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HEXAHYDROTETRAZINES FROM NITROSAMINES (1)

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The current interest in 1,3-dipoles (2) and a recent communication (3) demonstrating the lability of α-protons on simple nitrosamines has prompted us to report that we have synthesized hexahydrotetrazines from aliphatic nitrosamines. Hexahydrotetrazines have been synthesized previously from substituted hydrazines and reactive aldehydes, by dimerization of hydrazines and from azomethine imine salts (4). Some hexahydrotetrazines have been found to be precursors of azomethine imines and thus can be useful in heterocyclic synthesis (2,4b).

We have studied the reaction of phenyllithium with dimethyl, diethyl, and piperidine nitrosamines (5) and have found the products to be the corresponding "head-to-tail" dimers in fair yield (30-40%) (6). Compound I: m.p. 151-152°; ir (nujol), 6.24, 12.75, 13.41, 14.51 u; nmr (CCl_4,TMS) δ2.55 (s, 6H), 4.47 (s, 4H), 6.4-7.3 (m, 10H). II: m.p. 151-151.5°; ir (nujol) 6.23, 13.26. 14.39 u; nmr (CCl_4,TMS) δ 1.1-2.1 (m,12H) 2.83-3.21 (m,4H), 3.57 (d, 1H) 4.03 (s,1H) 6.37-7.20 (m, 10H). III: m.p. 184-185°; ir (nujol) 6.28, 13.50, 14.58 u; nmr ($CDCl_3$,TMS) δ 1.04 (t, 6H) 1.48 (d 6H), 2.89 (q, 4H), 4.70 (q,2H) 6.33-7.3 (m, 10H).

In a typical reaction an ether solution of phenyllithium is added dropwise to a virgorously stirred solution of the nitrosamine in ether at -60° to -65° (7). The reaction is quenched after 20 minutes to 1 hour by slowly adding water until

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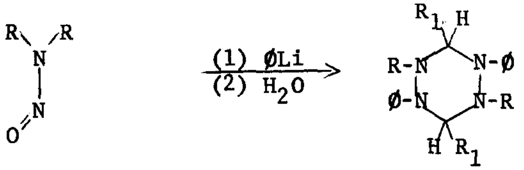
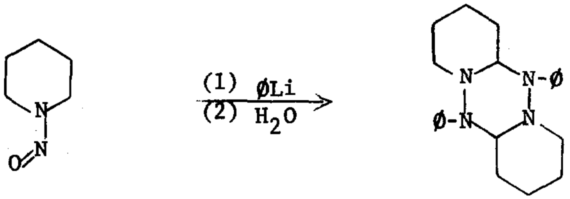
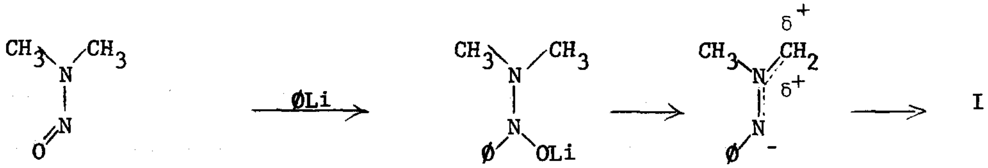


I, $R = CH_3$, $R_1 = H$
III, $R = CH_2\text{-}CH_3$, $R_1 = CH_3$



II



the temperature is above 0°. The pale yellow oil from the ether layer is triturated with methanol or hexane to give a white crystalline product on standing. During the addition of phenyllithium striking color changes are observed. Piperidine nitrosamine changes from yellow to green to blue to blue-black and the color changes are reversed with the addition of water. The mode of reaction suggests an azomethine imine intermediate formed either during reaction with phenyllithium or when quenched with water.

Compound I was compared to the product prepared by Knorr (4a) from 1-methyl-2-phenylhydrazine and formaldehyde and was found to be identical by nmr, ir, tlc, and mixed melting points. This suggests that the major product isolated by Knorr was the hexahydro-1,4-dimethyl-2,5-diphenyl-s-tetrazine and not its 1,5-dimethyl isomer.

This route offers a new approach to the synthesis of hexahydrotetrazines and demonstrates that nitrosamines should not be relegated to the position of derivatives, but looked upon as a source of new chemistry. Further studies are now in progress on the scope and mechanism of this reaction.

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REFERENCES

(1) This investigation was supported by the Public Health Service Grant No. CA-02857 from the National Cancer Institute.

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(5) These nitrosamines are available from Eastman Organic Chemicals, Rochester, New York.

(6) All compounds had satisfactory analyses for proposed structures.

(7) The reaction was conducted under an Argon atmosphere.