Small-Ring Heterocyclic Compounds. IV. Attempted Synthesis of 1,2-Thiazetidines and Thiazetes[1a-c]

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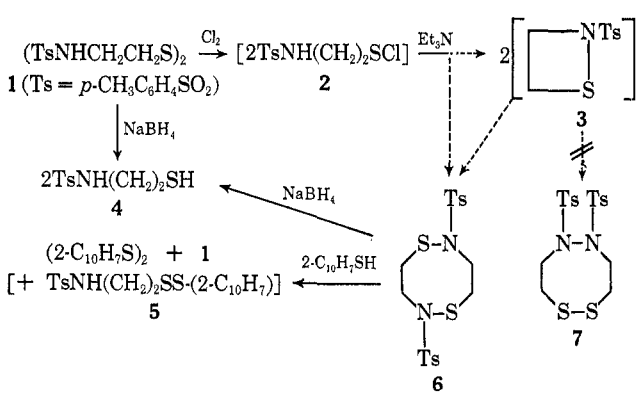
Although the 1,2-thiazetidine ring system, exemplified in structure **3** of Scheme I, is readily available in oxidized form through cycloaddition of N-sulfinyl- or N-sulfonylamine derivatives to olefins or ketenes,[2] we are unaware of any 1,2-thiazetidines, *per se*. Such systems are of interest for several reasons. (1) Both the sulfur and the nitrogen atoms of an aminoethanethiol moiety are latentiated, so that such compounds might be attractive antiradiation drugs.[3] (2) The nitrogen and sulfur lone pairs may be forced into essentially eclipsed positions in which electron repulsion should be high, so that the N–S bond might be unusually labile. (3) A benzothiazete such as **10** of Scheme II might be considered a bis heteroanalog of benzocyclobutadiene and consequently might have unusual chemical and physical characteristics. This paper reports the outcome of attempts to prepare the ring systems **3** and **10**.

In seeking **3**, we converted 2-tosylamidoethyl disulfide (**1**) into the sulfenyl chloride **2**, which was treated *in situ* with triethylamine (Scheme I).

SCHEME I



Sulfonamide **1** was used because of its acidity and because previous experience suggested that an acetamide would function less well.[4] The disulfide **1** was prepared conventionally from 2-aminoethyl disulfide with tosyl chloride, and its structure was assured by its spectra. Chlorinolysis of **1** and addition of triethylamine gave a crude product that showed only a weak ir absorption for NH. Analysis of the crude product by mass spectrometry showed only compounds of molecular weight 458 (**6**) and 460 (**1**); no ion was seen at *m/e* 229, the molecular weight of the thiazetidine **3**. Analysis of the crude product by tlc revealed the presence of only two compounds. One was identified as the original disulfide **1** by comparison with authentic **1**. No material remained at the origin, which would have indicated a polymer of **3**. Purification of the other product by fractional crystallization entailed large losses, but ultimately gave a new compound to which we assign structure **6**, that of a dimer of **3** (13–18% yield).

The assignment of structure **6** is based both on spectral and chemical considerations. The nmr spectrum showed the expected pattern for the aromatic protons (A_2B_2), for the methyl group (a singlet), and for the adjacent methylene protons (two multiplets approximating triplets). The ir spectrum showed no NH absorption, but did show bands corresponding to the aromatic ring and $>SO_2$ moieties. The mass spectrum showed a molecular ion at *m/e* 458 (with proper isotope abundancies at 459 and 460), a base peak at *m/e* 91 ($C_7H_7^+$), and an intense ion at *m/e* 155 ($C_7H_7SO_2^+$). The chemical reactions of **6** seem inconsistent with structure **7**. Thus **6** oxidized iodide ion to iodine, a characteristic of sulfenamides unlikely for **7**.[4] Reduction of **6** with sodium borohydride gave thiol **4** in 93% yield identical (essentially identical spectrum) with **4** prepared by reduction of **1** (Scheme I). The structure of **4** follows from its spectra. The nmr spectrum of **4** showed an A_2B_2 pattern for the aromatic protons, a methyl group, multiplets for the methylene protons, and the amide and thiol protons as multiplets both removable by D_2O exchange. The mass spectrum showed a molecular ion (*m/e* 231) with other ions at *m/e* 184 ($C_7H_7SO_2NHCH_2^+$), 155 ($C_7H_7SO_2^+$), and 91 ($C_7H_7^+$). Furthermore, **6** showed the behavior expected of a sulfenamide[4,5] in reacting with 2-naphthalenethiol to give the two possible symmetrical disulfides (*i.e.*, 2-naphthyl disulfide and **1**), together with a third product presumed to be 2-tosylamidoethyl 2-naphthyl disulfide (**5**).

That the yields of **6** isolated are much lower than the actual yield was indicated by reaction of 2-naphthalenethiol with crude product left after the isolation of **6** in 13% yield. Titration of the excess thiol, after its reaction, corresponded to the presence of **6** in 89% yield. The total yield of **6** calculated thus was 102%.

The failure to find any evidence for the thiazetidine **3** itself, taken along with the apparent high yield of the dimer **6**, requires comment. The dimer **6** seems unlikely to be the primary product, since a high yield would not be anticipated from condensation of two molecules of **2** followed by cyclization to give the eight-membered ring of **6**. It seems considerably more likely that the initial product is **3** and that it then dimerizes to **6**, as shown in Scheme I, to minimize ring strain and lone-pair–lone-pair repulsion.

Synthesis of the benzothiazete **10** was attempted as shown in Scheme II. Reaction of tosyl chloride with

(1) (a) Paper III: T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, 656 (1962). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts DA-49-193-MD-2030 and DADA17-69-C-9128. (c) Presented in part at the Third International Cork Mechanisms Conference, University College, Cork, Ireland, Sept 29–Oct 3, 1969. (d) To whom inquiries should be addressed.

(2) (a) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967, pp 307, 336; (b) G. M. Atkins, Jr., and E. M. Burgess, *J. Amer. Chem. Soc.*, **89**, 2502 (1967); (c) F. Effenberger and R. Gleiter, *Chem. Ber.*, **99**, 3903 (1966).

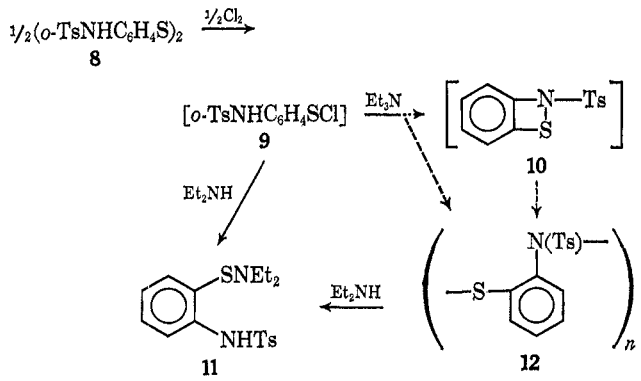
(3) For leading references on antiradiation drugs and latentiation, see L. Field, B. J. Sweetman, and M. Bellas, *J. Med. Chem.*, **12**, 624 (1969).

(4) N. E. Heimer and L. Field, to be published.

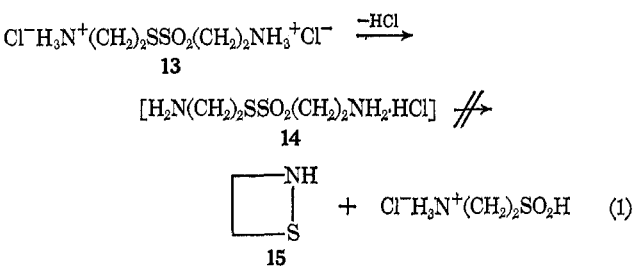
(5) (a) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968); (b) A. Fontana, F. Marchiori, L. Moroder, and E. Scoffone, *ibid.*, 2985 (1966).

o-aminophenyl disulfide gave **8**, which had appropriate spectra. Chlorinolysis of **8** to give the sulfenyl chloride **9** was followed by reaction *in situ* with triethylamine to give an insoluble white solid (**12**). This solid (**12**) showed no ir absorption for NH and was soluble only in secondary amines or in pyridine containing thiols. The mass spectrum of **12** showed no ion at *m/e* 277, as expected for **10**. Ions seen at *m/e* 556 corresponded to the disulfide **8** and at *m/e* 554 probably to the dimer of **10** analogous to **6**. The virtual insolubility of **12**, the absence of an ir band for NH, the relatively high intensity of the disulfide peak (**8**) in the mass spectrum of **12**, and the peak at *m/e* 554 suggest that **12** is polymeric, with small amounts of **8** and the dimer of **10** entrapped. This probability was enhanced by dissolution of **12** in diethylamine, followed by tlc and mass spectra analysis, both of which showed the presence of sulfenamide **11**. Attempts to purify **11** unfortunately led to its decomposition. For substantiation of its structure, the unstable sulfenamide **11** was prepared by reaction of diethylamine with the sulfenyl chloride **9** (Scheme II).

SCHEME II



Another possible route to a thiazetidine was suggested by the rapid decomposition after neutralization of **13**;[6] attack of an amino group on the bivalent sulfur atom (eq 1) might lead to **15** (or perhaps to a sulfenamide).[7]



However, weight loss after neutralization of **13** to **14**, then drying, was less than calculated from eq 1, and there was no ammoniacal odor. Tlc showed two products. Tosylation indicated that one was 2-aminoethyl disulfide. The other seemed to be taurine. Use of 2 mol of alkali with **13** also gave no **15** and, like eq 1, seemed unattractive for further study.

(6) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(7) *Cf.* J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).

Experimental Section[8]

2-Tosylamidoethyl Disulfide (**1**).—A solution of 14.2 g (75 mmol) of tosyl chloride in 200 ml of CH_2Cl_2 was added during *ca.* 90 min to 6.40 g (0.16 mol) of sodium hydroxide and 8.45 g (37.5 mmol) of 2-aminoethyl disulfide dihydrochloride in 200 ml of H_2O. The mixture was stirred overnight, and the CH_2Cl_2 layer then was separated, dried (Na_2SO_4), and evaporated: yield of **1**, 17.0 g (99%); mp 69–74°. Recrystallization twice from CH_3OH gave pure **1** with a constant melting point of 79–80°: nmr δ 2.37 (s, 3), 2.65 (t, 2), 3.20 (q, 2), 5.33 (t, 1), 7.20 (m, 2), and 7.69 (m, 2); ir (KBr) 1330 (s), 1150 (s), 1080, and 1055 cm^{-1}; mass spectrum *m/e* (rel intensity) 462 (1), 461 (1), 460 (4), 289 (6), 259 (4), 231 (5), 198 (22), 185 (6), 184 (57), 156 (7), 155 (73), 139 (7), 92 (12), 91 (100), 74 (5), and 65 (21).

Anal. Calcd for $C_{18}H_{24}N_2O_4S_4$: C, 46.93; H, 5.25. Found: C, 47.25; H, 5.40.

2-Tosylamidoethanethiol (**4**).—A solution of 1.70 g (3.70 mmol) of 2-tosylamidoethyl disulfide (**1**) in 30 ml of dioxane was reduced with 0.67 g (17.8 mmol) of $NaBH_4$ at 90° for 3 hr and then was let stand overnight at *ca.* 25°. Addition of 10% HCl to destroy the excess hydride, filtration, evaporation to near dryness and extraction with $CHCl_3$ gave 1.30 g (76%) of a pale yellow oil. Short-path distillation [*ca.* 100° (0.002 mm)] gave **4** as a colorless oil, $n^{25}D$ 1.5681. One more distillation gave **4**: $n^{25}D$ 1.5683; ir 3280, 2560 (w), 1600, 1500, 1420, 1325 (s), 1160 (s), 1085, 810, and 650 cm^{-1}; nmr δ 1.42 (m, 1, SH), 2.42 (s, 3, CH_3Ar), 2.63 (m, 2 CH_2S), 3.13 (m, 2, CH_2N), 5.63 (t, 1, NH), 7.32 (m, 2, ArH), and 7.79 (m, 2, ArH); mass spectrum *m/e* (rel intensity) 233 (0.2), 232 (2.2), 231 (1.5), 184 (39), 155 (56), 92 (10), 91 (100), 65 (24), 51 (5), 47 (6), 42 (5), and 41 (6).

Anal. Calcd for $C_9H_{13}NO_2S_2$: C, 46.74; H, 5.66. Found: C, 46.91; H, 5.73.

1,5-Ditosyl-2,6-dithia-1,5-diazocine (**6**). **A. Preparation.**—A solution of 3.22 g (7.0 mmol) of 2-tosylamidoethyl disulfide (**1**) in 30 ml of CH_2Cl_2 was cooled in Dry Ice and 0.42 ml (8.9 mmol) of Cl_2 was evaporated into the solution. After 1 hr at −30°, an excess (3 ml, 21 mmol) of Et_3N was added, and stirring was continued until the solution warmed to *ca.* 25°. The CH_2Cl_2 solution was washed thrice with water, dried (Na_2SO_4), and evaporated to give 3.7 g of thick oil; tlc showed the presence of two compounds, **1** (by comparison with authentic material) and a new compound (**6**). Trituration with EtOAc and recrystallization (Me_2CO) gave 0.4 g (13%) of **6** having a constant melting point of 233° dec (sample inserted at 225°, heated at *ca.* 3°/min). The remaining 2.8 g of material was dissolved in 25 ml of CH_2Cl_2, and 80.8 mg (0.505 mmol) of 2-naphthalenethiol and a trace of Et_3N were added to a 1.00-ml aliquot in 15 ml of EtOH. After 0.5 hr at *ca.* 25°, the solution was acidified with 50% AcOH (1 ml) and the excess thiol (0.01 mmol) was determined by titration with standard KI_3, yield of dimer **6** 6.19 mmol (89%), making a total yield of **6** of 102%. Data for the solid **6** follow: ir (Nujol) 1600, 1500, 1330 (s), 1150 (s), 1090, 870, 810, 700, and 675 cm^{-1}; nmr δ 2.43 (s, 3), 3.24 (m, 2), 3.81 (m, 2), 7.34 (m, 2), and 7.84 (m, 2); mass spectrum *m/e* (rel intensity) 460 (3), 459 (3), 458 (12), 303 (9), 184 (17), 156 (5), 155 (44), 139 (10), 123 (4), 120 (9), 106 (21), 92 (10), 91 (100), 79 (6), 74 (17), 65 (34), 64 (6), 63 (8), 60 (12), 51 (6), 46 (5), 45 (10), 42 (16), and 41 (6).

Anal. Calcd for $C_{18}H_{22}N_2O_4S_4$: C, 47.14; H, 4.84. Found: C, 47.08; H, 5.18.

B. Reduction of 6 with $NaBH_4$.—A suspension of 0.46 g (1.0 mmol) of **6** and 0.19 g (5 mmol) of $NaBH_4$ in dioxane was stirred overnight at *ca.* 25° and then was heated at 90° for 3 hr. The excess $NaBH_4$ then was decomposed with 10% HCl. The mixture was filtered, evaporated to near dryness, and extracted with CH-

(8) Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Mass spectra were obtained at 70 eV using the direct inlet system for **1**, **6**, **8**, and **11** and the glpc-inlet system (glass, 9-ft 1% SE-30 on Gas-Chrom Q column) for **4** on an LKB Model 9000 instrument, which was obtained through Science Development Program Grant GU-2057 from the National Science Foundation; we are indebted to Mr. Charles Wetter for these spectra. Ir spectra were obtained using a Beckman Model IR-10 with films of liquids and KBr pellets or Nujol mulls of solids; "s" signifies strong absorption (others reported are medium). Nmr spectra were obtained using a Varian Model A-60 spectrometer, with TMS as internal standard and $CDCl_3$ as solvent. We thank the National Science Foundation for Departmental Grant GP-1683 toward purchase of this instrument. Evaporation of solvents was done under reduced pressure using a rotary evaporator.

Cl_2 to give 0.43 g (93%) of 2-tosylamidoethanethiol (**4**) as a colorless oil having ir and mass spectra nearly identical with those of **4** obtained from the reduction of **1**.

C. Reaction with 2-Naphthalenethiol.—A suspension of 100 mg (0.22 mmol) of **6** and 74 mg (0.46 mmol) of 2-naphthalenethiol in 1:1 EtOH–CH_2Cl_2 was treated with 5 drops of Et_3N. The solid dissolved immediately. After *ca.* 16 hr, the solvent was evaporated and the residue was crystallized from EtOH. Analysis of both the solid and the filtrate by tlc (silica gel–benzene) showed the solid to be a mixture of two compounds; one of these, the more mobile, was evidently 2-naphthyl disulfide by tlc comparison; the other probably was 2-tosylamidoethyl 2-naphthyl disulfide (**5**) but was not positively identified. The filtrate contained three compounds; tlc comparison with authentic materials indicated two of them to be **1** and 2-naphthyl disulfide; the third presumably was **5**.

***o*-Tosylamidophenyl Disulfide (8).**—A solution of 10.0 g (40.3 mmol) of *o*-aminophenyl disulfide and 17.4 g (91 mmol) of tosyl chloride in 125 ml of pyridine was allowed to stand for 4 days. Filtration of the solution, dilution with EtOAc, and filtration removed a hygroscopic, water-soluble solid (presumably pyridine·HCl). The filtrate was washed several times with aqueous 10% HCl, dried, and evaporated to give a thick oil that slowly crystallized. Recrystallization from EtOAc and from Me_2CO gave 14.0 g (62%) of **8**: mp 162–167°; ir (Nujol) 3320, 1603, 1580, 1340 (s), 1280, 1165 (s), 1090, 1060, 925, 812, 767, and 660 cm^{-1}; nmr δ 2.16 (s, 3), and 6.7–7.9 (m, 9); mass spectrum *m/e* (rel intensity) 558 (6), 557 (8), 556 (29), 402 (5), 246 (20), 215 (10), 214 (45), 200 (10), 199 (60), 181 (7), 180 (6), 167 (5), 156 (5), 155 (8), 154 (14), 140 (8), 139 (13), 125 (11), 124 (67), 122 (7), 97 (8), 96 (17), 95 (5), 92 (20), 91 (100), 90 (5), 89 (6), 79 (28), 77 (7), 76 (7), and 65 (38).

Anal. Calcd for $C_{26}H_{24}N_2O_4S_4$: C, 56.09; H, 4.34. Found: C, 55.93; H, 4.48.

Attempted Synthesis of the Benzothiazete 10.—A solution of 4.90 g (8.80 mmol) of **8** in 50 ml of CH_2Cl_2 was cooled to −30°, and 8.8 mmol of Cl_2 in CCl_4 was added. The solution was stirred and allowed to warm to 0°. Then 3 ml of Et_3N was added (a considerable amount of solid appeared quickly, although Et_3N·HCl is soluble in the medium). Stirring was continued for 0.5 hr. The suspension was shaken twice with H_2O (solid remained in the organic phase), and then solid was separated to give 1.90 g (39%) of **12** as a white solid: mp >250° (insoluble in $CHCl_3$, CH_2Cl_2, EtOH, C_6H_6, C_5H_5N, H_2O, DMF, and $C_2H_2Cl_4$, soluble in secondary amines and in pyridine solutions of thiols); ir (Nujol) 1603, 1333 (s), 1300, 1170 (s), 1090, 915, 890, 851, 810, 731, and 669 cm^{-1}; mass spectrum *m/e* (rel intensity) 556 (24), 554 (4), 443 (15), 260 (5), 246 (18), 244 (9), 214 (50), 199 (57), 181 (6), 180 (6), 156 (8), 155 (14), 139 (17), 124 (43), 92 (10), 91 (100), and 65 (40). The filtrate contained only **8** (tlc).

Reaction of 12 with Diethylamine.—When 200 mg of **12** was placed in 30 ml of Et_2NH and heated under reflux for 5 min, dissolution occurred. After a reflux period of 3 hr, the excess Et_2NH was removed and the resulting oil was analyzed by tlc (silica gel, EtOAc) and by mass spectrometry, giving the same spectrum as authentic **11**. After 2 days at *ca.* 25°, analysis of the hardened oil by mass spectrometry showed only Et_2NH (trace) and disulfide **8**, consistent with virtually complete decomposition of **11**.

***o*-Tosylamidobenzenesulfenyl Diethylamide (11).**—A stirred solution of **8** (556 mg, 1.00 mmol) in 20 ml of CH_2Cl_2 was cooled to −30°, and Cl_2 (1.05 mmol) was added. After 0.5 hr, the solution was allowed to warm to *ca.* 25°, and 0.5 ml (4.9 mmol) of Et_2NH was added. After 0.5 hr, the solution was diluted with 30 ml of CCl_4, washed with H_2O, dried ($MgSO_4$), filtered, and evaporated to give 0.75 g (107%) of **11** as a light brown oil; tlc showed the same characteristics as solutions of **11** prepared from **12** and Et_2NH, *viz*, one large spot and two small ones. Attempted distillation resulted only in decomposition, and chromatography over Florisil (*ca.* 50% recovery) failed to provide **11** more pure than the crude product: ir (thin film) 3280, 2990, 1600, 1470, 1345, 1173 (s), 1090, 923, 820, 792, 760, and 665 cm^{-1}; nmr δ 1.10 (t, 6, CH_3CH_2), 2.27 (s, 3, CH_3Ar), 2.84 (q, 4, CH_2CH_3), 6.6–7.8 (m, 8, ArH), and 8.06 (s, 1, NH); mass spectrum *m/e* (rel intensity) 350 (36), 214 (19), 199 (19), 155 (6), 125 (7), 124 (42), 96 (7), 91 (42), 80 (16), 73 (23), 72 (92), 65 (14), 63 (5), 57 (100), 56 (9), 45 (5), 44 (23), 43 (6), 42 (20), and 41 (8).

Decomposition of 2-Aminoethyl 2-Aminoethanethiolsulfonate Monohydrochloride (14).—A solution (pH 4) of 10.0 mmol of **13** in water was neutralized with 10.0 mmol of NaOH (the pH increased to 7–8). Tlc (Brinkmann Polygram MN Polyamide, with 10:1:0.15 EtOH–Me_2CO–Et_2NH) showed two ill-defined spots, R_f 0.5 (by fluorescence) and 0.3 (by I_2 vapor). Evaporation and vacuum drying gave 2.73 g of residue (92% of the 2.97 g of **13** and NaOH used). Ethanol separated 0.35 g of taurine, mp > 210° (lit.[9] mp 300–305° dec); the ir spectrum was virtually identical with that of authentic taurine. The crude residue from an identical experiment was dissolved in H_2O, and 0.80 g of NaOH was added. The mixture then was treated with tosyl chloride. After 6 hr, a CH_2Cl_2 solution was washed thrice with water and evaporated to give 1.20 g, identified as **1** by tlc comparison with authentic **1** (silica gel–*n*-butyl acetate).

Registry No.—**1**, 23516-74-7; **4**, 23516-75-8; **6**, 23516-76-9; **8**, 3982-42-1; **11**, 23516-78-1.

(9) F. Cortese, *J. Amer. Chem. Soc.*, **58**, 191 (1936).

Thallium in Organic Synthesis. XI. Preparation of Azoxy Compounds[1,2]

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Thallium is abundant, inexpensive, and readily available in bulk in a high state of purity. Surprisingly, the literature is virtually devoid of descriptions of direct applications of the metal to organic synthesis. We wish to describe in this paper the use of thallium in a simple, high-yield procedure for the preparation of aromatic azoxy compounds.

During studies on the use of thallium salts in the synthesis of biaryls,[3] we were able to confirm an early report by Spencer and Wallace[4] that small amounts of biphenyl and thallium(I) iodide were formed when thallium and iodobenzene were heated together under reflux. Although more detailed investigation of this reaction has established that the overall process is of little synthetic value as a route to biaryls,[5] an interesting side reaction was observed when nitrobenzene was employed as solvent. In refluxing nitrobenzene thallium underwent slow oxidation to give thallium(III) oxide, with concomitant formation of significant amounts of azoxybenzene (eq 1). The conversion outlined in eq 1 also proceeds smoothly in a number of high boiling solvents such as dimethylformamide, *o*-dichlorobenzene, and diglyme, but extended reaction

$$2C_6H_5NO_2 + 2Tl \longrightarrow C_6H_5\overset{+}{N}(O^-)=NC_6H_5 + Tl_2O_3 \qquad (1)$$

(1) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.

(2) Part X: A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969).

(3) A. McKillop, L. F. Elsom, and E. C. Taylor, *J. Amer. Chem. Soc.*, **90**, 2423 (1968).

(4) J. F. Spencer and M. L. Wallace, *J. Chem. Soc.*, **93**, 1827 (1908).

(5) A. McKillop, J. S. Fowler, and E. C. Taylor, unpublished results.