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A NEW INDAZOLE RING SYNTHESIS

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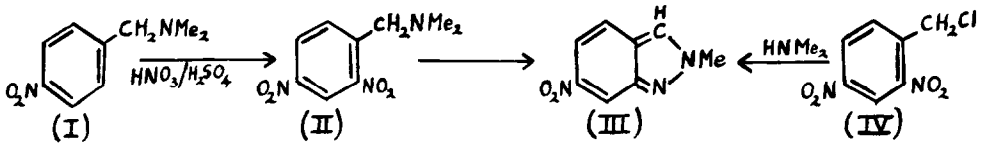
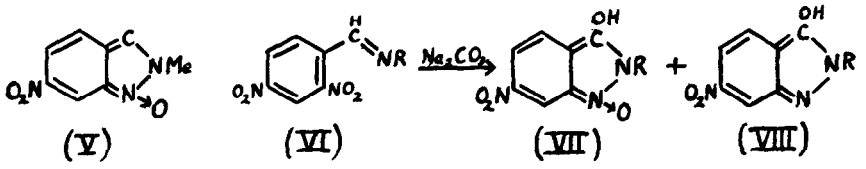
4-Nitrobenzyl dimethylamine (I) was nitrated with fuming nitric acid/fuming sulphuric acid, in good yield, to an unstable red oil which was the expected 2,4-dinitrobenzyl dimethylamine (II) τ(no solvent) 7.68 (6H,s,2Me), 6.12 (2H,s,CH_2), 1.93 (1H,d,H_6), 1.53 (1H,q,H_5), 1.39 (1H,d,H_3), (J_{3-5} 2.5c/s, J_{3-6} 0c/s, J_{5-6} 8.8c/s); ν (cm^{-1}) 3110, 2980, 2955, 2870, 2830, 2780, 1610, 1540. The six absorptions in the C-H stretching region of the i.r. spectrum of II were very similar to absorptions in the same region of the i.r. spectrum of I. When first isolated, the unstable red oil (II) contained a few yellow crystals and, after several days, the oil was transformed into a mass of yellow crystals, m.p.158.5-160° after crystallisation from ethanol. The yellow crystals were 2-methyl-6-nitroindazole (III) (lit[1,2] m.p.160°) as indicated by correct analysis; mass spectrum (molecular ion) 177; similar n.m.r. spectrum to the published data[2]; ν (cm^{-1}) 3150, 3060, 2940, 1525; λ (mμ) 265 (ε,6410), 293 (ε 2950), 355 (ε 295). This is an unequivocal synthesis of 2-methyl-6-nitroindazole and it confirms the original structural assignment of Auwers[3].



Another reaction, intended to yield II, in fact produced the indazole (III). When an ether solution of dimethylamine was slowly added to an ice-cold ether solution of 2,4-dinitrobenzyl chloride (IV) a vigorous exothermic reaction ensued and a 75% yield of the indazole (III) m.p.160-161° was obtained, which was identical with the previously obtained sample by all the above physical measurements. The indazole (III) was further

characterised by stannous chloride reduction to 6-amino-2-methylindazole m.p.154-6° (lit[3] m.p.156-7°). τ($CDCl_3$) 5.85 (3H,s,Me), 3.37 (H_5), 3.16 (H_7), 2.52 (H_4) (J_{4-5} 9c/s, J_{4-7} 1c/s, J_{5-7} 2c/s), 2.25 (H_3); ν(cm^{-1}) 3460, 3200, 3100, 1632. The amino compound was benzoylated to give white crystals of 6-benzamido-2-methylindazole, m.p. 223-5°, ν(cm^{-1}) 3260, 3140,, 1660, 1570.

In both methods of preparation of III, it is reasonable to assume that the intermediate is II and, since II survived the strong acid nitrating mixture in one case but not the alkaline dimethylamine in the other, the cyclisation to form an indazole ring clearly needs basic conditions. The mechanism of formation may involve the N-oxide (V) as intermediate, as this requires the loss of the elements of methanol from II. Several slightly similar alkaline cyclisations, of benzyl compounds with o-nitro substituents, to form indazole rings are known[4,5], the most similar being the reaction of 2,4-dinitrobenzalanilines (VI) with sodium carbonate to yield the N-oxide (VII) and the substituted indazole (VIII)[4].



(V) (VI) (VII) (VIII)

The scope and limitation of the reaction are being investigated.

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References

1. O.N. Witt, E. Noelting, and E. Grandmougin, Ber., 1890, 23, 3638. E.Noelting, Ber., 1904, 37, 2584. I.M.Barclay, N.Campbell, and G.Dodds, J., 1941, 117. R.R.Davies, J., 1955, 2412.
2. J.Elguero, A.Fruchier, and R.Jacquier, Bull.Soc.Chim., 1966, 2074.
3. K.Auwers and K.Schwegler, Ber., 1920, 53, 1211.
4. S.Secareanu and I.Lupas, Bull.Soc.Chim., [4], 1933, 53, 1436; [5], 1934, 1, 373; [5], 1935, 2, 69; 1936, 3, 1161; J.Prakt.Chem., 1934, 140, 90.
5. T.Naito, R.Domori, and M.Sano, J.Pharm.Soc.Japan, 1954, 74, 596. I.Tananescu and E.Tananescu, Bull.Soc.Chim., [5], 1933, 2, 1016.