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THE REACTIONS OF ISOTHIAZOLIUM SALTS WITH NITROGEN BASES

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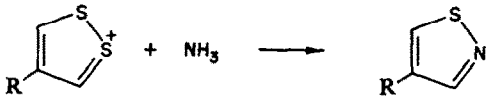
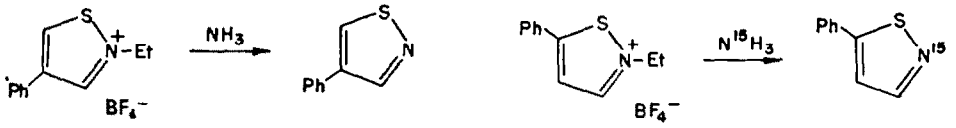
Abstract—Isothiazolium salts have been shown to react with ammonia to yield isothiazoles and with hydrazines to yield pyrazoles.

IN THE preceding paper[2] the reaction of 1,2-dithiolium salts (I) with ammonia to yield isothiazoles (II) is discussed. In the present study a similar reaction of isothiazolium



I II

salts, as exemplified by the formation of 4-phenylisothiazole (IV) on treatment of N-ethyl-4-phenylisothiazolium fluoborate (III) with ammonia in ethanol, is described.[3]



III IV V VI

Though this reaction is of little synthetic value, the isothiazoles obtained are products of no little mechanistic sophistication as revealed by the fact that N-ethyl-5-phenylisothiazolium fluoborate (V) gives isotopically undiluted 5-phenylisothiazole-N^{15} (VI) when treated with $N^{15}H_3$.[4]

Of the four remaining plausible mechanisms for this reaction (Chart, see preceding paper[2] for additional discussion) our initial inquiries exclude A and B as generally valid pathways. N-Ethyl-3-phenylisothiazolium fluoborate, though it does not retain the proton in the 3-position required by these mechanisms, still reacts to yield 3-phenylisothiazole.

The only evidence we have obtained which mitigates against mechanism D versus

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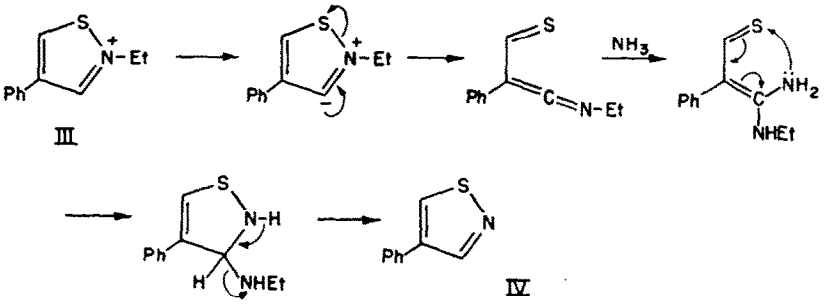
[2] R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson and D. M. McKinnon, *Tetrahedron* **22**, 2113 (1966).

[3] An analogous reaction of the benzisothiazolium cation has been discovered by K. Fries, K. Eishold and B. Vahlberg, *Liebigs Ann.* **454**, 264 (1927). The mechanistic conclusions reached in the present paper can probably also be transferred to this system.

[4] This reaction also confirms the fact that the isothiazoles studied are alkylated on nitrogen and not on sulfur.

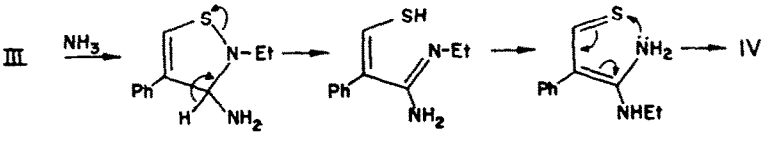
mechanism C is the fact that 5-phenylisothiazole (VI) is formed in higher yield than 4-phenylisothiazole (IV) (89% vs. 64%). The argument follows. Assume steric factors are most important in determining the relative rates of these reactions and that the rates of the yield lowering side reactions are not directly dependent on the same factors—a not highly probable set of preconditions. Then, if the displacement

Mechanism A:

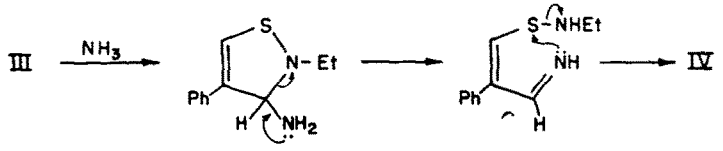


III IV

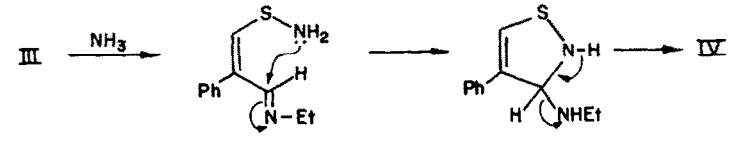
Mechanism B:



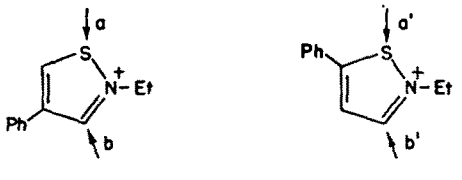
Mechanism C:



Mechanism D:



mechanism D is operative, attack at *a* should be favored over the more sterically hindered *a'* and a higher yield of IV should be obtained. In the addition-elimination pathway C, attack at *b'* should be favored over *b* and a higher yield of VI should be obtained. The latter is the experimental result.



III V

Other nucleophiles react with the isothiazolium cation to yield additional heterocyclic systems in analogous reactions. For example, N-ethyl-5-phenylisothiazolium fluoborate gives 3-phenylpyrazole on treatment with hydrazine and a mixture of 1,3-diphenylpyrazole and 1,5-diphenylpyrazole on treatment with phenylhydrazine.

EXPERIMENTAL

All m.ps were taken in soft glass capillary tubes in a Thomas–Hoover m.p. apparatus using a calibrated thermometer. The IR spectra were run on a Perkin–Elmer Model 21 Double Beam Recording Spectrophotometer equipped with NaCl optics; the UV spectra were run on a Cary Model 11 Recording Spectrophotometer; and the NMR spectra were measured on a Varian A-60 Spectrometer. A Consolidated Engineering Corp. Type 21-103C mass spectrometer was used to record the mass spectra, and VPC was carried out on an F & M Model 609 flame ionization gas chromatograph using disc chart intregation.

N-Ethyl-4-phenylisothiazolium fluoborate. A solution of 16·8 g (0·104 mole) 4-phenylisothiazole[4] in 25 ml CH_2Cl_2 was slowly added to 19·9 g (0·104 mole) triethyloxonium fluoborate[5] with external cooling. The product immediately separated as an oil which soon solidified. The white solid was filtered off, washed with ether, and dried yielding 26·0 g (90%) N-ethyl-4-phenyl-isothiazolium fluoborate. An analytical sample was prepared by dissolving the product in warm acetone and precipitating with ether; white needles, m.p. 126·5–127·5° (UV spectrum: 305 mμ (3,200), 225 mμ (16,400) in 0·1N HCl; NMR spectrum; 0·80 τ (singlet, 1 proton), 0·87 τ (singlet, 1 proton), 2·32–2·83 τ (multiplet; 5 protons), 5·51 τ (quartet, J = 6·5 c/s, 2 protons), CH_2 under solvent acetonitrile. (Found: C, 47·92; H, 4·62; N, 4·95; S, 11·48. $C_{11}H_{12}NSBF_4$ requires: C, 47·68; H, 4·37; N, 5·06; S, 11·57%.)

N-Ethyl-5-phenylisothiazolium fluoborate. This compound was prepared as above from 7·7 g (0·048 mole) 5-phenylisothiazole[4] and 9·1 g (0·048 mole) triethyloxonium fluoborate;[5] 11·8 g (89%) of the product was recrystallized from acetone–ether, white needles, m.p. 112·5–113·5° (UV spectrum: 306 mμ (13,700), 260 mμ, shoulder (4,500), 227 mμ, shoulder (4,200) in 0·1 N HCl; NMR spectrum: 1·23 τ (doublet, J = 3·0 c/s, 1 proton), 2·40 τ (doublet, J = 3·0 c/s) and 2·43–2·70 τ (multiplet) (6 protons), 5·51 τ (quartet, J = 6·5 c/s, 2 protons), CH_2 under solvent acetonitrile. (Found: C, 47·41; H, 4·38; N, 5·07; S, 11·69. $C_{11}H_{12}NSBF_4$ requires: C, 47·68; H, 4·37; N, 5·06; S, 11·57%.)

N-Ethyl-3-phenylisothiazolium fluoborate. The alkylation was carried out as above with 0·36 g (2·2 mmoles) 3-phenylisothiazole[4] and 0·42 g triethyloxonium fluoborate.[5] This reaction is much slower. The solvent was finally removed *in vacuo* after 3 days and the residue recrystallized from acetone–ether yielding 0·22 g (36%) white needles, m.p. 136·5–137·5° (UV spectrum: 281 mμ (17,300) in 0·1N HCl; NMR spectrum: 0·70 τ (doublet, J = 5·5 c/s, 1 proton), 2·55 τ (doublet, J = 5·5 c/s) and 2·60–2·83 τ (multiplet) (6 protons), 5·6 τ (quartet, J = 6·5 c/s, 2 protons), 8·80 τ (triplet, J = 6·5 c/s, 3 protons) in hexadeutero-acetone. (Found: C, 47·63; H, 4·42; N, 4·93. $C_{11}H_{12}NSBF_4$ requires: C, 47·68; H, 4·37; N, 5·06%.)

N-Ethyl-5-phenylisothiazolium-3-d fluoborate. N-Ethyl-5-phenylisothiazolium fluoborate, 1·1 g, was dissolved in 25 ml of a phosphate buffer in D_2O (99·75%; pD 7·6) at 60° and kept at that temp for 5 hr. The deuterated salt crystallized out when the reaction solution was cooled in ice. After filtration and recrystallization from acetone–ether, 0·53 g (48%) of white needles, m.p. 112–113°, was obtained (IR spectrum: 4·52 μ (C–D stretch), KBr; UV spectrum: 306 mμ (13,700), 260 mμ, shoulder (4,500), 227 mμ, shoulder (4,200) in 0·1N HCl; NMR spectrum: 2·40 τ (singlet) and 2·43–2·70 τ (multiplet) (6 protons), 5·51 τ (quartet, J = 6·5 c/s, 2 protons), CH_2 under solvent acetonitrile).

4-Phenylisothiazole. N-Ethyl-4-phenylisothiazolium fluoborate, 5·0 g (0·018 mole), was dissolved in 75 ml of a saturated solution of anhydrous ammonia in EtOH and the mixture allowed to stir for 2 hr at room temp. The solvent was removed in vacuum and the isothiazole distilled at reduced press, 0·15 mm at 95–100°, 1·9 g (64%), m.p. 36–37° (lit.[4] 35·5–36·5°); IR, UV, and NMR spectra were identical to those of authentic material.

Reaction of N-ethyl-5-phenylisothiazolium fluoborate with $N^{15}H_3$. The Dumas bulb of gaseous $N^{15}H_3$ (97·8% N^{15}), 0·5 g (0·0278 mole), obtained from Merck of Canada was fitted with a ground-glass male joint and attached to a 100 ml ground-glass jointed round-bottomed flask containing 30 ml

[5] H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939).

of anhydrous EtOH. The ammonia was condensed into a little well in the Dumas bulb and the EtOH was allowed to flow into the cooled bulb by breaking the break-seal with a magnet. The ethanolic ammonia solution was pipetted into a 100 ml round-bottomed flask containing 2·77 g (0·01 mole) N-ethyl-5-phenylisothiazolium fluoborate, and the mixture allowed to stir for 2½ hr at room temp. The solvent was removed at reduced press and the 5-phenylisothiazole-N^{15} sublimed directly from the reaction flask onto a cold finger, 0·1 mm at 55°, 1·42 g (89%), m.p. 46·5–47·5° (lit[3]. 46·5–47°). The material was spectroscopically identical with authentic 5-phenylisothiazole.

Mol. wt. by mass spectroscopy: 162; Theory for $C_9H_7N^{15}S$: 162; $\%N^{15} = 96{\cdot}2\%$ (determined from the relative intensities of m^{161}, m^{162}, m^{163} and m^{164}). 5-Phenylisothiazole shows a strong parent peak at 161 in the mass spectrometer. Also two important fragmentation particles are observed at m = 134 ($C_8H_6S^+$) and m = 115 ($C_9H_7^+$). (Three independent methods for measuring the ion masses were used.)

3-Phenylisothiazole. N-Ethyl-3-phenylisothiazolium fluoborate, 0·058 g, was treated with 5 ml EtOH saturated with ammonia and the mixture stirred for 2½ hr. The solvent was removed under vacuum and the residue extracted with $CHCl_3$. The $CHCl_3$ solution was analyzed directly by VPC. (8′ Fluorosilicone on Chromosorb P; 175°; He flow 75 ml/min). The single high boiling product had the same retention time, 20·5 min. as authentic 3-phenylisothiazole.[3]

Reaction of N-ethyl-5-phenylisothiazolium-3-d fluoborate with ammonia. This deuterated salt, 0·489 g (1·76 mmoles) was treated with 15 ml abs EtOH containing anhydrous ammonia (1 g) in the manner described for the reaction of the 5-isomer with $N^{15}H_3$. Completely protonated 5-phenylisothiazole, 0·207 g (73%), m.p. 46–47° (lit.[3] 46·5–47°) was isolated as shown by NMR (1·52 τ(doublet, J = 2·0 c/s, 1 proton), 2·27–2·77 τ (multiplet, 6 protons) in $CDCl_3$).

3-Phenylpyrazole. N-Ethyl-5-phenylisothiazolium fluoborate, 1·0 g (3·6 mmoles) was mixed with 20 ml abs EtOH and 0·5 g 95% hydrazine hydrate in 10 ml abs EtOH was added over a 10 min period. The mixture was stirred for 2½ hr at room temp and then heated on a steam bath for 10 min. EtOH was removed under vacuum and the residue extracted with $CHCl_3$. On evaporation of the $CHCl_3$, 3-phenylpyrazole, m.p. 73–77° (lit.[6] 75–76°); identified as the picrate, m.p. 169·5–170·5° (lit.[6] 169–170°) from EtOH. A small quantity of S was obtained when the residue remaining after $CHCl_3$ extraction was treated with CS_2.

1,3-Diphenylpyrazole; 1,5-diphenylpyrazole. N-Ethyl-5-phenylisothiazolium fluoborate, 1·0 g (3·6 mmoles) was mixed with 20 ml abs EtOH and 0·8 g (7·4 mmoles) phenylhydrazine in 10 ml abs EtOH was added over 15 min. The solution was stirred for ½ hr at room temp, 1 hr at reflux, and an additional hr at room temp. Removal of EtOH at reduced press, followed by extraction of the residue with $CHCl_3$ yielded 1·3 g of a brown oil which did not solidify. VPC (8′ Silicone gum rubber on Chromosorb P; 205°; He flow, 110 ml/min) showed two high boiling compounds to be present.

	Ret. time	Rel % in mixture
1,5-diphenylpyrazole	15 min	79
1,3-diphenylpyrazole	31 min	21

The oil was dissolved in benzene and was chromatographed through 30 g of alumina (Merck) using benzene as eluant; 10 fractions of 65 ml each were collected and gave varying amounts of solid on solvent removal.

Fraction 1 was subjected to fractional crystallization from ligroine. 1,3-Diphenylpyrazole was isolated as off-white needles, m.p. 84–85·5° (lit.[7] 84–85°). S was also isolated.

Vacuum sublimation, 44° at 0·65 mm, of the solid from fractions 3 and 4 gave 1,5-diphenylpyrazole as a white solid, m.p. 54–55° (lit.[7] 55–56°).

Acknowledgement—We wish to thank the U.S. Public Health Service for a grant (GM-09317) to support this research.

[6] B. Sjollema, *Liebigs Ann.* **279**, 248 (1894); L. Knorr, *Chem. Ber.* **28**, 696 (1895).

[7] K. v. Auwers and W. Schmidt, *Chem. Ber.* **58**, 529 (1925).