **21B**, 195 (1962).

fused to benzoheterocycles, representing novel approaches to the synthesis of these systems from pre-existing s-triazole moieties.

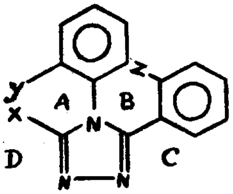
We now report four instances of such syntheses, three based on site A cyclisations and one on a site B cyclisation; the former exemplified by a substituted s-triazolo(3,4-b)-benzoxazole (IIIa, R = C_6H_5), a substituted s-triazolo(3,4-b)-benzthiazole (IIIb, R = C_6H_5), a disubstituted s-triazolo (4,3-a)-quinazoline (IV, R = R′= C_6H_5) and the latter by three s-triazolo (4,3-f)-phenanthridines (Va, b and c). The last two are new systems.

The synthesis of 3-phenyl-s-triazolo(3,4-b)-benzoxazole (IIIa) started from IIa, (m.p. 227°), which was converted in 80% yield to IIb (m.p. 150°) by $PCl_5/POCl_3$ in a sealed tube. Treatment of IIb with pyridine hydrochloride, followed by excess of pyridine gave the expected product (IIIa) in 82% yield, m.p. 143°, λ_{max}^{EtOH} 209 mμ (log ε 4.39), 248 mμ (log ε 4.16) and 285 mμ (log ε 4.07). The same product could also be obtained in a step-wise fashion by treating IIb with 48% HBr, when IIc (m.p. 245°) resulted. IId (m.p. 172°), liberated from IIc, could be cyclised, albeit in a slightly lower yield (62%), by excess of pyridine to IIIa. Direct refluxing of IIc with excess of pyridine also resulted in IIIa, in 65% yield. The structure of IIIa was confirmed by its analysis, insolubility in alkali, and its hydrolysis by concentrated HCl to IIe, identical with the product obtained by treatment of IId with dilute H_2SO_4 in the presence of acetic acid or IIa with 48% HBr or pyridine hydrochloride. The infrared absorption of IIIa exhibits a medium absorption at 8.5 μ assigned to a C - O - C linkage.

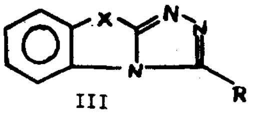
The s-triazolo-benzthiazole (IIIb) was synthesised from IIf (m.p. 230°) through IIg (m.p. 150°) and IIh (m.p. 231°) obtained by treatment with phosphorus halides followed by thiourea. An Ullmann type of cyclisation on the sodium salt of IIh directly with a trace of B.D.H. copper powder or



I

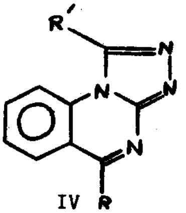


II

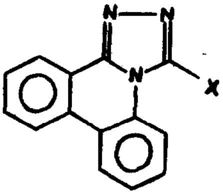


III

a : x = O
b : x = S



IV



V

a : x = OH

b : x = Cl

c : x = H

<u>II a to II j : z = H</u>

II a : x = OH , y = OMe

b : x = Cl , y = OMe

c : monohydrobromide of II d

d : x = Cl , y = OH

e : x = y = OH

II f : x = OH , y = Cl

g : x = y = Cl

h : x = SH , y = Cl

II i : x = NH_2 , y = H

j : x = NH-CO-Ph, , y = H

<u>II k to II o : y = H</u>

II k : x = OH , z = NO_2

l : x = OH , z = NH_2

m : x = Cl , z = NH_2

n : x = H , z = NH_2

o : x = OH or Cl or H, z = OH

better still in the presence of dimethyl formamide as a solvent afforded in 60% yield IIIb, (m.p. 157°), λ_{max}^{EtOH} 206 m (log ε 4.46), 248 mμ (log ε 4.17) and 295 mμ (log ε 3.85), which was neutral in behaviour and stable to both acids and alkalis even under drastic conditions. The infra-red absorption of this compound in chloroform revealed a strong band at 6.78 μ which is usually ascribed to a benzthiazole structure. This compound has been reported earlier[6] (m.p. 153°) as being obtained in 40% yield by refluxing 2-chlorobenzthiazole, benzhydrazide, sodium phenate and phenol for twenty hours.

The fused s-triazolo(4,3-a)-quinazoline (IV, $R = R' = C_6H_5$) was obtained from IIi, m.p. 221° through its benzoyl derivative, IIj, m.p. 226°, which on cyclisation with $POCl_3$ gave in 42% yield IV, m.p. 139°, tentatively assigned the s-triazolo(4,3-a)-quinazoline structure. The product is quite stable to hydrolysis with mineral acids, unlike the starting material IIj, which is easily hydrolysed under these conditions.

The site B cyclisations were effected through the Pschorr reaction. Thus, IIl (m.p. 149°) on diazotisation with sodium nitrite in sulphuric acid, followed by treatment with freshly precipitated copper powder gave an acidic product, Va, in 73% yield (shrinking at 248° and decomposing at 294°); λ_{max}^{EtOH} 205 mμ (log ε 4.42), 241 mμ (log ε 4.49), 259 mμ (log ε 4.35), 289 mμ (log ε 3.83) and 312 mμ (log ε 3.85). Va on treatment with $PCl_5/POCl_3$ in a sealed tube gave Vb (m.p. 200°) in 67% yield; λ_{max}^{EtOH} 204 mμ (log ε 4.24), 250 mμ (log ε 4.62) and 308 mμ (log ε 4.54). Vb could also be obtained, although in a smaller yield (60%), by a Pschorr cyclisation on IIm (m.p. 158°) obtained from IIk (m.p. 241°), through the usual reaction with phosphorus chlorides, followed by reduction with ammoniacal ferrous sulphate. Treatment of Vb with Zn and HCl gave Vc, m.p. 175°, λ_{max}^{EtOH} 204 mμ (log ε

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[6] G.A. Reynolds and J.A. VanAllan, J. Org. Chem. 24, 1478 (1959).

4.19), 250 mμ (log ε 4.51) and 308 mμ (log ε 3.51) in 40% yield. This product was identical with the one derived in 39% yield by a Pschorr cyclisation of IIn (m.p. 122°), which itself was prepared from IIm by reduction with Zn and HCl. The absorption around 308-312 mμ in phenanthridine is also evident in these compounds.

Structures assigned to the Pschorr cyclisation products were based on the following considerations. Analytical data ruled out structures of the type IIo or a benzotriazinium cation. Va on oxidation with alkaline permanganate gave phthalic acid and with sodium dichromate in sulphuric acid a mixture of phthalic acid and diphenyl o-carboxylic acid. Vb on distillation with zinc dust in the presence of hydrogen gave phenanthridine, authenticated by comparison with genuine samples of phenanthridine and its picrate. These reactions proved unequivocally the fusion through their o-positions of the two phenyl nuclei on the 3- and 4-positions of the s-triazole, resulting in the creation of a s-triazolo(4,3-f)-phenanthridine.

This approach is amenable to extension for the synthesis of s-triazoles fused to other benzoheterocycles by a suitable choice of the methods for cyclisation, the substituent on the 5-position and the o-positions of the 3- and 4-aryl residues in the s-triazole. The present route also appears to be more specific than the complementary ones based on creating the s-triazole ring on suitably substituted hydrazino derivatives of benzoheterocycles.

Satisfactory elemental analyses were obtained for C, H and N for all the new compounds. Further work is in progress and will be discussed in the detailed paper. The authors express their gratitude to Dr. R.A. Reed and Dr. R.F. Bridge of Messrs. Whiffen & Co. (Loughborough) for the generous gift of some chemicals, to Dr. L.T. Capell of Chemical Abstracts for advice regarding the nomenclature and numbering of the new systems synthesised now and to Prof. N.V. Subba Rao of the Osmania University for providing facilities for this work.