The Reaction of 1-Azirines with 2-Pyridyl Isothiocyanate:
Possible Approaches to Benzodiazepine and Benzotriazepine Derivatives
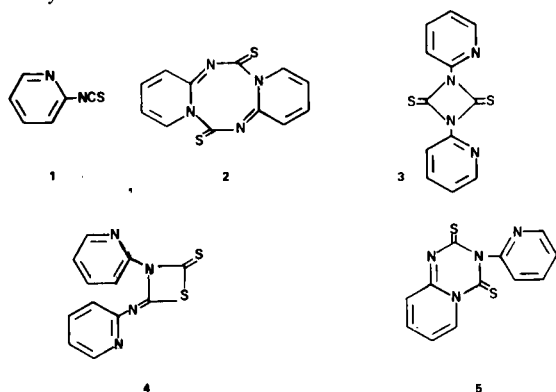
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The structure of the dimer (5) from 2-pyridyl isothiocyanate (1) has been confirmed by ^{13}C nmr spectral studies. The cycloaddition of 2-pyridyl isothiocyanate with 1-azirines results in the formation of thiazoles (10). Thermal decomposition of the vinyl azide (14) gives the pyrrole (15) and the pyridazine (16) instead of 2-(2-pyridyl)-1-azirine (12).

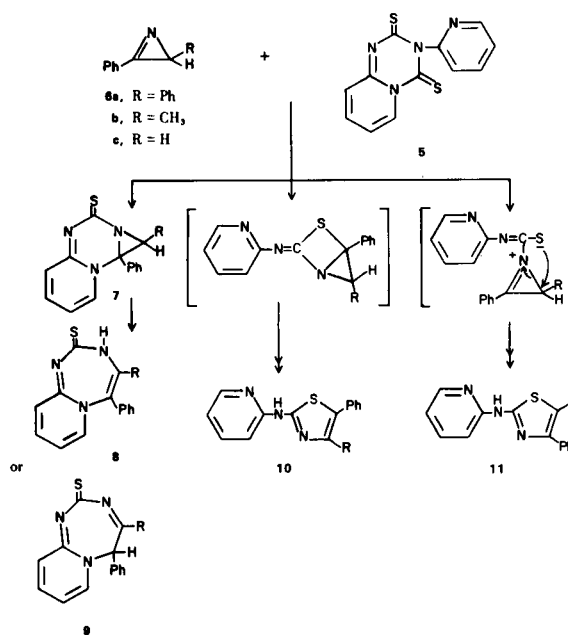2-Pyridyl isothiocyanate (1) is produced by the reaction of 2-aminopyridine and carbon disulfide in the presence of triethylamine (1,2). At room temperature this compound exists as a dimer. Several possibilities for the structure of the dimer are available in the form of structures 2, 3, 4 and 5. That the correct structure of the dimer was 5, the result of [4 + 2] cycloaddition of monomers, came from ^{1}H nmr studies (3) and by recognition of similar dimerization of imidoyl isothiocyanates (4). We have confirmed this by ^{13}C nmr spectral analysis at room temperature which clearly showed the presence of an unsymmetrical structure - two C=S carbons and ten aromatic ring carbons. Furthermore, when the probe temperature was increased to 70°, the spectrum changed dramatically and showed only six non-equivalent carbons consistent with dissociation of the dimer to monomeric pyridyl isothiocyanate.

triazepine system through cycloaddition with 1-azirines. However, when 2,3-diphenyl-1-azirine (6a) in toluene was treated with a half molar ratio of 2-(2-pyridyl)pyrido-[1,2-a][1,3,5]triazine-1,3-dithione (5) under reflux for 4 hours, an adduct m.p. 203° was obtained in 73% yield. Its mass spectral parent ion peak and elemental analysis were consistent with the molecular formula $C_{20}H_{15}N_3S$. Several possibilities exist for the structure of the adduct. A [4 + 2] cycloaddition would furnish 7a or its rearranged products 8a and 9a. Product 10a is the eventual result of

6a, R = Ph
b, R = CH₃
c, R = H

We were particularly interested in the enophilic properties of 1 because of the potential for entry into the benzo-

a $[\pi 2_s + \pi 2_a]$ cycloaddition and hydrogen shift(s). Compound **11a** results from initial nucleophilic attack, 1,3-bond scission and cyclization, and a 1,5-sigmatropic shift. Spectroscopic and related data allowed differentiation among these and other possibilities. Infrared data which shows N-H absorption rule out structures **7a** and **9a**. Carbon-13 nmr spectral analysis (5) showed no C=S carbon, removing structure **8a** as a possibility. The mass spectrum exhibited a fragmentation pattern characteristic of a thiazole ring system (particularly the thiirene peak at m/e 210 (6). Mass spectral data, however, rule out imidazole derivatives, the eventual result of cycloaddition across the C=N bond of pyridyl isothiocyanate. Final confirmation of the structure of the adduct as **10a** came from careful comparison of the ^{1}H nmr spectra of known thiazole derivatives (7,8). Thiazoles **10b** and **10c** were obtained from azirines **6b** and **6c**, respectively. As expected, these cycloaddition products were thermally very stable even at relatively high temperatures (145°).

The formation of [2 + 2] type cycloadducts rather than [4 + 2] cycloadducts from the reaction of 2-pyridyl isothiocyanate and 1-azirines is puzzling but not entirely unexpected in the light of results with benzoyl isothiocyanate (8). It can be stated finally that in reactions of 1-azirines with heterocumulenes containing the C=S bond, preferential addition in a regiospecific manner to the C=S bond occurs probably through a dipolar transition state where the inherent ability of sulfur to stabilize the residual negative charge results in a lower energy electronic pathway to the cycloadducts.

Another possible one-step approach to benzotriazepine (and benzodiazepine) derivatives would be through a conjugated azirine system where part of this structure would behave as a diene. A molecular system that would behave not only as a very reactive ene but also as a possible diene is 2-(2-pyridyl)-1-azirine (**12**). However, when the synthesis of this azirine was attempted starting with 2-vinyl pyridine (see Scheme I), the corresponding vinyl azide **13** decomposed spontaneously and exothermically at room temperature to give a considerable amount of intractable polymeric material and two crystalline compounds in low yields.

The first compound (m.p. 94-95°) showed a mass spectral molecular ion peak at 221 and subsequent elemental analysis suggested the molecular formula $C_{14}H_{11}N_3$. Its infrared spectrum showed N-H absorption at 3455 cm^{-1}. Its ^{1}H nmr spectrum showed 10 hydrogens in the aromatic region in the ratio of 1:1:2:1 and an exchangeable hydrogen at δ 10.52. The ^{13}C nmr spectrum showed only 7 carbon absorptions (between 109 and 150 ppm) suggesting a symmetrical structure. Collectively, the data are consistent with the compound being 2,5-bis-(2-pyridyl)pyrrole (**15**).

The structure of the second compound was established

Scheme I
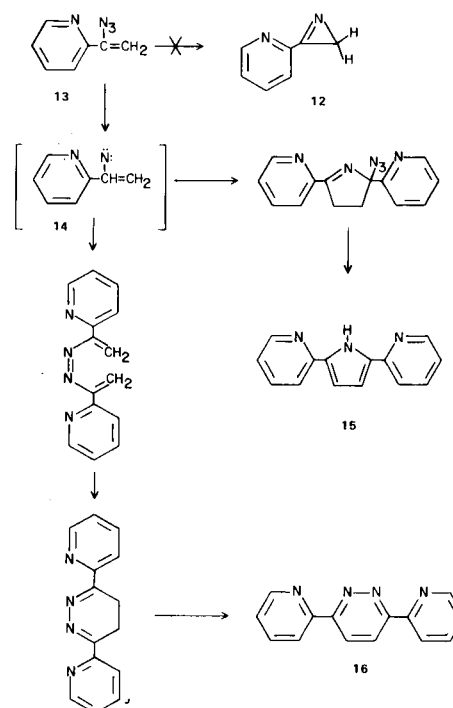
from mass spectral and spectroscopic data as 3,6-bis-(2-pyridyl)pyridazine (**16**). An authentic sample of this, prepared from 2-cyanopyridine, confirmed the structure (9).

On the basis of some previous work on the thermal decomposition of α-styryl azide (10), it is apparent that the formation of **15** and **16** does not occur via 2-(2-pyridyl)-1-azirine (**12**). The formation of both compounds, however, can be rationalized as occurring through the intermediacy of the pyridyl nitrene **14** (10). Cycloadditive capture of this fugitive species by the vinyl azide **13** and subsequent elimination of hydrogen azide would furnish **15**. Dimerization of **14**, followed by electrocyclization, and air oxidation would produce **16**.

EXPERIMENTAL

Dimer of 2-Pyridyl Isothiocyanate (5).

A mixture of 2-aminopyridine (12.54 g.), carbon disulfide (12.00 g.), triethylamine (22.00 g.), 10 ml. of absolute ethanol was stirred at room temperature for 2 days. The product which had separated was filtered and washed with a little ethanol and with acetone affording triethyl ammonium N-2-pyridyl dithiocarbamate as yellow prisms (29.60 g., 82%), m.p. 87-88° (lit. (1) m.p. 88-89°).

Triethylammonium N-2-pyridyl dithiocarbamate (25.00 g.) was suspended in 200 ml. of benzene and a solution of 12.5% phosgene in benzene (120 ml.) was added dropwise with stirring during 1.5 hours at 0°. After being stirred overnight at room temperature,

the solid was filtered, washed with benzene, air-dried, and triturated with 200 ml. of water. The residue was filtered and washed with water and finally with 50 ml. of acetone, affording the dimer of 2-pyridyl isothiocyanate as a brick-red solid (14.50 g., 70.6%), m.p. 106-107° (lit. (1) m.p. 110-111°); ^{1}H nmr δ TMS (DMSO-d$_6$): 7.13-7.55 (m, 4H), 7.90-8.21 (m, 2H), 8.53-8.64 (m, 1H), 9.19-9.27 (m, 1H); ^{13}C nmr δ TMS (DMSO-d$_6$): 116.78, 123.53, 124.07, 124.23, 133.02, 139.28, 143.75, 146.94, 149.58, 155.78, 173.21, 178.39.

The dimer (0.10 g.) in DMSO-d$_6$ (1 ml.) was heated at 80° for a few minutes until the solution became yellow, and was checked by ^{13}C nmr at 75°. The monomeric 2-pyridyl isothiocyanate showed the following absorptions: ^{13}C nmr δ TMS (DMSO-d$_6$): 114.71, 119.45, 135.11, 138.23, 146.88, 152.86.

Reaction of 2,3-Diphenyl-1-azirine (6a) with 2-Pyridyl Isothiocyanate.

To a solution of 0.772 g. (4 mmoles) of 2,3-diphenyl-1-azirine in 15 ml. of toluene was added 0.544 g. (2 mmoles) of the dimer of 2-pyridyl isothiocyanate 5, and the reaction mixture was heated under reflux for 4 hours. The solvent was removed in vacuo and dichloromethane-ether was added for crystallization. The crude product was recrystallized from dichloromethane-ether, filtered, and washed with ether to give 0.957 g. (72.7%) of white powderish crystals, m.p. 202-203°; ir ν max (Nujol): 3250 (N-H), 3195 (N-H), 1615 (C=N), 1555, 1485, 1420, 1335 cm^{-1}; ^{1}H nmr δ TMS (DMSO-d$_6$): 6.82-7.86 (m, 13H), 8.30 (d, 1H), 11.44 (s, br, 1H, exchange with deuterium oxide); ^{13}C nmr δ TMS (DMSO-d$_6$): 110.85, 115.92, 123,36, 127.30, 128.11, 128.44, 128.71, 129.19, 132.70, 135.34, 137.88, 143.59, 146.40, 151.63, 157.46; mass spectrum: (70 eV, direct inlet) m/e 329 (M$^+$), 210 [Ph-(c-C$_2$S)-Ph], 178 (Ph-C≡C-Ph), 151 [M$^+$ - Ph-(c-C$_2$S)-Ph], 121 (PhCS), 103 (PhCN), 78, 77, 44.

Anal. Calcd. for C$_{20}$H$_{15}$N$_3$S: C, 72.9; H, 4.6; N, 12.7. Found: C, 72.8; H, 4.6; N, 12.7.

Reaction of 3-Methyl-2-phenyl-1-azirine (6b) with 2-Pyridyl Isothiocyanate.

To a solution of 0.524 g. (4 mmoles) of 3-methyl-2-phenyl-1-azirine in 15 ml. of toluene was added 0.544 g. (2 mmoles) of 5, and the reaction mixture was heated under reflux for 6 hours. The solvent was removed and the residue was chromatographed on preparative plates carrying silica gel PF$_{254}$ with 30% dichloromethane-ether as the developing solvent. The middle band (R$_f$ = 0.54) was removed, washed with 5% methanol-dichloromethane, and crystallized from dichloromethane-ether to give white crystals (0.372 g., 34.8%), m.p. 199-200°, ir ν max (Nujol): 3230 (N-H), 3160 (N-H), 1620 (C=N), 1600, 1525, 1480, 1410, 1370, 900 cm^{-1}; ^{1}H nmr δ TMS (DMSO-d$_6$): 2.37 (s, 3H), 6.79-7.85 (m, 8H), 8.33 (d, 1H), 11.27 (s, br, 1H, exchange with deuterium oxide); ^{13}C nmr δ TMS (DMSO-d$_6$): 16.07, 110.80, 115.81, 121.85, 126.44, 128.22, 128.71, 132.91, 137.77, 141.76, 151.68, 156.86; mass spectrum: (70 eV, direct inlet) m/e 267 (M$^+$), 151 (M$^+$ - Ph-C≡C-CH$_3$), 148 [Ph-(c-C$_2$S)-CH$_3$], 121 (PhCS), 116 (Ph-C≡C-CH$_3$), 103 (PhCN), 78 (2-pyridyl+), 77, 51, 32.

Anal. Calcd. for C$_{15}$H$_{13}$N$_3$S: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.0; H, 4.8; N, 15.4.

Reaction of 2-Phenyl-1-azirine (6c) with 2-Pyridyl Isothiocyanate.

To a solution of 0.468 g. (4 mmoles) of 2-phenyl-1-azirine in 15 ml. of toluene was added 0.544 g. (2 mmoles) of 5 and the reaction mixture was heated under reflux for 20 hours. The solvent was removed and the residue was separated by preparative

layer chromatography (silica gel PF$_{254}$) using 20% dichloromethane-ether as the developing solvent. The middle band (R$_f$ = 0.65) was removed, washed with 10% methanol-dichloromethane, and evaporated to give 0.302 g. of crude product. It was recrystallized with dichloromethane-ether to give 0.289 g. (28.5%) of pale yellow crystals, m.p. 223-224°; ir ν max (Nujol): 3240 (N-H), 3180 (N-H), 1610 (C=N), 1540, 1430 cm^{-1}; ^{1}H nmr δ TMS (DMSO-d$_6$): 6.80-7.88 (m, 9H), 8.45 (d, 1H), 11.32 (s, br, 1H, exchange with deuterium oxide); mass spectrum: (70 eV, direct inlet 200°) m/e 253 (M$^+$), 237, 136, 134 [Ph-(c-C$_2$S)-H], 121 (PhCS), 103 (PhCN), 94, 78, 77, 51.

Anal. Calcd. for C$_{14}$H$_{11}$N$_3$S: C, 66.4; H, 4.4; N, 16.6. Found: C, 66.3; H, 4.5; N, 16.3.

Attempted Synthesis of 2-(2-Pyridyl)-1-azirine. Isolation of 2,5-bis-(2-Pyridyl)pyrrole (15) and 3,6-bis-(2-Pyridyl)pyridazine (16).

Bromine (60.00 g., 0.375 mole) in 60 ml. of carbon tetrachloride was added slowly to a stirred, cooled (5-10°) solution of 2-vinyl pyridine (39.20 g., 0.375 mole) in 300 ml. of carbon tetrachloride. After the addition was complete, the reaction mixture was stirred at room temperature for 1 hour. A slight amount of dark yellow precipitate which formed during the reactions was removed, and the resulting solution was concentrated in vacuo to give a viscous oil, ^{1}H nmr δ TMS (deuteriochloroform): 3.92-4.63 (m, 2H), 5.17-5.42 (m, 1H), 7.01-7.75 (m, 4H).

The foregoing oil in 400 ml. of DMSO was placed in a three necked 1000 ml. flask fitted with a heavy-duty mechanical stirrer and a nitrogen gas inlet tube. With the aid of an ice bath, the solution was maintained at 10-15° during the addition of 40 g. of sodium azide, and the reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was cooled to 10°. Stirring was continued at ambient temperature for an additional 18 hours, and the sluggish mixture was poured into 500 ml. of cold water. Extraction with ether, drying (sodium sulfate) of the ethereal solution, and evaporation of the solvent gave a thick oil, which immediately started decomposing at room temperature with effervescence. Ether (20 ml.) was added to this product and it was placed in the hood for 2 hours at room temperature. Then it was concentrated in vacuo, and separated by column chromatography (alumina activity I) using ether-pentane mixture as the eluent. The first eluate gave a colorless needle type crystalline compound (4.58 g., 12.3%), m.p. 94-95°; ir ν max (Nujol): 3455 (N-H), 1580, 1550, 1420, 765 cm^{-1}; ^{1}H nmr δ TMS (deuteriochloroform): 6.71 (d, 2H), 6.83-7.06 (m, 2H), 7.36-7.57 (m, 4H), 8.41-8.54 (m, 2H), 10.52 (s, br, 1H, exchanges with deuterium oxide); ^{13}C nmr δ TMS (deuteriochloroform): 108.98, 118.24, 120.67, 133.07, 136.15, 149.04, 150.10; mass spectrum: (70 eV, direct inlet) m/e 221 (M$^+$), 117, 89, 78, 63, 51, 39.

Anal. Calcd. for C$_{14}$H$_{11}$N$_3$: C, 76.1; H, 5.0; N, 19.0. Found: C, 76.4; H, 5.0; N, 19.2.

The second eluate, after solvent removal, gave light orange rectangular crystals, and the melting point of the compound was quite broad. Purification by silica gel plates and subsequent recrystallization of the compound gave colorless needles (1.25 g., 2.9%), m.p. 179-180° (lit. (9) 180°). An authentic sample of 3,6-bis-(2-pyridyl)pyridazine (16), prepared from 2-cyanopyridine according to literature methods (9), was found to be identical to that isolated above.

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