Synthesis of *cis*-2-Aza-3-oxo-4-oxabicyclo[4.2.0]octane and *cis*-2-Aza-3-oxo-4-oxabicyclo[4.1.0]heptane

C. C. SHROFF,[1] W. S. STEWART,[1] S. J. UHM,[1] AND J. W. WHEELER*

Department of Chemistry, Howard University, Washington, D. C. 20001

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Internal urethanes, *cis*-2-aza-3-oxo-4-oxabicyclo[4.2.0]octane (**17**) and *cis*-2-aza-3-oxo-4-oxabicyclo[4.1.0]heptane (**7**), have been synthesized. Reactions of these compounds and of their trans counterparts are discussed. The difference in reactivities of several comparable intermediates in the cyclopropane and cyclobutane systems is marked.

Although cyclopropanes[2] and cyclobutanes[3] containing functional groups on C_1 and C_2 have been studied extensively, disubstituted molecules containing different functional groups have received scant notice.[4,5] We have investigated a series of 1,2-disubstituted three- and four-membered rings with known stereochemistry.

Our starting point for each synthesis was the 1,2-diacid **1**[6] or **10**.[7] The cis series was prepared from the anhydride **2** (or **11**) as outlined in Schemes I and II. Reduction of acid chloride ester **13** gave cyclobutane alcohol ester **14**.[8] Although the cyclopropane alcohol ester **4** spontaneously closed to lactone **5**,[4d,e] cyclobutane alcohol ester **14** was somewhat more stable. Maier and Sayrac,[4d] and Kirmse and Dietrich[4e] have prepared lactone **5** by two alternate routes, both procedures involve separation from other products.

While reduction of cyclobutane acid ester **12** to alcohol ester **14** by diborane was accomplished cleanly with formation of little diol as a by-product, reduction of cyclopropane acid ester **3** to alcohol ester **4** was grossly incomplete. Further reduction of the mixture gave 5–10% of diol as well as **4**.

Since reduction of carboxylic acids with diborane involves formation of a triacylborate,[9] intramolecular hydrogen bonding might account for the difference in reduction of **4** and **12**. McCoy[10a,b] has determined the pK_1 of **1b** and Bode[10c] has determined the pK_1 of **10b**. The small difference in acid strength between these two molecules (3.56 *vs.* 4.20) and an observation noted in the reduction of acid esters **4** and **12** indicates that relative solubilities of the intermediate boron compounds are important. While turbidity disappears upon further introduction of diborane with the cyclobutyl compound, a viscous gum precipitates on the sides of the flask and does not redissolve with the cyclopropyl analog.

This difference in the behavior of cyclopropane and cyclobutane systems was amplified in conversion of hydrazides **6** and **16** to cyclic urethanes **7** and **17**. Treatment of cyclobutane alcohol hydrazide **16** with nitrous acid gave 2-aza-3-oxo-4-oxabicyclo[4.2.0]octane (**17**) in good yield under a variety of conditions. In contrast, treatment of cyclopropane alcohol hydrazide **6** with nitrous acid gave large amounts of lactone **5** as well as 2-aza-3-oxo-4-oxabicyclo[4.1.0]heptane (**7**). Urethane **7** could be prepared in satisfactory yield only by rigorous control of both the acidity of the solution and temperature. Formation of lactone **5** was greatly facilitated by addition of ferric chloride, a Lewis acid used to convert azides to isocyanates.[11] The two substituents (hydroxymethyl and azide) which are necessarily eclipsed in the cyclopropane case must be ideally situated so that the hydroxyl group can participate. Lewis acid complexation of the carbonyl oxygen facilitates nucleophilic attack at the carbonyl carbon by the hydroxyl group. Loss of hydrazine from the protonated hydrazide and loss of azide ion from azide leads not to urethane **7** but to lactone **5**. This became most apparent when the azide reverted to lactone **5** even in a chloroform extract which was free of acid. In contrast, the cyclobutane substituents are not eclipsed and formation of lactone **15** presents no serious problem.

Treatment of either urethane **7** or **17** in dioxane with gaseous hydrogen bromide gave bromomethylamine hydrobromide **8** or **18**. Although cyclobutane **18** is stable at room temperature, the cyclopropane analog **8** is unstable even at 5° on prolonged standing.

Ring expansion of urethanes **7** or **17** might occur on treatment with hydrogen bromide. However, the spectroscopic properties of the products **8** and **18** indicate that cyclopropane and cyclobutane rings are intact. The strong absorptions at 8.0 μ in the infrared spectra of the two products can be assigned to a CH_2–Br wagging vibration.[12]

Treatment of **8** or **18** with thallium (or sodium) thiosulfate in either water or methanol gave crude materials

(1) Abstracted from the Ph.D. Dissertations of C. C. Shroff and W. S. Stewart, 1969, and the M.S. Thesis of S. J. Uhm, 1970, Howard University.

(2) J. K. Hecht, J. J. Flynn, and F. P. Boer, *J. Org. Chem.*, **34**, 3645 (1969); F. W. Breitbeil, D. T. Dennerlein, A. E. Fiebig, and R. E. Kuznicki, *ibid.*, **33**, 3389 (1968); S. Sawada, K. Takehana, and Y. Inouye, *ibid.*, **33**, 1767 (1968); O. L. Chapman and R. A. Fugiel, *J. Amer. Chem. Soc.*, **91**, 216 (1969); T. J. Curphey, C. W. Amelotti, T. P. Layloff, R. L. McCartney, and D. B. Priddy, *ibid.*, **91**, 3677 (1969); T. Shono, T. Morikawa, A. Oku, and R. Oda, *Tetrahedron Lett.*, 791, 1964; L. L. McCoy, *J. Amer. Chem. Soc.*, **84**, 2246 (1962), and references therein.

(3) L. I. Peterson, R. B. Hager, A. F. Vellturo, and G. W. Griffin, *J. Org. Chem.*, **33**, 1018 (1968); J. J. Gajewski and C. N. Shih, *J. Amer. Chem. Soc.*, **91**, 5900 (1969); P. Heimbach and W. Brenner, *Angew. Chem.*, **79**, 814 (1967).

(4) (a) K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Amer. Chem. Soc.*, **79**, 4994 (1957); (b) W. G. Dauben and G. W. Shaffer, *J. Org. Chem.*, **34**, 2301 (1969); (c) S. J. Rhoads and R. D. Cockroft, *J. Amer. Chem. Soc.*, **91**, 2815 (1969); (d) G. Maier and T. Sayrac, *Ber.*, **101**, 1354 (1968); (e) W. Kirmse and H. Dietrich, *ibid.*, **98**, 4028 (1965).

(5) (a) R. Gelin, S. Gelin, and C. Boutin, *C. R. Acad. Sci.*, **260**, 6393 (1965); (b) P. G. Gassman and K. T. Mansfield, *J. Org. Chem.*, **32**, 915 (1967).

(6) L. L. McCoy, *J. Amer. Chem. Soc.*, **80**, 6568 (1958).

(7) E. C. Coyner and W. S. Hillman, *ibid.*, **71**, 324 (1949); subsequently purchased from Aldrich Chemical Co.

(8) Contrary to expectations considerable amounts of diol were formed when diborane was bubbled through the solution for a longer period (H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 43). The original literature indicates that acid chlorides are relatively inert. See ref 9.

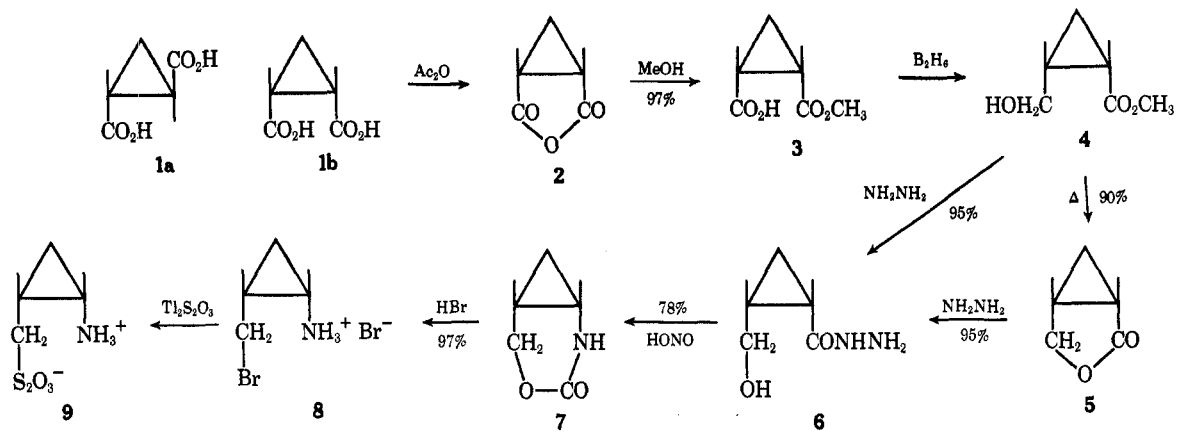
(9) H. C. Brown and W. Korytnyk, *J. Amer. Chem. Soc.*, **82**, 3866 (1960); H. C. Brown and B. C. Subba Rao, *ibid.*, **82**, 681 (1960).

(10) (a) L. L. McCoy, *ibid.*, **85**, 1321 (1963); (b) L. L. McCoy, *J. Org. Chem.*, **30**, 3762 (1965); (c) H. Bode, *Ber.*, **67B**,332 (1934).

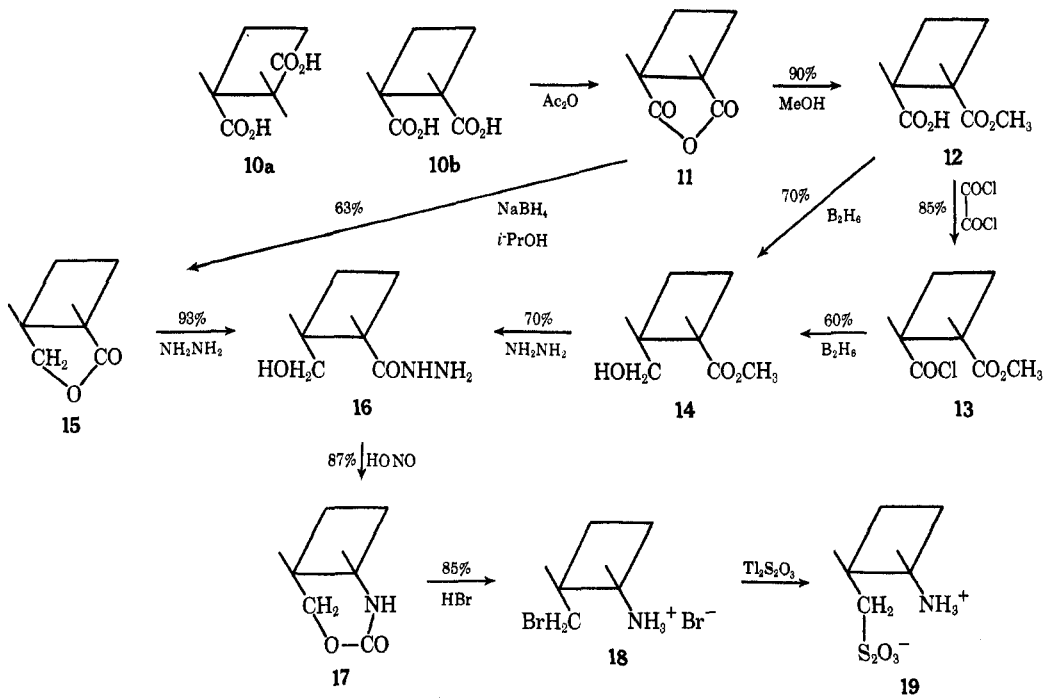
(11) M. S. Newman, *J. Amer. Chem. Soc.*, **70**, 317 (1948); R. A. Coleman and M. S. Newman, *ibid.*, **76**, 4534 (1954).

(12) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1968, p 102.

SCHEME I



SCHEME II



in excellent yield which were spectroscopically consistent with the Bunte salts **9** and **19**. However, repeated attempts at purification did not yield materials giving acceptable analyses, in distinct contrast to the reported stability of Bunte salts.[13] Attempts to prepare the corresponding thiols using sodium sulfide or sodium hydrosulfide gave elimination products instead, as indicated by the appearance of vinyl hydrogens in the pmr spectrum and unsaturation in the infrared spectrum.

Syntheses of the trans series followed the same general procedure (Schemes III and IV). Cyclopropane acid ester **29** was converted to urethane ester **31**. Attempts to reduce this compound to the amine alcohol failed. Although thionyl chloride was used to synthesize the trans acid chloride, this reagent for the cis resulted in epimerization which was circumvented by using oxalyl chloride.[5a]

Cyclobutane acid ester **21** was converted to benzyl urethane alcohol **24** by two alternate routes: **21** → **22** → **23** → **24** and **21** → **25** → **26** → **24**. Treatment of **26** with nitrous acid followed by benzyl alcohol gave the same benzyl urethane alcohol **24** that was obtained by diborane reduction of **23**. However, the presence of an ester group in **22** hindered the conversion of azide to isocyanate, stabilizing the azide in some manner.[14] Both trans urethanes **24** and **27** were treated with gaseous hydrogen bromide in various solvents. Only polymeric material could be isolated. This difference in behavior between internal urethane **17** and the urethane alcohol **24** (or **27**) indicates that formation of bromomethylamine hydrobromide **18** from the internal urethane must occur under conditions which do not facilitate polymerization of the bromoamine. Cleavage of the trans cyclopropyl urethane **31** gave polymeric material as well. An attempted Schmidt reaction on the cis amide acid **32** was unsuccessful.

Carbenoid additions to unsaturated precursors for the synthesis of *cis*- and *trans*-**9** (as well as **33**) were totally unsuccessful.[1,15] Witiak and Lu[16] have recently reported the synthesis of the *cis*- and *trans*-2-(2′-tetra-

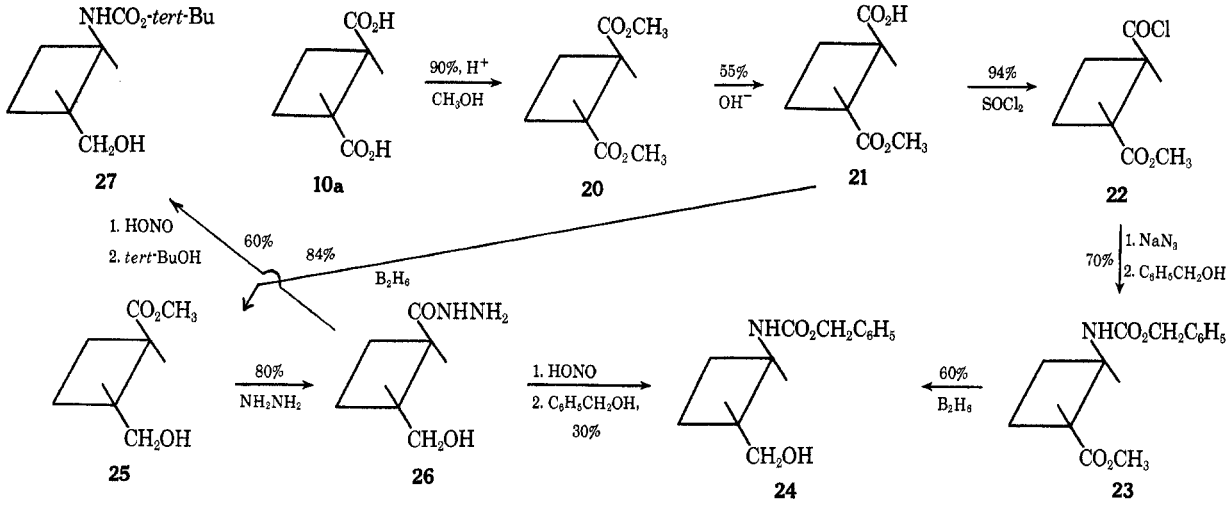
(13) D. L. Klayman and R. J. Shine, *Quart. Rep. Sulfur Chem.*, **3**, 191 (1968).

(14) M. Juang, C. C. Shroff, and W. S. Stewart, unpublished results.

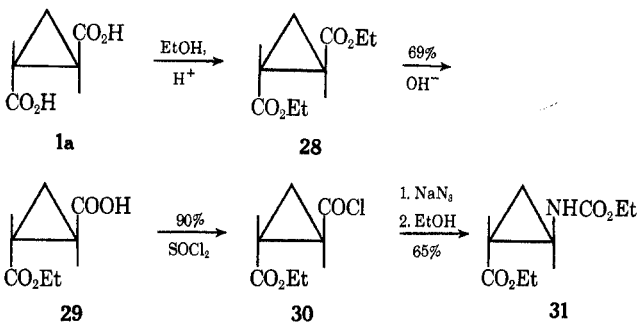
(15) W. E. Parham and S. H. Green, *J. Org. Chem.*, **31**, 1694 (1966) W. E. Parham and J. R. Potoski, *ibid.*, **32**, 275 (1967).

(16) D. T. Witiak and M. S. Lu, *ibid.*, **35**, 4209 (1970).

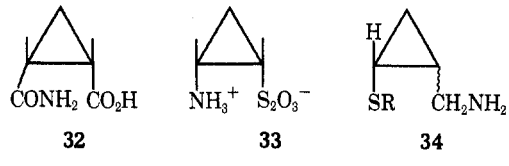
SCHEME III



SCHEME IV



hydropyranylthio)cyclopropylmethylamines (**34a**) by a carbenoid addition. However, they were not able to effect cleavage to the free thiols (**34b**).



a, R = tetrahydropyranyl
b, R = H

Experimental Section

All melting points and boiling points are uncorrected. Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries. Infrared spectra were taken on a Perkin-Elmer Model 137B Infracord with sodium chloride optics using polystyrene as a calibration. Proton magnetic resonance spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Gas chromatography was done on an Aerograph Model 661 flame ionization instrument using 5 ft × 1/8 in. stainless steel columns. Thin layer chromatography was done on 250-μ silica gel GF plates obtained from Analtech, Inc., Wilmington, Del. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

***cis*-Methyl Hydrogen Cyclopropane-1,2-dicarboxylate (3).**—Acid anhydride **2**[6] (10.0 g, 0.089 mol) in methanol (25 ml) was refluxed for 4 hr. Removal of the methanol gave a thick oily residue which crystallized upon cooling. Digestion in pentane gave colorless crystals (12.5 g, 97%): mp 51–52°; ir (Nujol) 5.77 and 5.87 μ; pmr ($CDCl_3$) δ 1.10–1.55 (m, 1), 1.60–1.82 (m, 1), 2.00–2.30 (m, 2), 3.70 (s, 3), and 11.5 (s, 1).

Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.98; H, 5.75.

Methyl *cis*-2-(Hydroxymethyl)cyclopropanecarboxylate (4) and *cis*-3-Oxa-2-oxobicyclo[3.1.0]hexane (5).—Diborane gas, generated by the dropwise addition of a diglyme solution of sodium borohydride (5.84 g, 0.154 mol) to boron trifluoride etherate (79.6 g, 0.28 mol), was bubbled through a capillary tube into acid ester **3** (10.0 g, 0.069 mol) in ether (150 ml) at room temperature. Generation was continued until dense turbidity appeared and then material precipitated on the walls of the flask giving a clear solution. Hydrolysis with methanol was followed by evaporation giving a colorless liquid which was a mixture of starting material and product. A second reduction under the same conditions gave the desired hydroxy ester plus diol. The diol was separated by alumina column chromatography (ether–methanol) but further purification of the hydroxymethyl ester was hampered by formation of lactone on heating or even on prolonged standing at room temperature. Lactone **5** was obtained in 90% yield (6.13 g) by distillation at 80° (7 mm).

Methyl *cis*-2-(hydroxymethyl)cyclopropanecarboxylate (**4**): ir (neat) 2.82, 5.82, and 9.77 μ; pmr ($CDCl_3$) δ 0.7–1.3 (m, 2), 1.3–2.0 (m, 2), 3.50 (s, 1), 3.68 (s, 3), and 3.60–4.25 (m, 2).

cis-3-Oxa-2-oxobicyclo[3.1.0]hexane (**5**): ir (neat) 5.65[4d,e] and 9.65 μ; pmr (CCl_4) δ 0.6–0.9 (m, 1), 1.0–1.5 (m, 1), 1.6–2.0 (m, 1), 2.0–2.4 (m, 1), and 3.6–4.6 (m, 2).

Anal. Calcd for $C_5H_6O_2$: C, 61.20; H, 6.17. Found: C, 60.83; H, 6.26.

cis-1,2-Di(hydroxymethyl)cyclopropane: ir (neat) 2.97, 8.02, 8.72, and 9.74 μ; pmr (CCl_4) δ 0.0–0.3 (m, 1), 0.4–0.9 (m, 1), 0.9–1.5 (m, 2), 2.9–3.4 (m, 2), 3.7–4.1 (m, 2), and 4.5 (s, 2).

Hydroboration of acid ester **12** was carried out under identical reaction conditions for comparative purposes. The turbidity disappeared upon further bubbling of diborane gas. Hydrolysis with methanol after 1 hr gave little bubbling and a product consisting only of hydroxymethyl ester.

***cis*-2-(Hydroxymethyl)cyclopropane Hydrazide (6).**—Hydrazine (1.4 g, 97%) in methanol (10 ml) was added to hydroxy ester **4** (3.0 g, 0.023 mol) in methanol (50 ml). After 3 hr of refluxing, the methanol and excess hydrazine were removed at 50°. The crude product was crystallized from ethanol giving 2.84 g (95%) of hydrazide **6**: mp 110–113°; ir (Nujol) 3.18, 6.14, and 6.42 μ; pmr (D_2O) δ 0.9–1.4 (m, 2), 1.5–2.0 (m, 2), 3.73 (m, 2), and 4.77 (s, 4).

Removal of the excess reagent and methanol on a vacuum pump gave a different crystalline form: mp 95–97°; ir (Nujol) 3.05, 6.17, and 6.55 μ. The pmr spectrum was the same as that of the 110° form and recrystallization of the 95° form from ethanol gave the other.

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.14; H, 7.75; N, 21.52. Found: C, 46.12; H, 7.64; N, 21.40.

Treatment of acid ester **3** with hydrazine gave *cis*-1,2-cyclopropane dihydrazide: mp 187–189°; ir (Nujol) 3.03, 6.08, and 6.57 μ; pmr (D_2O) δ 1.00–1.70 (m, 2), 1.90–2.20 (m, 2), and 4.70 (s, 6).

Anal. Calcd for $C_5H_{10}N_4O_2$: C, 37.97; H, 6.37; N, 35.42. Found: C, 37.57; H, 6.27; N, 35.40.

***cis*-2-Aza-3-oxo-4-oxabicyclo[4.1.0]heptane (7).**—Hydroxy hydrazide **6** (6.00 g, 0.046 mol) was dissolved in water (18 ml), and

sodium nitrite (4.75 g, 0.069 mol) and ether (50 ml) were added to the solution. It was then cooled to just above its freezing point. Hydrochloric acid (11.5 ml, 6 *N*) was added dropwise to the solution from a buret with stirring keeping the temperature below −5°. After the addition was complete, the mixture was transferred to a separatory funnel containing chloroform (300 ml) previously cooled to −10°. After the contents of the separatory funnel had been shaken for 15 min, the aqueous layer was separated and extracted with more chloroform. The combined chloroform was washed with 5% sodium bicarbonate and water, and dried. Concentration of the chloroform layer to half its volume at room temperature was followed by addition of toluene (100 ml) and removal of the remaining chloroform on a rotary evaporator (<40°). Additional toluene (200 ml) was added and the solution digested on a steam bath for 3 hr. Vigorous bubbling occurred above 80°. The solvent was removed and recrystallization from toluene and sublimation gave 3.96 g (78%) of urethane **7**: mp 99.5–100.5°; ir (Nujol) 3.05, 5.95, 6.95, 9.70, and 9.85 μ; pmr ($CDCl_3$) δ 0.5–1.15 (m, 2), 1.15–1.80 (m, 1), 2.7–3.1 (m, 1), 3.85–4.25 (m, 1), 4.50–4.90 (m, 1), and 7.20 (s, 1).

Anal. Calcd for $C_6H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.11; H, 6.04; N, 12.63.

Alternate procedures which added the hydrochloric acid to the hydrazide or ferric chloride to facilitate rearrangement of azide to isocyanate gave large amounts of lactone **5** and low yields of **7**.

Urethane **17** was prepared by the same method. Hydroxy hydrazide **16** (5.00 g, 0.03 mol), sodium nitrite (3.10 g, 0.045 mol), and hydrochloric acid (7.5 ml, 6 *N*) gave an 87% yield (3.80 g) of urethane **17**. The azide readily rearranged to isocyanate in chloroform at room temperature and gave no lactone **15** as a by-product.

***cis*-2-Bromomethylcyclopropylamine Hydrobromide (8).**—Urethane **7** (4.00 g, 0.034 mol) in chloroform (40 ml) was saturated with hydrogen bromide gas giving crystalline material slightly soluble in chloroform. The crude product was washed with small amounts of cold chloroform and dried on a vacuum pump: 7.95 g (97%); mp 124–126°; ir (Nujol) 3.10–4.05, 5.10, 6.25, 8.20, 9.70, 10.48, and 11.80 μ; pmr (D_2O) δ 1.0–1.35 (m, 1), 1.35–1.70 (m, 1), 1.75–2.5 (m, 1), 3.15 (m, 1), 3.50–3.90 (m, 1), 3.90–4.30 (m, 1), and 4.8 (s, 3).

Anal. Calcd for $C_4H_9NBr_2$: C, 20.80; H, 3.93; N, 6.07; Br, 69.20. Found: C, 20.82; H, 3.95; N, 6.24; Br, 69.38.

***cis*-2-Aminocyclopropylmethanethiosulfuric Acid (9).**—Bromomethylamine hydrobromide **8** (0.497 g, 0.002 mol) in methanol (10 ml) was treated with thallous thiosulfate (1.121 g, 0.002 mol) for 3 days at room temperature. The precipitated thallous bromide was filtered (1.197 g, 100%) and the brown filtrate was concentrated on a rotary evaporator. Removal of the aqueous solvent at high vacuum (0.007 mm) gave 0.426 g of crystalline product. Thin layer chromatography (MN 300 Cellulose) showed two spots using a 1-butanol–acetic acid–water (6:1:4) solvent system: R_f 0.415 and 0.895; ir ($CHCl_3$) 3.14, 8.24, 8.37, 9.47, 9.86 and 12.47 μ; pmr (DMSO-d_6) δ 1.1–3.8 (complex), 7.12 (t, 3, J = 51 Hz).

Anal. Calcd for $C_4H_9NS_2O_3$: C, 26.22; H, 4.95; N, 7.64; S, 35.00. Found: C, 13.96; H, 6.00; N, 10.31; S, 24.82; Tl, 0.92.

Further purification was attempted by dissolving the compound in methylene chloride. A white solid precipitated leaving a foul-smelling brown material. Elemental analyses of the white solid indicated that the solvent (methanol) was participating in the reaction. When water was used as the solvent, the crude white solid obtained showed vinyl protons in its pmr spectrum and a peak at 11.0 μ in its ir spectrum indicating that the cyclopropane ring had cleaved. Attempts to prepare the thiol from the corresponding thiosulfate or from the bromide were unsuccessful.

***cis*-Methyl Hydrogen Cyclobutane-1,2-dicarboxylate (12).**—Acid anhydride **11**[7] (10.0 g) in methanol (50 ml) was refluxed for 15 hr. Methanol was removed and the residue distilled: bp 111–112° (3 mm) (11.5 g, 90%); ir (neat) 5.78, 5.9 and 8.3 μ; pmr ($CDCl_3$) δ 2.0–2.8 (m, 4), 3.3–3.6 (m, 2), 3.88 (s, 3), and 11.6 (s, 1).

Methyl *cis*-(2-Chloroformyl)cyclobutanecarboxylate (13).—To acid ester **12** (7.9 g, 0.05 mol) dissolved in dry benzene (50 ml) was added oxalyl chloride (3.2 g, 0.025 mol) and the mixture was refluxed for 4 hr. After removal of the benzene, the precipitated oxalic acid was filtered from the chilled solution and the residue distilled at 60–61° (1 mm) to give **13** (7.5 g, 85%): ir (neat) 5.59, 5.8, and 8.35 μ; pmr (CCl_4) δ 2.0–2.8 (m, 4), 3.2–4.0 (m, 2), and 3.68 (s, 3). The acid chloride was used without further purification for the next step.

Partial Reduction of 11 to *cis*-3-Oxa-2-oxobicyclo[3.2.0]heptane (15).—Sodium borohydride (1.8 g, 0.047 mol) was stirred with 2-propanol (60 ml) for 30 min and anhydride **11** (4.3 g, 0.034 mol), dissolved in warm 2-propanol (40 ml), was added dropwise. The mixture was refluxed for 2.5 hr. After removal of the solvent at reduced pressure, the resultant white solid was decomposed with concentrated hydrochloric acid in ice. The hydrolyzed mixture was stirred 1 hr, heated on a steam bath for 30 min, and extracted with ether. The ether extracts were combined, washed with sodium bicarbonate and water, and dried. Evaporation of ether gave lactone **15** (2.4 g, 63%): bp 63–64° (1 mm) [lit.[5a,b] 108° (17 mm), 74° (1.5 mm)]; ir (neat) 2.87, 5.68, and 8.7 μ; pmr (CCl_4) δ 1.1–2.75 (m, 4), 2.75–3.6 (m, 2), and 3.8–4.5 (m, 2).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 63.98; H, 7.17.

Diborane Reduction of 13.—The procedure used was that described for preparing **4**. Acid chloride ester **13** (3.52 g, 0.02 mol) gave **14** (1.7 g, 60%): bp 70–72° (1 mm); ir (neat) 2.91, 5.79, and 8.38 μ; pmr (CCl_4) δ 1.7–2.4 (m, 4), 2.6–3.0 (m, 1), 3.0–3.3 (m, 1), 3.50 (d, 2, J = 6 Hz), 3.6 (s, 3), and 4.2 (broad absorption, 1).

Diborane Reduction of 12.—Acid ester **12** (3.2 g, 0.02 mol) was reduced by the method described for **4**. Removal of methanol gave **14** (2.0 g, 70%): bp 75–76° (1 mm); the ir and pmr spectra were identical with those of the product obtained in the preceding experiment.

***cis*-(2-Hydroxymethyl)cyclobutanecarboxylic Acid Hydrazide (16) from 14.**—Hydroxy ester **14** (1.44 g, 0.01 mol) was treated as **4** was converted to **6**. Recrystallization from ethanol gave **16** (1.0 g, 70%): mp 114–115°; ir (Nujol) 3.05, 5.99, and 6.10 μ; pmr (DMSO-d_6) δ 1.50–2.25 (m, 4), 2.25–2.75 (m, 1), 2.75–3.25 (m, 1), 3.48 (d, 2, J = 7 Hz), and 3.7–4.3 (broad absorption, 4).

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 50.07; H, 8.18; N, 19.23.

***cis*-(2-Hydroxymethyl)cyclobutanecarboxylic Acid Hydrazide (16) from 15.**—As described in the conversion of **4** to **6**, lactone **15** (3.36 g, 0.03 mol) and hydrazine hydrate (1 ml) in anhydrous *n*-butyl alcohol (50 ml) were refluxed for 8 hr. A similar work-up gave **16** (4.0 g, 93%); ir and pmr spectra were identical with those of the product obtained in the preceding experiment. Lower boiling alcohols were much less effective as solvents.

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 49.91; H, 8.59; N, 19.20.

***cis*-2-Aza-3-oxo-4-oxabicyclo[4.2.0]octane (17).**—Hydroxy hydrazide **16** (2.5 g, 0.017 mol) was converted to urethane **17** in the same manner as **6** was converted to **7**. Removal of toluene gave crystalline urethane **17** upon chilling (1.3 g, 59%): mp 89.5–90.5°; ir (Nujol) 3.14, 5.88, and 5.95 μ; pmr ($CDCl_3$) δ 1.75–2.63 (m, 4), 2.65–3.15 (m, 1), 3.70–4.15 (m, 1), 4.28 (d, 2, J = 5 Hz), and 6.9–7.5 (broad absorption, 1).

Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.59; H, 7.03; N, 11.08.

***cis*-2-Bromomethylcyclobutylamine Hydrobromide (18).**—Urethane **17** (1.27 g, 0.01 mol) was converted to **18** by the same method as **7** was converted to **8** except that dioxane was used as solvent. The crystalline residue was recrystallized from chloroform to give **18** (2.1 g, 85%): mp 169.5–170.0°; ir (Nujol) 3.1–4.2, 5.42, 8.0, and 14.95 μ; pmr (D_2O) δ 1.50–2.5 (m, 4), 2.85–3.40 (m, 1), 3.74 (d, 1, J = 7.0 Hz), 3.74 (d, 1, J = 9.0 Hz), 3.95–4.30 (m, 1), and 4.60–4.85 (s, 3).

Anal. Calcd for $C_5H_{11}NBr_2$: C, 24.51; H, 4.53; N, 5.72; Br, 65.24. Found: C, 24.19; H, 4.43; N, 5.85; Br, 63.43.

***cis*-2-Aminocyclobutylmethanethiosulfuric Acid (19).**—Bromomethylamine hydrobromide **18** (1.22 g, 0.005 mol) dissolved in distilled water (25 ml) and thallium (ous) thiosulfate (2.6 g, 0.005 mol) were refluxed for 36 hr with stirring. The contents of the flask were filtered to remove the thallium bromide precipitate (2.84 g, 100%), chilled overnight, and refiltered. The filtrate was freeze-dried yielding a white, crystalline product (1.0 g, 100%), mp 172–173° dec. The product gave a positive test for nitrogen and sulfur[17] and a negative test for bromine:[17]

(17) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Wiley, New York, N. Y., 1966, pp 1041, 1042.

ir (Nujol) 3.1–4.35, 5.0, 6.16, and 9.75 μ; pmr (D_2O) δ 1.7–2.7 (m, 4), 3.0–3.6 (m, 1), 3.38 (d, 1, J = 6.0 Hz), 3.41 (d, 1, J = 9.0 Hz), 3.9–4.3 (m, 1), and 4.7 (s, 3).

Analyses were consistently low in carbon, hydrogen, and sulfur even after purification by tlc. A large ash content was always observed but analysis showed no thallium present.

trans-**Dimethylcyclobutane-1,2-dicarboxylate** (**20**).—Diacid **10a**[7] (50.0 g, 0.34 mol), anhydrous methanol (250 ml), and concentrated sulfuric acid (1 ml) were refluxed with stirring for 35 hr, allowed to cool, and distilled giving 52.2 g (90%) of a colorless liquid: bp 74° (3 mm) [lit.[18] 105–107° (13 mm)]; ir (neat) 5.75 and 8.0 μ; pmr ($CDCl_3$) δ 3.68 (s, 6), 3.41 (m, 2), and 2.17 (m, 4).

trans-**Methyl Hydrogen Cyclobutane-1,2-dicarboxylate** (**21**).—Anhydrous methanol (100 ml) and **20** (43.0 g, 0.25 mol) were heated to reflux and a solution of sodium hydroxide (10.4 g, 0.26 mol) in water was added over a period of 2 hr. The solution was cooled and concentrated at 15-mm pressure. The residue was diluted with water and concentrated again for a short period of time, and the aqueous solution was extracted with ether. The aqueous solution was then acidified to pH 3, extracted with ether, dried, concentrated, and distilled under reduced pressure to give 22.0 g (55%) of colorless liquid **21**: bp 106–108° (1 mm); ir (neat) 3.2, 5.70, 5.80, and 7.9 μ; pmr ($CDCl_3$) δ 2.20 (m, 4), 3.45 (m, 2), 3.68 (s, 3), and 11.4 (s, 1).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.90; H, 6.40.

Methyl *trans*-**2-(Chloroformyl)cyclobutanecarboxylate** (**22**).—Acid ester **21** (10.8 g, 0.062 mol) and thionyl chloride (18.0 g, 0.15 mol) were stirred and heated under reflux for 2 hr. The reaction mixture was distilled at atmospheric pressure to remove the excess thionyl chloride and distilled under reduced pressure to give 11.8 g (94%) of acid chloride **22**: bp 52° (1 mm); ir (neat) 5.50, 5.73, and 8.0 μ; pmr ($CDCl_3$) δ 2.30 (m, 4), 3.45 (m, 1), 3.70 (s, 3), and 3.85 (m, 1).

Anal. Calcd for $C_7H_9O_3Cl$: C, 47.72; H, 5.11. Found: C, 47.54; H, 5.15.

Methyl *trans*-**2-(*N*-Carbobenzyloxyamino)cyclobutanecarboxylate** (**23**).—Acid chloride **22** (11.3 g, 0.065 mol) was dissolved in dry acetone and cooled to 0°. Sodium azide (6.6 g, 0.01 mol) dissolved in water was added dropwise, and the resulting mixture was stirred for 2 hr at 0°, poured into ice-water, and extracted with ether. The ethereal extracts were dried, filtered, and concentrated. The oily residue that remained was refluxed in 100 ml of dry toluene with 10 ml of benzyl alcohol for 4 days. The solution was concentrated and chromatographed on alumina. An 8:2 solution of petroleum ether–methylene chloride eluted 3.2 g of pure urethane ester **23**. All subsequent fractions contained benzyl alcohol as the principal contaminant. A total of 13.5 g (70%) of **23** was obtained by repeated chromatography: ir (neat) 2.9, 5.75, and 7.5 μ; pmr ($CDCl_3$) δ 2.0 (m, 4), 3.0 (m, 1), 3.55 (s, 3), 4.37 (m, 1), 5.0 (s, 1), 5.85 (broad s, 1), and 7.2 (s, 5).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.00; H, 6.67; N, 5.14.

Diborane Reduction of 23.—Urethane ester **23** (10.0 g, 0.036 mol) was reduced with diborane as in the preparation of **4**. Crystallization from cyclohexane–methylene chloride gave 5.1 g (60%) of white urethane **24**: mp 82–83°; ir (Nujol) 2.9, 5.87, and 7.80 μ; pmr ($CDCl_3$) δ 2.0 (m, 4), 3.55 (m, 4), 3.75 (s, 1), 5.15 (s, 2), 5.4 (s, 1), and 7.4 (s, 5).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.40; H, 7.54; N, 6.20.

trans-**Methyl 2-Hydroxymethylcyclobutanecarboxylate** (**25**).—Acid ester **21** (10.0 g, 0.062 mol) was reduced with diborane as in the preparation of **4**. Distillation under reduced pressure gave 7.6 g (84%) of a colorless liquid: bp 81–82° (1 mm); ir (neat) 2.9, 5.75 and 8.0 μ; pmr ($CDCl_3$) δ 1.95 (m, 4), 2.85 (m, 2), 3.5 (d, 2, J = 5 Hz), 3.6 (s, 3), and 3.9 (s, 1).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.06; H, 8.40.

trans-**2-Hydroxymethylcyclobutane Hydrazide** (**26**).—Hydroxy ester **25** (5.0 g, 0.034 mol) was treated as **4** was converted to **6**. The resulting oily material was crystallized from absolute ethanol–ether to give 4.0 g (80%) of a white solid: mp 88–89°; ir (KBr) 3.0 and 6.1 μ; pmr (D_2O) δ 1.9 (m, 4), 2.7 (m, 2), 3.55 (d, 2, J = 6 Hz), and 4.65 (s, 4).

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 50.17; H, 8.57; N, 19.58.

trans-**2-Hydroxymethyl(*N*-carbobenzyloxy)cyclobutylamine** (**24**).—Hydroxy hydrazide **26** (2.5 g, 0.017 mol) was converted to azide in the same manner as **6** was converted to **7**. The ethereal solution of azide alcohol was added dropwise to refluxing toluene containing 2.0 g (0.02 mol) of benzyl alcohol and the ether was allowed to distill. After removal of ether, the resulting solution was refluxed, with stirring, for 12 hr. Concentration of the cooled reaction mixture and crystallization of the remaining oil from cyclohexane–methylene chloride gave 1.3 g (30%) of a crystalline white urethane **24**, mp 82–83°. This material was identical with the product obtained from the diborane reduction of **23**, admixture mp 82–83°.

trans-**2-Hydroxymethyl(*N*-carbo-*tert*-butoxy)cyclobutylamine** (**27**).—The procedure used was identical with that employed in the preparation of **24** including quantities of materials, except that *tert*-butyl alcohol was used in place of benzyl alcohol. The crude product was purified by sublimation at 60° (1 mm) to give 2.0 g (60%) of a white urethane **27**: mp 69–70°; ir (Nujol) 2.9, 5.95, 6.5, and 7.75 μ; pmr ($CDCl_3$) δ 1.4 (s, 9), 1.9 (m, 4), 3.5 (d, 2, J = 7 Hz), 4.85 (s, 1), and 5.0 (broad s, 1).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.43; H, 9.78; N, 6.87.

Reaction of 24 with Hydrogen Bromide.—Gaseous hydrogen bromide was passed into a solution of **24** (1.0 g, 0.004 mol) in anhydrous, purified chloroform (75 ml) for 30 min. The resulting mixture was stirred overnight at room temperature. The chloroform solution was decanted from the semisolid that remained (0.5 g) and the combined chloroform extracts were concentrated. A tlc (chloroform–ether, 1:1) indicated two components, the R_f values of both being different from that of the starting material. The ir and pmr spectra indicated a mixture of benzyl bromide and *trans*-2-bromomethyl(*N*-carbobenzyloxy)-cyclobutylamine. No attempt was made to further separate or characterize these materials. Similar reactions were attempted using other solvents. The results in each case were identical with those just described.

trans-**Ethyl Hydrogen Cyclopropane-1,2-dicarboxylate** (**29**).—Partial hydrolysis of diester **28** by the method of Wiberg[4a] gave the title compound in 69% yield: mp 56–57° (lit.[4a] 58–60°); ir (CCl_4) 2.7–3.3, 5.76, 5.88, and 8.35–8.45 μ; pmr ($CDCl_3$) δ 1.4 (t, plus m, 5), 2.25 (m, 2), 4.3 (q, 2, J = 7 Hz), and 11.7 (s, 1).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.87; H, 6.28.

trans-**2-Carbethoxycyclopropanecarboxylic Acid Chloride** (**30**).—To thionyl chloride (11.9 g, 0.02 mol) was added acid ester **29** (3.2 g, 0.02 mol) and the solution was refluxed for 4 hr. Excess thionyl chloride was removed and the residue distilled at 65–66° (1 mm) giving 3.15 g (90%) of acid chloride **30**: ir (neat) 5.62, 5.8, 8.3, and 10.05 μ; pmr ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz), 1.72 (m, 2), 2.53 (m, 2), and 4.18 (q, 2, J = 7 Hz). The acid chloride was used without further purification for the next step.

Ethyl *trans*-**(2-*N*-Carbethoxyamino)cyclopropanecarboxylate** (**31**).—The acid chloride (1.76 g, 0.01 mol) was converted to azide by the same method as used for **23**. The crude azide was added to toluene and heated until nitrogen evolution ceased (about 2 hr). Addition of ethanol was followed by refluxing and solvent was removed. The oily residue solidified upon cooling. Recrystallization from chloroform–cyclohexane or sublimation at 100° (1 mm) gave urethane **31** (1.3 g, 65%): mp 59.5–60.0°; ir (Nujol) 3.05, 5.85, 5.95, 6.56, and 8.5 μ; pmr ($CDCl_3$) δ 1.0–1.5 (m plus t, 8, J = 7 Hz), 1.5–1.9 (m, 1), 2.9–3.3 (m, 1), 3.9–4.4 (overlapping q, 4, J = 7 Hz), and 5.6 (s, 1).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.79; H, 7.33; N, 7.23.

cis-**2-Amidocyclopropanecarboxylic Acid** (**32**).—To acid anhydride **2**[6] (7.5 g, 0.067 mol) was added ammonium hydroxide (50 ml) over a period of 1 hr with cooling. The excess ammonia was removed on a steam bath under a stream of nitrogen. Concentrated hydrochloric acid was added until precipitation was complete and the flask was cooled in a refrigerator. The amide acid **32** was filtered, washed with water, and recrystallized from hot water. The yellowish white product (4.3 g, 50%) had mp 179.5–180°; ir (Nujol) 2.95, 5.80, and 6.0 μ; pmr (DMSO-d_6) δ 0.7–1.55 (m, 2), 1.65–2.20 (m, 2), 6.7–7.4 (s, 1), and 7.4–8.0 (s, 2).

Anal. Calcd for $C_5H_7NO_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.63; H, 5.30; N, 10.71.

(18) R. Kuhn and A. Wasserman, *Helv. Chim. Acta*, **11**, 600 (1928); H. Bode, *Ber.*, **67**, 332 (1934).

Attempted Hofmann Degradation of 32.—To a mixture of sodium hydroxide (14.0 g, 0.35 mol) and **32** (6.45 g, 0.05 mol) in an ice–water mixture (50 g) was added bromine (16.0 g, 0.1 mol) dropwise over 30 min. After heating the reaction mixture on a steam bath until it was clear, hydrochloric acid was added and the mixture was extracted three times with ether. Removal of ether gave a negligible residue as did continuous extraction of the aqueous layer.

Registry No.—**3**, 31420-47-0; **4**, 31443-73-9; **5**, 4606-09-1; **6**, 31420-49-2; **7**, 31420-50-5; **8**, 31420-51-6; **9**, 31392-62-8; **12**, 31420-52-7; **13**, 31420-53-8; **14**, 31420-54-9; **15**, 7687-28-7; **16**, 31420-56-1; **17**, 31420-57-2; **18**, 31420-58-3; **19**, 31392-63-9; **20**, 7371-67-7; **21**, 31420-60-7; **22**, 31443-74-0; **23**, 31420-61-8; **24**, 31420-62-9; **25**, 31420-63-0; **26**, 31420-64-1; **27**, 31420-65-2; **29**, 31420-66-3; **30**, 17868-78-9; **31**, 31420-68-5; **32**, 15982-33-9; *cis*-1,2-di(hydroxymethyl)-cyclopropane, 2345-68-8; *cis*-1,2-cyclopropane dihydrazide, 2374-08-5.

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The Synthesis of 2,5- and 2,6-Bis(bromomethyl)-1,4-diphenylpiperazines and Their Conversion into 2,5-Diphenyl-2,5-diazabicyclo[2.2.2]octane[1]

DAVID A. NELSON,* JAMES J. WORMAN, AND BRIAN KEEN

Department of Chemistry, University of Wyoming, Laramie, Wyoming 82070

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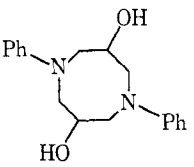
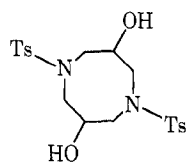
Treatment of *cis*-1,5-diphenyl-3,7-dihydroxyoctahydro-1,5-diazocine (**1**) with phosphorus tribromide yielded a mixture of *cis*-2,6-bis(bromomethyl)-1,4-diphenylpiperazine (**4**) and *cis*-2,5-bis(bromomethyl)-1,4-diphenylpiperazine (**5**). The structures of **4** and **5** were confirmed by conversion to the corresponding dimethyl-1,4-diphenylpiperazines (**6** and **7**) by lithium aluminum hydride. Compounds **6** and **7** were synthesized from *cis*-2,5- and *cis*-2,6-dimethylpiperazines. Both **4** and **5** on treatment with magnesium in tetrahydrofuran were converted to 2,5-diphenyl-2,5-diazabicyclo[2.2.2]octane (**8**). The interconversion of **4** and **5** is discussed.

As part of a study of the chemistry of 3,7-disubstituted 1,5-diphenyloctahydro-1,5-diazocines, we have investigated the reaction of 1,5-diphenyl-3,7-dihydroxyoctahydro-1,5-diazocine (**1**) with phosphorus tribromide. The synthesis of **1** was first reported by Gaertner,[2] but the question of the stereochemistry of the hydroxyl groups was not settled. Thin layer chromatography on silica gel of **1** as it crystallized from the reaction mixture shows it to be essentially homogeneous, with only a trace of a second, faster moving component. Recrystallization from ethyl acetate–methanol gives a product homogeneous to thin layer chromatography under a variety of conditions. Paudler and coworkers[3] have presented arguments for distinguishing the cis and trans isomers of 1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocine (**2**) by the separation of the nmr resonances of the ring methylene hydrogens. Thus, with their systems, it would appear that the ring methylene hydrogens are more nearly magnetically equivalent in the trans isomer than in the cis isomer, and with both isomers in hand, they assign the stereochemistry on this basis. Although the methylene signals of **1** show a comparable separation with *cis*-**2**, 0.89 *vs.* 0.80 ppm, an examination of both Dreiding and CPK space filling models show that the *N*-phenyl groups of **1** can cause a similar degree of magnetic nonequivalence of the ring methylene hydrogens in a variety of conformations of both cis and trans isomers. Without isolation of a second isomer, we hesitate to assign stereochemistry on the basis of Paudler's criteria alone. However, the separation of the methylene resonances together with the stereochemistry of the dibromo derivative discussed below lead us to the conclusion that we are dealing with the cis isomer of **1**.



1



2

Treatment of **1** with phosphorus tribromide at 115° yields, after hydrolysis with water, a compound, $C_{18}H_{21}Br_3N_2$ (**3**), which, from its infrared spectrum, was deduced to be a hydrobromide salt. The nmr spectrum of **3** was not that to be expected from a dibromodiazocine, but clearly indicated its structure to be a bis(bromomethyl)-1,4-diphenylpiperazine monohydrobromide. The most significant signal in the spectrum of **3** was a doublet at δ 2.4 (4 H) which was assigned to the methylene hydrogens of the bromomethyl groups, split by the tertiary hydrogen (H_X). The signal from the tertiary hydrogens appeared as a broad multiplet at δ 4.5 (2 H). Irradiation of the signal at δ 4.5 collapsed the signal at δ 2.4 to a singlet. The remaining signals of the ring methylenes appeared as the AM part of an AMX system from δ 3 to 4.

Neutralization of **3** with ammonium hydroxide yielded a solid which upon recrystallization gave a compound $C_{18}H_{20}N_2Br_2$, mp 132–134°.[4] Concentration of the mother liquor from the recrystallization gave an isomeric compound **5**, mp 117–119°.

Compounds **4** and **5** were characterized as bromomethylpiperazines by their identical mass spectra, which showed a peak for the loss of a CH_2Br fragment from the molecular ion, and by their reduction to the

(1) (a) This research was supported, in part, by Public Health Service Grant GM-13117. (b) Presented in part at the First International Conference on Heterocyclic Chemistry, Albuquerque, N. M., June 1967. (c) Abstracted in part from the Ph.D. thesis of J. J. W., University of Wyoming, Aug 1968.

(2) V. R. Gaertner, *Tetrahedron Lett.*, 141 (1964).

(3) (a) W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 277 (1966); (b) W. W. Paudler, A. G. Zeiler, and G. R. Gapski, *ibid.*, **34**, 1001 (1969).