HETEROCYCLES. IX.[1] SYNTHESIS OF 1,5-DIPHENYL-1H-IMIDAZO[1,5-b]-s-TRIAZOLES

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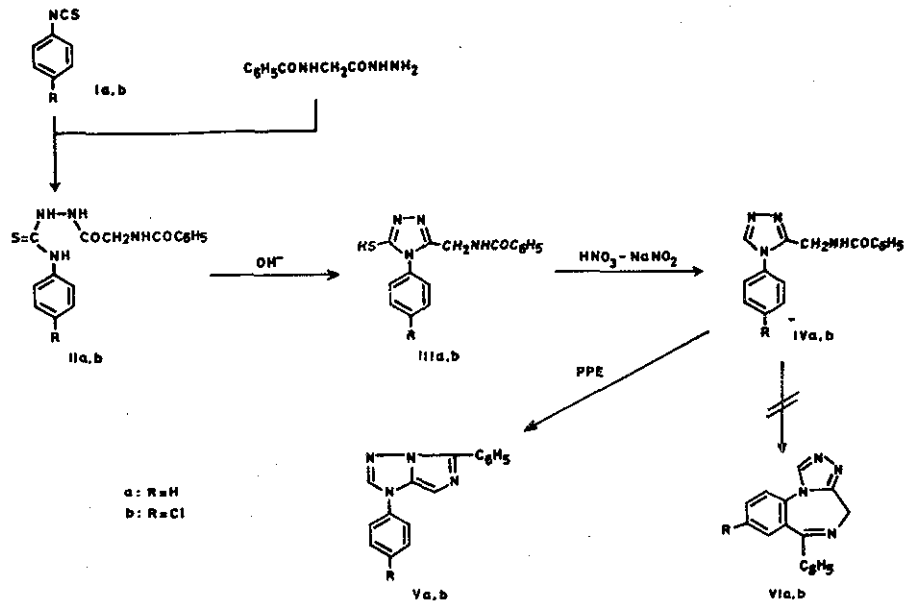
Cyclization of 3-benzamidomethyl-4-phenyl-4H-1,2,4-triazoles (IVa,b) with polyphosphate ester gave 1,5-diphenyl-1H-imidazo[1,5-b]-s-triazole derivatives (Va,b)

In a previous paper,[2] we reported a novel route for the synthesis of 4H-s-triazolo[4,3-a][1,4]benzodiazepines which are highly active as central nervous system (CNS) depressants.[3] As another aproach to these useful compounds, we attempted a Bischler-Napieralski type cyclization of 3-benzamidomethyl-4-phenyl-4H-1,2,4-triazole derivatives (IVa,b).

Compounds IVa,b were prepared by the following process: Reaction of phenyl isothiocyanates (Ia,b) with hippuric hydrazide in ethanol at 70° gave 1-hippuryl-4-phenylthiosemicarbazide derivatives IIa (93%), mp 198° (decomp.), and IIb (88%), mp 190° (decomp.). Upon heating in aqueous sodium hydroxide, IIa,b were cyclized to triazole-thiols IIIa (94%), mp 243-246°, and IIIb (97%), mp 246-249°. The mercapto group of IIIa and IIIb was



then removed by oxidative desulfurization[4] using nitric acid in the presence of sodium nitrite to afford IVa, mp 165-166°, and IVb, mp 195-197°, in 71% and 81% yield, respectively.

When IVa was heated with five-fold amount of polyphosphate ester (PPE)[5] at 150° for 30 minutes, the corresponding dehydrated compound Va, mp 225-226°, was obtained in 62% yield. Compound Va analyzed for $C_{16}H_{12}N_4$ (Calcd: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.53; H, 4.95; N, 21.26) and its IR spectrum showed the absence of -NHCO- group which was present in IVa [ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1660 (C=O)]. The NMR spectrum[6] of Va exhibited two singlets at 7.08 and 9.32 ppm attributable to an imidazole and a triazole proton, respectively, in addition to multiplets due to aryl protons

(10 H, 7.2-8.4 ppm). These data revealed that the cyclized compound (Va) was not the expected triazolobenzodiazepine (VIa) but rather the 1,5-diphenyl-4H-imidazo[1,5-b]-s-triazole which formed by cyclization on $N_{(2)}$ of the triazole ring of IVa. Similarly cyclization of IVb with PPE gave Vb, mp 232-233°, in 76% yield. Formation of triazolobenzodiazepines (VIa,b) was not observed in these reaction mixtures as indicated by TLC-analyses.

As far as we know, only a few compounds having imidazo[1,5-b]-s-triazole skeleton are reported in the literature, e.g. 2,5,7-tricyano-[7] and 2,5,7-tris(trifluoromethyl)-imidazo[1,5-b]-s-triazole[8] which was prepared by addition reaction of hydrogen cyanide with cyanogen and trifluoroacetonitrile, respectively. The present reaction offers a simple method for the synthesis of a variety of imidazo[1,5-b]-s-triazole derivatives whose pharmacological properties are hitherto unknown. Compounds described in this paper do not show noticeable CNS activity.

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