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Synthesis and Chemical Properties of α-Alkyl(aryl)thiovinyl Isocyanates

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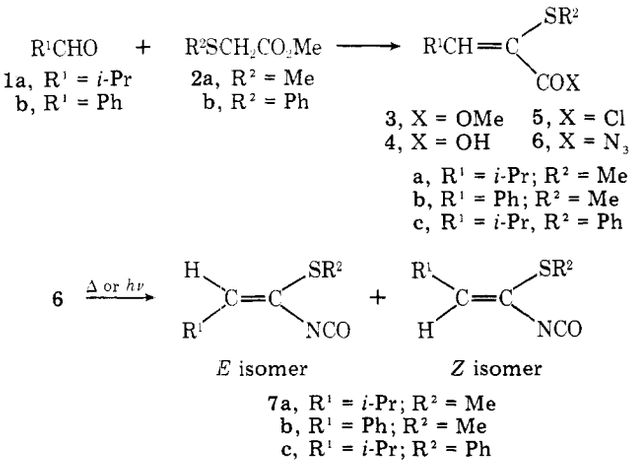
Received June 28, 1977

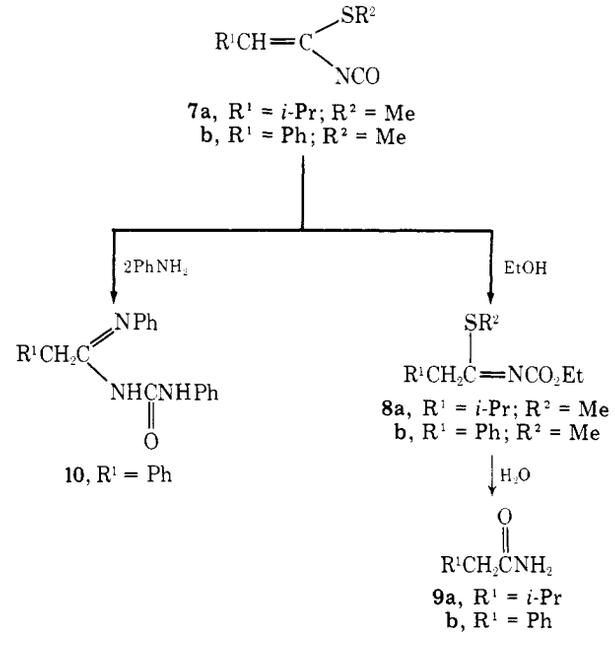
Thermolysis or photolysis of α-alkyl(aryl)thioacrylyl azides **6** gave α-alkyl(aryl)thiovinyl isocyanates **7** in good yields. The isocyanates **7** reacted with aromatic hydrazines to give the triazoles **11** and the triazolinone **12**. In the reaction of **7a** with enamines, the pyridone **15a** or the azadecalin **15b** were isolated. Thermolysis of **7a** gave 4-methylthio-5-isopropyluracil (**16**) quantitatively, while **7b** led to 3-methylthioisocarbostyril (**17**). 3-Methylthio-4-chloroisocarbostyril (**19a**) and 3-methylthio-4-bromoisocarbostyril (**19b**) were obtained by the treatment of **17** with $CuCl_2$–CuO and Br_2–CuO, respectively.

In recent years, the chemical properties of acyl isocyanates have been widely investigated and many heterocyclic compounds were derived from them.[1] In spite of their great synthetic utility, difficulty in the preparation of aliphatic acyl isocyanates[2] and instability of aromatic acyl isocyanates have restricted the utilization of acyl isocyanates. The synthesis of reagents equivalent to acyl isocyanates has been undertaken to overcome these limitations.

Since the vinyl sulfide group is easily converted to the carbonyl group,[3] α-alkyl(aryl)thiovinyl isocyanates are expected to be potentially useful in place of acyl isocyanates in organic synthesis. We also expect them to provide new routes for the synthesis of various heterocyclic compounds containing the sulfide group, since α,β-unsaturated isocyanates have been used in the synthesis of heterocyclic compounds.[4] From these points of view, we wish to report here the synthesis and some chemical properties of α-alkyl(aryl)thiovinyl isocyanates.

Thermolysis or photolysis of a mixture of (*E*)- and (*Z*)-α-alkyl(aryl)thioacrylyl azides **6**, prepared from aldehydes **1** and methyl methyl(phenyl)thioacetates **2**, gave α-alkyl(aryl)-thiovinyl isocyanates **7** in good yields. The structures of **7** were established by spectral data and chemical evidence. The IR spectrum of **7a** displays characteristic absorption bands at 2240 and 1620 cm^{-1} assignable to NCO and olefinic linkage, respectively. The NMR spectrum shows two doublets at 5.17 and 5.40 ppm in the ratio of 87:13. The peak at higher field would be assignable to the vinyl proton of the *E* isomer and the other to that of the *Z* isomer. Treatment of **7a** and **7b** with ethanol gave the amides **9** which were formed from the imino sulfides **8** by hydrolysis. Only **8a** as intermediate was isolated. With aniline, **7b** led to the amidine **10**.





The isocyanate **7a** reacted with *p*-nitrophenylhydrazine at room temperature to give 1-*p*-nitrophenyl-3-hydroxy-5-

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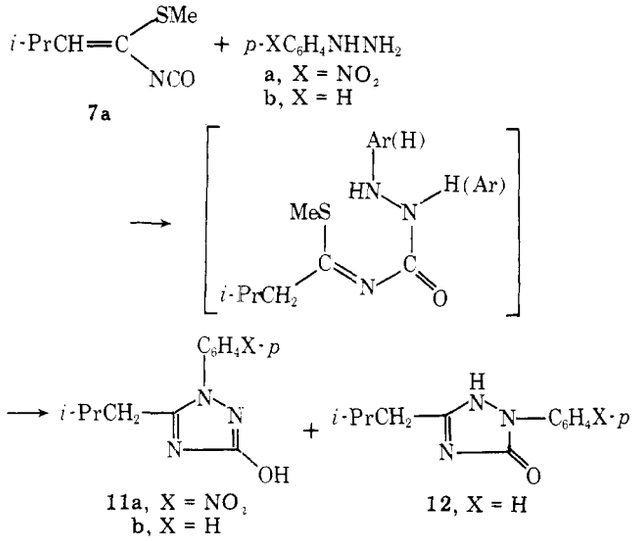
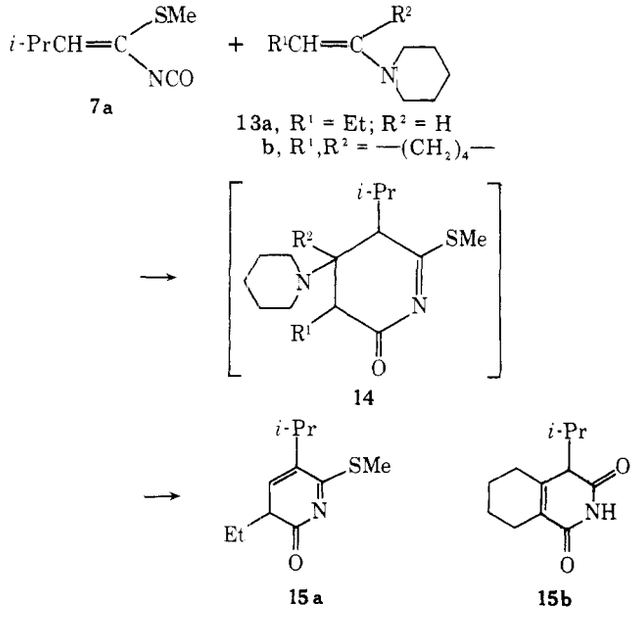
isobutyl-1,2,4-triazole (**11a**) quantitatively. With phenylhydrazine, **11b** and its isomer **12** were obtained in 57 and 43% yields, respectively. The IR spectrum of **11b** displays no absorption at the carbonyl region. The mass spectrum exhibits the parent peak at *m/e* 217 and other peaks at *m/e* 175 ($M^+ - NCO$), 106 ($PhNNH^+$), and 91 (PhN^+). On the other hand, the IR spectrum of **12** displays a strong carbonyl absorption at 1700 cm^{-1}. The mass spectrum exhibits the peak at *m/e* 119 ($PhNCO^+$) in addition to those of **11b**. On the basis of the spectral data, **11b** and **12** were assigned to 1-phenyl-3-hydroxy-5-isobutyl-1,2,4-triazole and 2-phenyl-5-isobutyl-1*H*-1,2,4-triazolin-3-one, respectively. These results suggest addition and condensation reactions of the aromatic hydrazines with the acyl isocyanate analogous to the synthesis of the triazine from the acyl isocyanate and the benzamidine.[5]

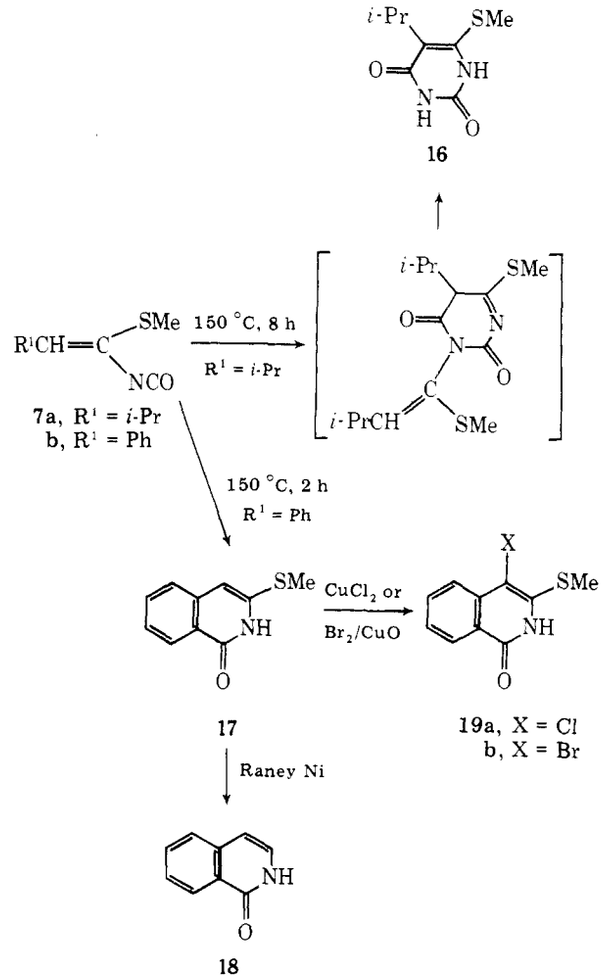


The isocyanates having a double bond adjacent to a cumulative bond are known to react with nucleophilic olefins to give 1,2- and/or 1,4-cycloadducts.[6] The reaction of **7a** with 1-piperidino-1-butene (**13a**) gave the pyridone **15a** in 69% yield. The product **15a** might be formed from **14** with elimination of the piperidine under the reaction conditions. Similar treatment of **7a** with 1-piperidino-1-cyclohexene (**13b**) led to the azadecalin derivative **15b** in 89% yield. In this case, the imino sulfide group was hydrolyzed to yield the amide group during workup in a similar way to that of **8**. Other reactions



of **7a** with dihydropyran and butyl vinyl sulfide were unsuccessful, showing lower reactivity than those of other conjugative isocyanates containing carbonyl, imidoyl and thiocarbonyl groups.

The α-alkyl(aryl)thiovinyl isocyanates **7** are stable at room temperature and remained unchanged in refluxing benzene for 15 h, while acyl isocyanates are easily decomposed under these conditions. Thermolysis of **7a** at 150 °C in neat solution gave the uracil **16** quantitatively. However, an attempt to trap other decomposition species failed; the uracil **16** was presumably formed by the dimerization reaction similar to the formation of oxadiazine derivatives from benzoyl isocyanates.[7] On the other hand, thermolysis of **7b** led to the isocarbostyril **17** quantitatively, which was easily changed to the isocarbostyril (**18**) by treatment with Raney Ni. In order to change the vinyl sulfide group to the carbonyl group, **17** was treated with $CuCl_2$–CuO in aqueous acetonitrile,[8] but the chloroisocarbostyril **19a** was obtained unexpectedly. In the absence of CuO, **19a** was not obtained and **17** was recovered. Similarly, bromination at the 4-position of **17** was achieved by the treatment with bromine in the presence of CuO. From these results, the isocyanates **7** are as useful as α-chloro- and β-



cyano-α,β-unsaturated isocyanates whose thermal treatment in the presence of hydrochloric acid also gave isocarbostyril and uracil derivatives.[4]

In conclusion, α-alkyl(aryl)thiovinyl isocyanates are prepared in good yields and are relatively stable. In the reaction with bifunctional nucleophiles such as hydrazines, the isocyanates have an equivalent value to acyl isocyanates owing to the facile elimination of the sulfide group. Furthermore, the isocyanates are applicable to the simple synthesis of uracil and isocarbostyril derivatives containing the sulfide group.

Experimental Section

General. All melting points of products were determined with a Yanagimoto micro melting point apparatus and were uncorrected. The NMR spectra were obtained on a JEOL JNM-PMX-60 and JNM-PS-100 spectrometer with tetramethylsilane as an internal standard. The IR spectra were recorded with a JASCO IRA-1 spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

Synthesis of α-Alkyl(aryl)thiovinyl Isocyanates 7. The acid chlorides **5** were prepared from the aldehydes **1** and the methyl methyl(phenyl)thioacetates **2** according to the established method.[9] The acid chloride **5a** (44.6 g, 0.25 mol) in dry ether (50 mL) was added to a stirred aqueous solution of sodium azide (23.1 g, 0.36 mol) below 5 °C, and stirring was continued at 15–20 °C until IR absorption of the acid chloride disappeared. The organic layer was extracted with ether and dried over sodium sulfate. The ethereal solution of the acyl azide **6a** was added dropwise to 150 mL of dry benzene at 70 °C, and the mixture was stirred until evolution of nitrogen gas ceased (for ~1 h). After removal of the solvent, the residue was distilled in vacuo to give 17.7 g (45%) of 1-methylthio-3-methylbut-1-enyl isocyanate (**7a**). Photolysis of the acyl azide **6b** was carried out in dry benzene at room temperature with a high-pressure mercury lamp for 10 h. **7a:** bp 34–41 °C (3 mm); IR (neat) 2240, 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 157 (M^+); NMR ($CDCl_3$) δ 1.00 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.28 (s, 3 H, SCH_3), 2.43–3.03 (m, 1 H, CH), 5.17 and 5.40 (d, *J* = 9.0 Hz, total 1 H, ratio 87:13, CH=C). α-Methylthiostyryl isocyanate (**7b**): 82% yield (thermolysis), 59% yield (photolysis); bp 78–80 °C (0.015 mm); IR (neat) 2240, 1610 cm^{-1}; mass spectrum (70 eV) *m/e* 191 (M^+); NMR ($CDCl_3$) δ 2.10 (s, 3 H, SCH_3), 5.92, and 6.28 (s, total 1 H, ratio 94:6, CH=C), 7.04–7.28 (m, 3 H, aromatic), 7.32–7.50 (m, 2 H, aromatic). 1-Phenylthio-3-methylbut-1-enyl isocyanate (**7c**): 63% yield; bp 115–120 °C (0.5 mm); IR (neat) 2240, 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 219 (M^+); NMR ($CDCl_3$) δ 1.02 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.54–3.18 (m, 1 H, CH), 5.62, and 6.53 (d, *J* = 9.4 Hz, total 1 H, ratio 75:25, CH=C), 7.12–7.66 (m, 5 H, aromatic).

Treatment of 7a with Ethanol. To the soltuion of **7a** (1.6 g, 10 mmol) in dry benzene (20 mL) was added 5 mL of absolute ethanol, and the mixture was stirred for 4 h at room temperature. After removal of the solvent, the residue was chromatographed on silica gel with hexane–benzene to give crude *N*-carboethoxy-1-methylthioisoamylideneimine (**8a**). Distillation in vacuo gave the pure sample (1.8 g, 89%). **8a:** bp 57–58 °C (1.5 mm); IR (neat) 1720, 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 203 (M^+); NMR ($CDCl_3$) δ 1.00 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 1.37 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.73–2.80 (m, 3 H), 2.37 (s, 3 H, SCH_3), 4.30 (q, *J* = 7.2 Hz, 2 H, OCH_2).

Anal. Calcd for $C_9H_{17}NO_2S$: C, 53.19; H, 8. 43; N, 6.89. Found: C, 53.01; H, 8.49; N, 6.94.

Hydrolysis of 8a. The imino sulfide **8a** (0.7 g, 3 mmol) was chromatographed on alumina with benzene–ethanol to give 3-methylbutyramide (**9a**) quantitatively: mp 134–135 °C (benzene–ethanol); IR (Nujol) 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 101 (M^+); NMR ($CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 1.87–2.33 (m, 3 H), 5.83 (br, 2 H, NH_2).

Anal. Calcd for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.25; H, 11.16; N, 13.81.

Hydrolysis of 7a. The isocyanate **7a** (0.7 g, 4 mmol) was chromatographed on alumina with benzene–ethanol to give **9a** (0.35 g, 95%).

Hydrolysis of 7b. Similar treatment of **7b** (2.7 g, 14 mmol) on alumina gave 1.4 g (74%) of phenylacetoamide (**9b**): mp 165–167 °C (ethanol); IR (Nujol) 3320, 3160, 1625 cm^{-1}; mass spectrum (70 eV) *m/e* 135 (M^+); NMR (Me_2SO-d_6) δ 2.35 (s, 2 H, CH_2), 6.84 (br, 1 H, NH), 7.16–7.32 (m, 5 H, aromatic), 7.44 (br, 1 H, NH).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.14; H, 6.70; N, 10.22.

Reaction of 7b with Aniline. A mixture of **7b** (0.4 g, 2 mmol) and aniline (0.4 g, 4 mmol) in dry benzene (20 mL) was stirred for 1 h at room temperature. After removal of the solvent, the residue was chromatographed on alumina with benzene–hexane to give 0.5 g (76%) of *N*-phenyl-*N'*-phenylcarbamoylphenylacetoamidine (**10**): mp 179–180 °C (ethanol); IR (Nujol) 3220, 1700, 1650, 1575 cm^{-1}; mass spectrum (70 eV) *m/e* 329 (M^+); NMR ($CDCl_3$) δ 3.62 (s, 2 H, CH_2), 6.70–7.62 (m, 16 H, aromatic and NH), 11.96 (br, 1 H, NH).

Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.42; H, 5.68; N, 12.76.

Reaction of 7a with Aromatic Hydrazines. To the solution of **7a** (1.6 g, 10 mmol) in dry benzene (30 mL) was added *p*-nitrophenylhydrazine (1.7 g, 11 mmol) under a nitrogen atmosphere and stirring was continued for 1 h at room temperature. Crystals precipitated and were filtered to give 2.7 g (100%) of **11a:** mp 277–278 °C (methanol); IR (Nujol) 3080, 1590, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 262 (M^+); NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 1.87–2.60 (m, 1.5 H), 2.92 (d, *J* = 7.0 Hz, 2 H, CH_2), 7.66–8.00 (m, 2 H, aromatic), 8.27–8.57 (m, 2 H, aromatic).

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.95; H, 5.38; N, 21.37. Found: C, 54.85; H, 5.25; N, 21.46.

A mixture of **7a** (1.6 g, 10 mmol) and phenylhyrazine (1.1 g, 10 mmol) in dry benzene (30 mL) was stirred for 1 h at room temperature under a nitrogen atmosphere. After removal of the solvent, the residue was chromatographed on silica gel with benzene–ethanol to give **11b** and **12** in 57 (1.23 g) and 43% (0.93 g) yields, respectively.

11b: mp 194–195 °C (benzene–hexane); IR (Nujol) 1590 cm^{-1}; mass spectrum (70 eV) *m/e* 217 (M^+, 23%), 175 (M^+ − NCO, base peak), 106 ($PhNNH^+$, 11%), 91 (PhN^+, 23%); NMR ($CDCl_3$) δ 0.97 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.17 (m, 1 H, CH), 2.65 (d, *J* = 7.0 Hz, 2 H, CH_2), 7.36–7.56 (m, 5 H, aromatic), 12.53 (br, 1 H, OH).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.60; H, 7.04; N, 18.97.

12: mp 159–159.5 °C (ethanol); IR (Nujol) 1700, 1590 cm^{-1}; mass spectrum (70 eV) *m/e* 217 (M^+, 72%), 175 (M^+ − NCO, base peak), 119 ($PhNCO^+$, 6%), 91 (PhN^+, 54%); NMR ($CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.13 (m, 1 H, CH), 2.53 (d, *J* = 7.0 Hz, 2 H, CH_2), 7.20–7.67 (m, 3 H, aromatic), 7.83–8.13 (m, 2 H, aromatic), 12.10 (br, 1 H, NH).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.30; H, 6.92; N, 19.25.

Reaction of 7a with Enamines. To the solution of **7a** (1.6 g, 10 mmol) in dry benzene (20 mL) was added 1-piperidino-1-butene (**13a**) (1.4 g, 10 mmol) with stirring under a nitrogen atmosphere and the mixture was refluxed for 6 h. After removal of the solvent, the residue was chromatographed on silica gel with hexane–benzene to give 1.45 g (69%) of 3-ethyl-5-isopropyl-6-methylthio-2-pyridone (**15a**): mp 125–125.5 °C (benzene–exane); IR (Nujol) 1630, 1595, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 211 (M^+); NMR ($CDCl_3$) δ 1.00 (t, *J* = 6.0 Hz, 3 H, CH_3), 1.24 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.21–2.62 (m, 2 H, CH_2), 2.51 (s, 3 H, SCH_3), 3.09–3.57 (m, 2 H, allylic), 7.20 (d, *J* = 7.0 Hz, 1 H, vinylic).

Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.54; H, 8.11; N, 6.63; S, 15.15. Found: C, 62.55; H, 8.17; N, 6.59; S, 15.54.

After similar treatment of **7a** (1.6 g, 10 mmol) with 1-piperidino-1-cyclohexene (**13b**) (1.7 g, 10 mmol), the residue was chromatographed on alumina with hexane–benzene to give 1,3-dioxo-4-isopropyl-9,10-dehydro-2-azadecalin (**15b**) in 89% (1.85 g) yield. **15b:** mp 107.5–109 °C (ether); IR (Nujol) 3200, 3075, 1730, 1660 cm^{-1}; mass spectrum (70 eV) *m/e* 207 (M^+); NMR ($CDCl_3$) δ 1.03 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 1.66–2.63 (m, 7 H), 3.06–3.36 (m, 2 H), 4.36 (d, *J* = 8.6 Hz, 1 H, *i*-PrCH), 8.03 (br, 1 H, NH).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.42; N, 6.69.

Thermolysis of 7a. The isocyanate **7a** (0.9 g, 6 mmol) was heated in neat solution at 150 °C for 8 h and the reaction mixture was solidified after cooling. The solid was washed with ether and recrystallized from benzene–ethanol to give 0.4 g (100%) of **16:** mp 235–237 °C; IR (Nujol) 3220, 3120, 1710, 1650, 1560 cm^{-1}; mass spectrum (70 eV) *m/e* 200 (M^+); NMR (Me_2SO-d_6) δ 1.20 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.57 (s, 3 H, SCH_3), 3.18 (m, 1 H, CH), 10.40–11.23 (br, 2 H, 2 NH).

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.99; H, 6.04; N, 13.99; S, 15.99. Found: C, 47.95; H, 5.92; N, 13.82;, S, 16.03.

Thermolysis of 7b. The thermolysis of **7b** (1.9 g, 10 mmol) was carried out in neat solution at 150 °C for 2 h. After similar workup described above, **17** was obtained quantitatively (1.9 g). **17:** mp 170–171 °C (benzene–ethanol); IR (Nujol) 3150, 1640, 1610, 1600, 1550 cm^{-1}; mass spectrum (70 eV) *m/e* 191 (M^+); NMR ($CDCl_3$) δ 2.60 (s, 3 H, SCH_3), 6.24 (s, 1 H, vinylic), 7.20–7.66 (m, 3 H, aromatic), 8.28–8.44 (m, 1 H, aromatic), 12.04 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_9NOS$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.66; H, 4.58; N, 7.44.

Treatment of 17 with Raney Ni. A suspension of **17** (1.0 g, 5 mmol) in 30 mL of ethanol containing excess Raney Ni was refluxed for 15 h. The organic layer was separated and concentrated. Recrystallization of the residue from benzene gave 0.6 g (79%) of **18:** mp 203–205 °C (lit.[10] mp 210.5–211 °C); IR (Nujol) 3160, 1650, 1625, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 145 (M^+); NMR ($CDCl_3$) δ 6.57 (d, *J* = 7.6 Hz, 1 H), 7.13–7.73 (m, 4 H), 8.33–8.60 (m, 1 H), 11.87 (br, 1 H).

Anal. Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.41; H, 5.04; N, 9.52.

Chlorination of 17. A suspension of **17** (1.0 g, 5 mmol), $CuCl_2 \cdot 2H_2O$ (1.8 g) and CuO (1.8 g) in acetonitrile–water (25:1 mL) was refluxed

for 6 h with stirring. The mixture was filtered, extracted with ether, and dried over sodium sulfate. After concentration, 0.45 g (40%) of **19a** was obtained. **19a:** mp 217–218 °C (ethanol); IR (Nujol) 3140, 1660, 1600, 1580, 1550 cm^{-1}; mass spectrum (70 eV) *m/e* 225 (M^+); NMR (Me_2SO-d_6) δ 2.53 (s, 3 H, SCH_3), 7.37–7.87 (m, 3 H, aromatic), 8.10–8.33 (m, 1 H, aromatic), 11.63 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_8NOSCl$: C, 53.22; H, 3.55; N, 6.21; S, 14.19; Cl, 15.74. Found: C, 53.07; H, 3.40; N, 6.21; S, 14.02; Cl, 15.52.

Bromination of 17. To a suspension of **17** (0.5 g, 2.6 mmol) and CuO (0.5 g) in ethanol (30 mL) was added bromine (1 g) at room temperature and the mixture was heated at 60 °C for 7 h with stirring. After cooling, the precipitate was filtered and washed with hot ethanol. The filtrate was concentrated to give 0.7 g (100%) of **19b:** mp 220–222 °C (ethanol); IR (Nujol) 3120, 1650, 1600, 1570, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 269 (M^+); NMR ($CDCl_3$) δ 2.66 (s, 3 H, SCH_3), 7.33–7.94 (m, 3 H, aromatic), 8.12–8.36 (m, 1 H, aromatic), 11.61 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_8NOSBr$: C, 44.44; H, 2.96; N, 5.19. Found: C, 44.42; H, 2.81; N, 5.11.

Registry No.—**5a,** 64188-42-7; **5b,** 64188-40-5; **5c,** 64188-38-1; (*E*)-**6a,** 64188-36-9; (*Z*)-**6a,** 64188-34-7; (*E*)-**6b,** 64188-33-6; (*Z*)-**6b,** 64188-35-8; (*E*)-**6c,** 64188-32-5; (*Z*)-**6c,** 64188-56-3; (*E*)-**7a,** 64188-55-2; (*Z*)-**7a,** 64188-54-1; (*E*)-**7b,** 64188-53-0; (*Z*)-**7b,** 64188-52-9; (*E*)-**7c,** 64188-50-7; (*Z*)-**7c,** 64188-51-8; **8a,** 64188-49-4; **8b,** 64188-48-3; **9a,** 541-46-8; **9b,** 103-81-1; **10,** 64188-47-2; **11a,** 64188-46-1; **11b,** 64188-45-0; **12,** 28669-33-2; **13a,** 7182-10-7; **13b,** 2981-10-4; **15a,** 64188-44-9; **15b,** 64188-43-8; **16,** 64188-41-6; **17,** 64188-39-2; **18,** 491-30-5; **19a,** 64188-37-0; **19b,** 64201-56-5; aniline, 62-53-3; *p*-nitrophenylhydrazide, 100-16-3; phenylhydrazide, 100-63-0.

References and Notes

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Synthesis of *N*-Methyl-1-oxa-5-aza[10]paracyclophane: A Conformationally Restricted Analogue of Phenoxypropylamines[1a]

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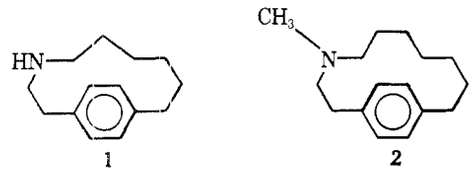
Received June 30, 1977

The synthesis of *N*-methyl-1-oxa-5-aza[10]paracyclophane (**4**) is reported; this represents the first example of this ring system being formed via an intramolecular halo–phenoxide reaction (ether synthesis). Attempts to synthesize phenoxyethylamine and phenoxypropylamine analogues by the acyloin reaction or by the intramolecular amine–ester reaction failed to yield the desired paracyclophanes.

Many compounds have been prepared as conformationally restricted analogues of phenethylamine in order to assess stereochemical requirements of the drug receptor.[2] These served as a stimulant for the recent publication[3] of the synthesis of 3-aza[10]paracyclophane (**1**) and *N*-methyl-3-aza[10]paracyclophane (**2**). In this paper, we are reporting the results of synthesis of conformationally restricted analogues **3** and **4** of adrenergic antagonists which contain the basic ar-



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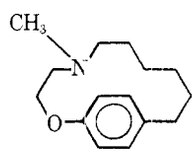

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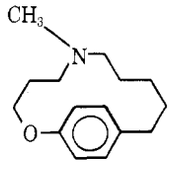


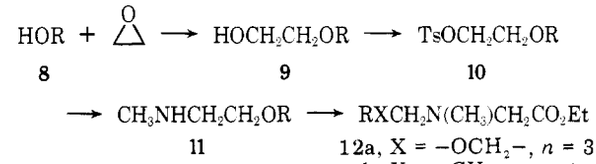
4

yloxyethylamine or aryloxypropylamine structure (e.g., phenoxybenzamine and propranolol).

Since the acyloin reaction is perhaps the most important method for preparing paracyclophanes,[4] the first approach studied attempted to synthesize an oxazaparacyclophane (**3**) by utilizing the appropriate diester (**12a**) in an acyloin reaction (Scheme I). The diester was obtained in a straightforward manner through Friedel–Crafts acylation[5] of anisole by succinic anhydride. The keto acid **5** was reduced by the Clemmensen method,[6] and the resulting acid **6** was treated with 48% hydrobromic acid. The phenolic acid **7** was esterified[7] and the phenolic ester **8** reacted with ethylene oxide followed by tosylation and amination to give the amino ester **11.** Alkylation with ethyl bromoacetate resulted in the diester **12a.** However, under normal acyloin reaction conditions,[9] this diester failed to undergo the cyclization reaction. Only starting material and a polymeric substance were isolated from the reaction mixture.

Recently, Wu and co-workers[3b,8] found that a diester (**12b**) with an ester group one carbon length away from the nitrogen atom would not cyclize in the acyloin reaction. However, with

Scheme I[a]



$RXCH_2N(CH_3)(CH_2)_2CO_2Et$

13a, X = $-CH_2-$, n = 3
b, X = $-OCH_2-$, n = 3

[a] R = $-Ph(CH_2)nCO_2Et$, n = 3, 4.

0022-3263/78/1943-0405$01.00/0