Hofmann Elimination of Heterocycles Containing Bridgehead Hydrazines. I. 2,6-Benzodiazonine and Dibenzo[c,h][1,6]diazecine[1a] Derivatives

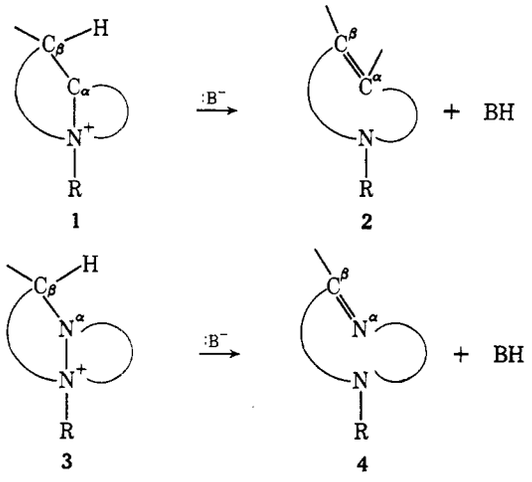
PAUL AEBERLI[1b] AND WILLIAM J. HOULIHAN[1c]

Sandoz Pharmaceuticals, Hanover, New Jersey 07936

Received October 25, 1968

Treatment of the methyl halide salts of the bridgehead hydrazines, 5-(*p*-chlorophenyl)-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazine (**9**) and 5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazine(**19**), with sodium methoxide–methanol gave the medium-sized heterocycles 1-(*p*-chlorophenyl)-6-methyl-4,5,6,7-tetrahydro-3H-2,6-benzodiazonine (**10**) and 6-methyl-5,6,7,14-tetrahydrodibenzo[*c*,*h*][1,6]diazecine (**22**). The lithium aluminum hydride reduction of 2-(4-chlorobutyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (**5e**) resulted in an unusual N–N cleavage and ring formation to give 2-pyrrolidinomethylbenzhydrylamine (**16**).

The base elimination (Hofmann elimination[2]) of heterocycles containing a quaternary bridgehead nitrogen atom has been demonstrated[3] to be a useful technique for preparing medium-sized nitrogen-containing rings. In a simplified model system **1** this reaction occurs by the removal of a proton from a carbon atom β to the quaternary nitrogen atom to give the unsaturated amine **2**. In all cases reported[2,3] to date the α atom in this system has been carbon (**1**, C_α) and the resultant product has been an olefin amine (**2**, $C_\beta{=}C_\alpha$). Replacement of the α atom in this system by N (**3**, N_α) suggests that this reaction can be modified to produce imino amines such as **4**.



If such a transformation could be accomplished this would allow a convenient preparation of medium-sized heterocycles containing at least two nitrogen atoms. In this paper we report the successful application of the generalized reaction **3** → **4** in the preparation of the 2,6-benzodiazonine and dibenzo[*c*,*h*][1,6]diazecine ring system and an unusual lithium aluminum hydride reduction of a phthalazinone.

The reaction of *o*-(4-chlorobenzoyl)benzoic acid with 3-hydrazinopropanol in toluene gave 3-hydroxypropylphthalazinone **5**. Reduction of this compound with excess lithium aluminum hydride[4] in refluxing tetrahydrofuran for 96 hr afforded the tetrahydrophthalazine **6a** (Scheme I). Treatment of **6a** with thionyl chloride followed by distillation gave the pyrazolo[1,2-*b*]phthalazine **7a**. This compound was also obtained when the chloropropylphthalazinone **5b**, obtained from **5a** and thionyl chloride, was reduced with lithium aluminum hydride. In addition a small amount of a polar, water-soluble chloride was obtained. Spectral and analytical data indicate that this substance is probably the imminium salt **8a**. Treatment of **7a** with methyl iodide gave a quaternary salt that could be assigned as the N-4 or N-11 derivative. The nmr spectrum of this compound gave a single methyl signal and the $ArCH_2N$ protons relative to the ArCHAr'N proton have undergone a larger downfield shift indicating that the quaternary N is at N-11 (**9**). Inspection of models also indicate that methylation at N-11 is sterically more favorable. When **9** was treated with sodium methoxide in refluxing methanol an unsaturated amine was isolated. This compound gave a typical benzophenonimine ultraviolet[5] spectrum, an $ArCH_AH_BN$ quartet, a CH_3N singlet, six aliphatic and eight aromatic protons in agreement with structure **10**, the Hofmann elimination product resulting from removal of the benzhydryl β hydrogen in **9**. The products resulting from β elimination[6] at positions C-2 and C-3 were not detected. Attempted reduction of the C=N bond in **10** with lithium aluminum hydride in refluxing tetrahydrofuran (96 hr) resulted in recovered starting material. The platinum-catalyzed hydrogenation of **10** in acetic acid proceeded easily to give the desired **11**.

The reduction of the hydroxybutylphthalazinone **5c** with lithium aluminum hydride resulted in a mixture of dihydro- and tetrahydrophthalazines **12a** and **6b** with the former predominating. The tetrahydro compound **6b** underwent dehydrogenation to **12a** at a rate sufficient to exclude it as a useful intermediate to prepare the pyrazinophthalazine **7b**. In an attempt to utilize **12a** as an intermediate to prepare **7b** it was treated with thionyl chloride with the hope of obtaining the imminium salt **8b** rather than the spiro salt **13**. In order to distinguish between **13** and **8b** the model quaternary salt **13b** was prepared by partial lithium aluminum hydride reduction of **5d** to the imine **12b** followed by treat-

(1) (a) Portions of this paper were presented by W. J. Houlihan and R. E. Manning at the First International Congress of Heterocyclic Chemistry, the University of New Mexico, Albuquerque, N. M., June 1967. (b) Sandoz Ltd., Basle, Switzerland. (c) To who inquiries should be sent.

(2) A. C. Cope, *Org. Reactions*, **11**, Chapter 5 (1960).

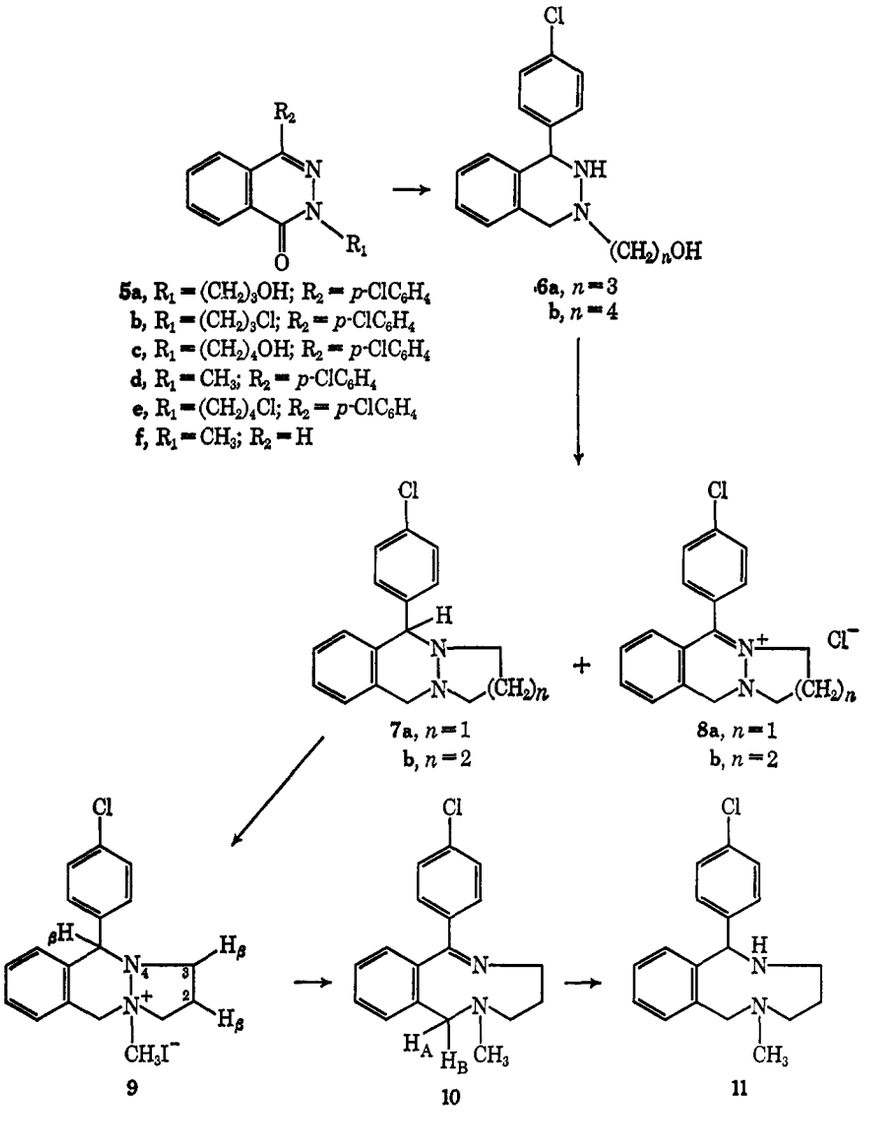
(3) See ref 2 and E. Gellert, T. R. Govindachari, M. V. Laksmikanthan, *J. Chem. Soc.*, 1008 (1962); M. G. Reinecke, L. R. Kray, and R. F. Francis, *Tetrahedron Lett.*, 3549 (1965; L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965); *J. Org. Chem.*, **30**, 228 (1965); L. A. Paquette and M. K. Scott, *ibid.*, **33**, 2379 (1968).

(4) The lithium aluminum hydride reduction of the C=N bond in phthalazinones has been reported to be sluggish: Yu. S. Shabarov, N. I. Vasil'er, N. K. Mamaeva, and R. Ya. Levina, *J. Gen. Chem. USSR*, **33**, 1182 (1963).

(5) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1954.

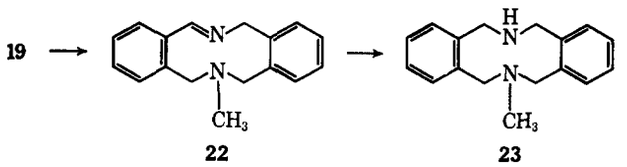
(6) For some comments on the olefin(s) expected from the β elimination of quaternary ammonium salts, see ref 2 and D. V. Banthrope, "Elimination Reactions," Elsevier Publishing Co., Amsterdam, The Netherlands, 1963.

SCHEME I

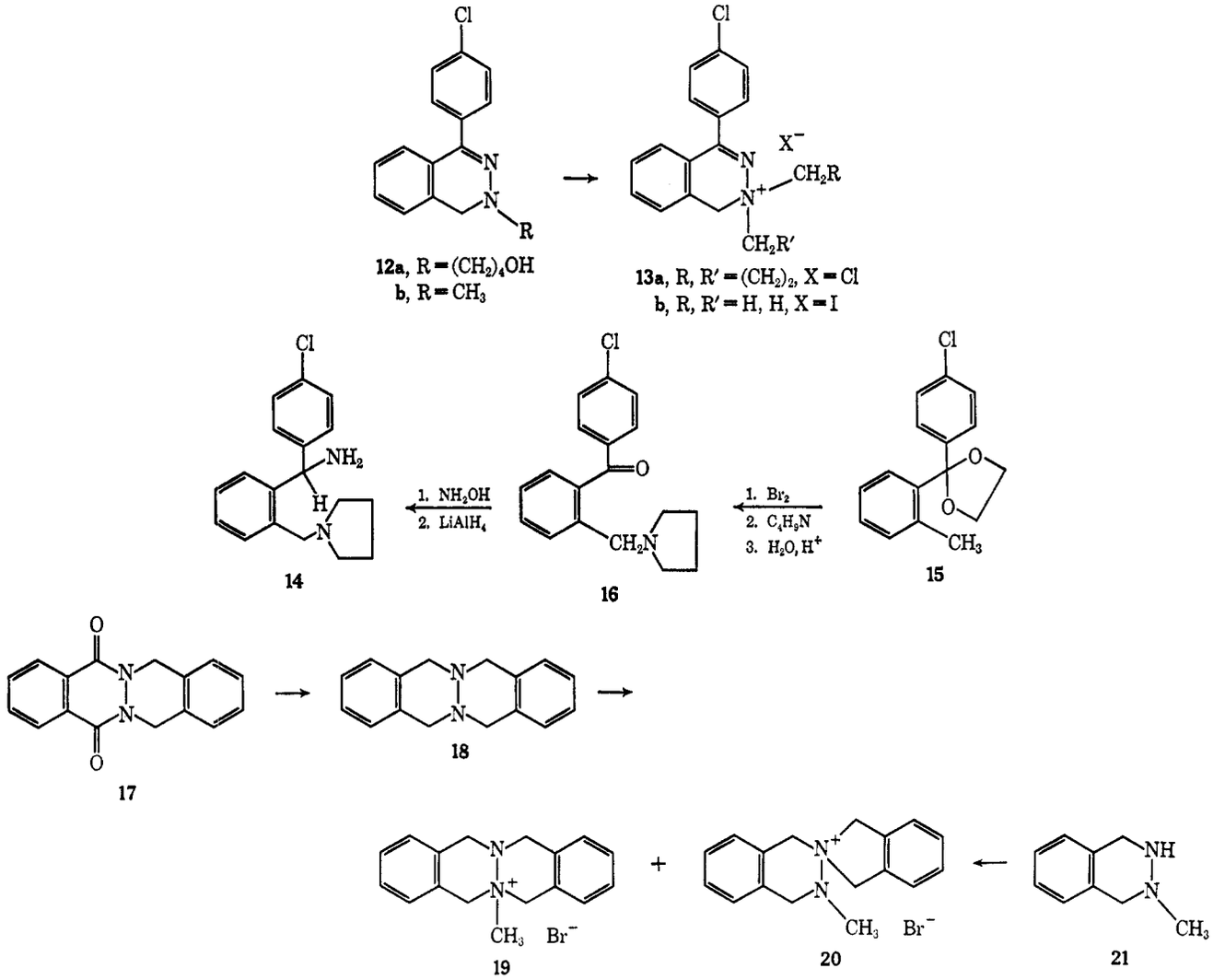


ment with methyl iodide. The structure of **13b** was confirmed by an nmr spectrum that gave a 6 H singlet indicating $^+N(CH_3)_2$ rather than $=N^+(CH_3)N(CH_3)-$. Comparison of the position of the nmr benzyl singlet in **13b** (δ 5.52) and the salt (δ 5.73) obtained from **12a** and thionyl chloride indicated that both were in a similar environment. These data, together with the result that **12b** methylated only on the tertiary amine nitrogen, indicate the spiro salt **13**. In an additional attempt to prepare **7b**, the chlorobutylphthalazone **5e** was treated with lithium aluminum hydride under conditions that converted **5b** into **7a**. Instead of **7b** a diamine that formed a monoacetyl derivative and gave two D_2O exchangeable hydrogens was obtained. On the basis of nmr data and possible mechanistic pathways, structure **14** was postulated for this compound. This assumption was then synthetically established by lithium aluminum hydride reduction of the oxime of the pyrrolobenzophenone **16** to **14** (Scheme II). The ketone was prepared by monobromination of the ketal **15**, followed by treatment with pyrrolidine and acid hydrolysis.

Lithium aluminum hydride reduction of the known dione **17** gave the tetracycle **18** which on treatment with methyl bromide afforded the quaternary salt **19**. The same compound was obtained when the tetrahydrophthalazine **21**, obtained from lithium aluminum hydride reduction of **5f**, was treated with α,α'-dibromo-*o*-xylene. In addition a second quaternary salt was isolated from this reaction that has been assigned the spiro salt **20**. When **19** was treated with sodium methoxide in refluxing methanol the dibenzo[*c*,*h*][1,6]diazecine **22** was obtained. The structure of **22** was established by nmr and ultraviolet data. Platinum-catalyzed hydrogenation of **22** in acetic acid gave **23**.



SCHEME II



Experimental Section[7]

2-(3-Hydroxypropyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (5a).—A mixture of 54 g (0.60 mol) of 3-hydrazinopropanol,[8] 130.5 g (0.50 mol) of 2-*p*-chlorobenzoylbenzoic acid, and 2000 ml of toluene was stirred and refluxed in a flask equipped with a Dean–Stark tube. After the level of the water layer was constant (19.0 ml) the solvent was removed *in vacuo* and the residue crystallized from methanol–water to give 143 g (91%) of **5a**: mp 104–106°; ir (KBr) 2.98 (OH), 6.07 μ (C=O); nmr ($CDCl_3$) δ 2.07 (2 H, quintet, J = 6 cps, CCH_2C), 3.65 (3 H, t, J = 6 cps, CH_2OH, 1 H, D_2O exchangeable), 4.43 (2 H, t, J = 6 cps, NCH_2), 7.30–7.90 (8 H, m, C_6H_4 and C_6H_4Cl).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.9; H, 4.8; Cl, 11.3; N, 8.9. Found: C, 65.2; H, 5.0; Cl, 11.3; N, 8.7.

1-*p*-Chlorophenyl-3-(3-hydroxypropyl)-1,2,3,4-tetrahydrophthalazine (6a).—A slurry of 84.5 g (2.20 mol) of lithium aluminum hydride and 2500 ml of diethyl ether (nitrogen atmosphere) was stirred and refluxed (96 hr) through a Soxhlet apparatus containing 100.0 g (0.32 mol) of **5a**. After cooling in an ice bath the reactants were treated with 169 ml of 2 *N* sodium hydroxide, 253 ml of water, and 150 g of anhydrous sodium sulfate. The salts were filtered off and washed with ether. The filtrate was concentrated *in vacuo* to give 91.9 g of **6a** as an oil: R_f 0.50, $CHCl_3$–CH_3OH (95:5); nmr ($CDCl_3$) δ 1.72 (2 H, quintet, J = 6.0 cps, $-CCH_2C-$), 2.68 (2 H, t, J = 6.0 cps, CH_2N), 3.48 (2 H, t, J = 6.0 cps, CH_2OH), 3.66 (2 H, D_2O exchangeable, NH, OH), 3.27 (2 H, s, $ArCH_2N$), 51.3 (1 H, s, -CHN), 6.83–7.43 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{17}H_{19}ClN_2O$: C, 67.3; H, 6.3; Cl, 11.7. Found: C, 67.0; H, 6.3; Cl, 11.9.

5-(*p*-Chlorophenyl)-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazine (7a) and (*p*-Chlorophenyl)-1,2,3,11-tetrahydropyrazolo[1,2-*b*]phthalazinium Chloride (8a). A. From Thionyl Chloride Treatment of 6a.—A solution of 6.0 g (0.02 mol) of **6a**, 2.4 g (0.20 mol) of thionyl chloride, and 50 ml of chloroform was stirred and refluxed for 18 hr. The solution was washed with 2 *N* Na_2CO_3, water, dried ($MgSO_4$), filtered, and concentrated to give 4.7 g (83%) of **7a**: mp 123–125° (ether–pentane); nmr ($CDCl_3$) δ 1.99 (2 H, m, CCH_2C), 2.28–3.07 (3 H, m, CH_2-$NNCH_A$), 3.32 (1 H, m, CH_BN), 3.72 (H_A), 4.14 (H_B, q, J = 14 cps, $ArCH_AH_BN$), 4.48 (1 H, s, ArCHAr'), 6.64–7.37 (8 H, m, C_6H_4, C_6H_5Cl).

Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.7; H, 6.0; Cl, 12.4; N, 9.8. Found: C, 71.5; H, 6.0; Cl, 12.4; N, 9.7.

Treatment of **7a** in ether with anhydrous HCl gave the hydrochloride **7** (hygroscopic), mp 189–192° (CH_2Cl_2–ether).

Anal. Calcd for $C_{17}H_{18}Cl_2N_2$: C, 63.6; H, 5.6; Cl, 22.1; N, 8.7. Found: C, 63.2; H, 6.0; Cl, 22.4; N, 8.6.

B. From Lithium Aluminum Hydride Reduction of 5b.—Following the $LiAlH_4$ Soxhlet procedure given above, 50.0 g (0.15 mol) of **5b**, 28.5 g (0.75 mol) of $LiAlH_4$, and 2000 ml of diethyl ether (reflux 48 hr) gave 43.7 g of oil. Crystallization

(7) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million from an internal $SiMe_4$ standard. Infrared spectra were determined using a Perkin-Elmer Infracord. Ultraviolet spectrum were determined in 95% C_2H_5OH on a Beckman Model DB or a Cary Model 15 spectrometer. Mass spectra were determined on a Consolidated Electronics Co. mass spectrometer Model 21-103 C, equipped with an all-glass heated inlet. Thin layer chromatography (tlc) was determined on glass plates coated with silica gel HF-254, Merck AG.

(8) G. Gever, *J. Amer. Chem. Soc.*, **76**, 1283 (1954).

of the oil from ether afforded 19.6 g of **7a**, mp 123–125°. Chromatography of the filtrate on silica gel (developed with $CHCl_3$–CH_3OH 95:5) gave 16.1 g of **7a** (total yield 83%) and 2.0 g of **8a**: mp 203–205° (CH_3OH–ether–pentane); nmr ($CDCl_3$) δ 2.38 (2 H, quintet, J = 7 cps, $-CCH_2C-$), 3.90 (2 H, t, J = 6.0 cps, CH_2N), 4.55 (2 H, t, J = 7 cps, CH_2N^+), 5.00 (2 H, s, $ArCH_2N$), 6.90–8.00 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{17}H_{16}Cl_2N_2$: C, 63.9; H, 5.0; Cl, 22.3; N, 8.8. Found: C, 63.6; H, 5.2; Cl, 22.1; N, 8.5.

2-(3-Chloropropyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (5b).—A mixture of 15.8 g (0.04 mol) of **5a**, 8.9 g (0.075 mol) of thionyl chloride, and chloroform (250 ml) was stirred and refluxed for 20 hr in a nitrogen atmosphere. The solution was washed with 2 *N* sodium bicarbonate (100 ml), saturated sodium chloride (100 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue gave 13.1 g (97%) of **5b**: mp 112–113° (ether); ir (KBr) 6.05 μ (C=O); uv maxima 245 mμ (ϵ 17,425), 295 (10,560); nmr ($CDCl_3$) δ 2.35 (2 H, quintet, J = 6.0 cps, CCH_2C), 3.63 (2 H, t, J = 6.0 cps, CH_2Cl), 4.43 (2 H, J = 6.0 cps, CH_2N), 7.43–7.96 (8 H, m, C_6H_4 and C_6H_4Cl).

Anal. Calcd for $C_{17}H_{14}Cl_2N_2O$: C, 61.3; H, 4.2; Cl, 21.3; N, 8.4. Found: C, 61.5; H, 4.3; Cl, 21.5; N, 8.2.

5-*p*-Chlorophenyl-11-methyl-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalainium Iodide (9).—A solution of 12.0 g (0.042 mol) of **7a**, 12.0 g (0.084 mol) of methyl iodide, and 250 ml of dry tetrahydrofuran was stirred at room temperature for 18 hr. The resultant solid was filtered to give 16.7 g (93%) of **9**: mp 215–217° (CH_2Cl_2–C_6H_6); nmr ($CDCl_3$) δ 2.48 (2 H, m, CCH_2C), 3.28 (2 H, m, NCH_2C), 3.63 (3 H, s, N^+CH_3), 3.95 (H_A), 4.78 (H_B, m, $NC^+H_ACH_BC$), 4.97 (H_A'), 5.67 (H_B', q, J = 14 cps, $ArCH_A'H_B'N^+$), 5.42 (1 H, s, ArCHAr'N), 6.78–7.54 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{18}H_{20}ClIN_2$: C, 50.7; H, 4.7; I, 29.0; N, 6.6. Found: C, 50.7; H, 4.8; I, 29.4; N, 6.4.

1-(*p*-Chlorophenyl)-6-methyl-4,5,6,7-tetrahydro-3H-2,6-benzodiazonine (10).—To a freshly prepared solution of 4.0 g (0.17 mol) of sodium in 100 ml of dry methanol maintained under a nitrogen atmosphere there was added 16.0 g (0.037 mol) of **9** in 150 ml of dry methanol. The solution was refluxed for 24 hr and then the solvent removed *in vacuo*. The residue was treated with 100 ml of chloroform and 50 ml of water. The chloroform was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 5.8 g (52%) of oily **10**: uv maxima 253 mμ (16,000); nmr ($CDCl_3$) δ 1.68 (2 H, m, CCH_2C), 2.28 (3 H, s, NCH_3), 2.68 (2 H, m, NCH_2C), 3.08 (H_A), 3.78 (H_B, t-d, J = 10 cps, J' = 4.0 cps, $C{=}NCH_A$-H_B), 3.32 (H_A), 3.58 (H_B, q, J = 14 cps, $ArCH_AH_B$), 6.87–7.68 (8 H, m, C_6H_4, C_6H_4Cl).

Treatment of a tetrahydrofuran solution of **10** with dry hydrogen chloride gave the dihydrochloride of mp 215–217° (CH_2Cl_2–CCl_4).

Anal. Calcd for $C_{18}H_{21}Cl_3N_2$: C, 58.2; H, 5.7; Cl, 28.6; N, 7.5. Found: C, 57.9; H, 5.8; Cl, 28.9; H, 7.3.

1-*p*-(Chlorophenyl)-6-methyl-2,3,4,5,6,7-hexahydro-1H-2,6-benzodiazonine (11).—A mixture of 5.4 g of **10**, 0.6 g of platinum oxide, and 100 ml of acetic acid was hydrogenated (50 psi, 26°) on a Parr hydrogenation apparatus. After hydrogen uptake (theory 17.0 psi; actual 16.2 psi) had ceased (18 hr) the catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was made basic with 2 *N* Na_2CO_3, extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated *in vacuo* to give 4.3 g (78%) of **11**: mp 132–134° (ether–pentane); ir ($CHCl_3$) 2.92 (NH); nmr ($CDCl_3$) δ 1.58 (2 H, m, $-CCH_2C-$), 2.32 (3 H, s, NCH_3), 2.50 (H_A), 3.47 (H_B, m, CH_AH_B), 2.98 (H_A'), 4.45 (H_B', J = 13 cps, $ArCH_A'H_B'N$), 3.78 (1 H, D_2O exchangeable, NH), 5.58 (1 H, s, CHN), 6.50 (1 H, m, C$_6$H), 6.90–7.75 (7 H, m, C_6H_3, C_6H_4Cl).

Anal. Calcd for $C_{18}H_{21}ClN_2$: C, 71.8; H, 7.0; Cl, 11.9; N, 9.3. Found: C, 72.1; H, 7.1; Cl, 11.7; N, 9.6.

2-(4-Hydroxybutyl)-4-*p*-chlorophenylphthalazin-1-(2H)-one (5c).—Following the procedure used to prepare **5** a mixture of 31 g (0.03 mol) of 4-hydrazinobutanol,[8] 73 g (0.28 mol) of 2-*p*-chlorobenzoylbenzoic acid, and 400 ml of toluene gave 70.8 g (77%) of **5c**: mp 116–118° ($CHCl_3$–pentane); ir (KBr) 3.00 (OH), 6.06 μ (C=O); nmr ($CDCl_3$) δ 1.45–2.10 (4 H, m, CCH_2-CH_2C), 2.83 (1 H, D_2O exchangeable, OH) 3.72 (2 H, t, J = 6.0 cps, CH_2OH), 4.33 (2 H, t, J = 6.0 cps, CH_2N), 7.42–7.92 (7 H, m, C_6H_3, $C_6H_3C_6H_4Cl$), 8.42 (1 H, m, HC=CCO).

Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.8; H, 5.2; Cl, 10.8; N, 8.05; O, 9.7. Found: C, 65.4; H, 5.3; Cl, 11.2; O, 9.7.

2-(4-Hydroxybutyl)-4-*p*-chlorophenyl-1,2-dihydrophthalazine (12a) and 1-(*p*-Chlorophenyl)-3-(4-hydroxybutyl)-1,2,3,4-tetrahydrophthalazine (6b).—Following the procedure for **6a**, 50.0 g (0.15 mol) of **5c**, 28.8 g (0.76 mol) of lithium aluminum hydride and 1500 ml of diethyl ether (reflux 96 hr) gave 47.8 g of oil containing two components, R_f 0.4 and 0.6 ($CHCl_3$–CH_3OH, 95:5). Crystallization from ether–pentane gave 20.1 g of **12a**: mp 76°; R_f 0.6; ir (CH_2Cl_2) nmr ($CDCl_3$) δ 1.84 (4 H, m, CCH_2CH_2C), 2.40 (1 H, D_2O exchangeable, OH), 3.21 (2 H, t, J = 6.0 cps, CH_2N), 3.57 (2 H, t, J = 6.0 cps, CH_2O), 3.93 (2 H, s, $ArCH_2$), 7.05–7.70 (8 H, m, C_6H_4, C_6H_4Cl). The filtrate from **12a** was chromatographed on silica gel (500 g, C_6H_6–$CHCl_3$, 50:50 eluent) to give (1) 18.8 g of **12a** (total, 38.9 g) and (2) 6.2 g of **6b** as an oil: nmr ($CDCl_3$) δ 1.66 (4 H, m, CCH_2CH_2C), 2.57 (2 H, t, J = 6.0 cps, CH_2N), 3.00 (2 H, D_2O exchangeable, NH, OH), 3.42 (2 H, t, J = 6.0 cps, CH_2O), 5.18 ((1 H, s, ArCHAr'), 6.80–7.58 (8 H, m, C_6H_4, C_6H_4Cl). When **6b** was rechecked by tlc *ca.* 2 hr after it was isolated the presence of **12a** (R_f 0.6) was detected. Further evaluation after 4 and 8 hr revealed that the intensity of the R_f 0.6 spot (**12a**) had increased.

Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.7; H, 6.1; Cl, 11.3. Found: C, 68.3; H, 6.1; Cl, 11.3.

Anal. Calcd for $C_{18}H_{21}ClN_2O$: C, 68.1; H, 6.6; Cl, 11.2. Found: C, 68.2; H, 6.5; Cl, 11.0.

4-(*p*-Chlorophenyl)spiro[phthalazine-2(1H)-1′-pyrrolidinium] Chloride (13).—A solution containing 2.0 g (0.0063 mol) of **12a**, 0.91 g (0.0076 mol) of thionyl chloride, and 20 ml of dry chloroform was stirred and refluxed for 18 hr. The solution was washed with saturated $NaHCO_3$ and H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. There was obtained 1.6 g (76%) of **13**: mp 149–150° (CH_2Cl_2–pentane); nmr ($CDCl_3$) δ 2.42 (4 H, m, CCH_2CH_2C), 3.78 (2 H, m, CH_2N^+), 5.73 (2 H, s, $ArCH_2N^+$), 7.32–7.98 (8 H, m, C_6H_4, C_6H_4Cl).

When **13** was dissolved in $CHCl_3$–CCl_4 it crystallized as **13**·CCl_4, mp 129–130°. The nmr of **13**·CCl_4 was identical with pure **13**.

Anal. Calcd for $C_{18}H_{18}Cl_2N_2$: C, 64.9; H, 5.4; Cl, 21.3; N, 8.4. Found: C, 64.7; H, 5.8; Cl, 21.0; N, 8.7.

Anal. Calcd for $C_{19}H_{18}Cl_6N_2$: C, 46.9; H, 3.7; Cl, 43.7; N, 5.7. Found: 46.5; H, 3.8; Cl, 43.4; N, 5.8.

4-*p*-Chlorophenyl-2-methylphthalzin-1(2H)-one (5d).—Following the procedure given in the preparation of **5a**, 130.5 g (0.50 mol) of 2-*p*-chlorobenzoylbenzoic acid, 27.6 g (0.60 mol) of methylhydrazine and 750 ml of toluene gave 117.2 g (87%) of **5d**: mp 152–154° (CCl_4–$CHCl_3$); ir (KBr) 6.01 μ (C=O); nmr ($CDCl_3$) δ 3.88 (3 H, s, CH_3), 7.50–7.90 (7 H, m, C_6H_4, C_6H_3), 8.41 (1 H, m, CH=CCO).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.4; H, 4.1; Cl, 13.1. Found: C, 66.5; H, 4.0; Cl, 13.4.

4-*p*-Chlorophenyl-2-methyl-1,2-dihydrophthalazine (12b).—Following the procedure given in the preparation of **6a**, 50.0 g (0.185 mol) of **5d**, 13.4 g (0.348 mol) of $LiAlH_4$, and 1500 ml of diethyl ether (reflux 80 hr) gave 41.3 g (81%) of **12b**: mp 137–138° (CH_2Cl_2–pentane); ir (CH_2Cl_2) 6.01 μ (C=N); nmr ($CDCl_3$) δ 3.08 (3 H, s, NCH_3), 3.92 (2 H, s, CH_2N), 7.10–7.70 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{15}H_{13}ClN_2$: C, 70.2; H, 5.1; N, 10.9. Found: C, 70.1; H, 5.4; N, 10.7.

4-*p*-Chlorophenyl-2,2-dimethyl-1,2-dihydrophthalazinium Iodide (13b).—A mixture of 8.0 g (0.03 mol) of **12b**, 8.7 g (0.062 mol) of methyl iodide, and 200 ml of dry tetrahydrofuran were stirred for 56 hr at room temperature and then diluted with 250 ml of dry diethyl ether to give 7.4 g (60%) of **13b**: mp 163–166°; nmr ($CDCl_3$–C_2D_6SO) δ 3.67 (6 H, s, $CH_3NC^+H_3$), 5.52 (2 H, s, $ArCH_2N^+$), 7.40–7.80 (8 H, m, C_6H_4Cl, C_6H_4).

Anal. Calcd for $C_{15}H_{16}ClIN_2$: C, 48.2; H, 4.0; I, 31.8. Found: C, 48.4; H, 3.8; I, 31.5.

2-(4-Chlorobutyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (5e).—Following the procedure given for the preparation of **5b** a mixture of 50.0 g (0.15 mol) of **5c**, 27.0 g (0.23 mol) of thionyl chloride, and 400 ml of chloroform gave 51.5 g (97%) of **5e**: mp 148–151° (CH_2Cl_2–ether); ir (KBr) 6.05 μ (C=O); nmr ($CDCl_3$) δ 1.85 (4 H, m, CCH_2CH_2C), 3.68 (2 H, t, J = 6.0 cps, CH_2Cl), 4.40 (2 H, t, J = 6.0 cps, CH_2N), 7.38–7.89 (8 H, m, C_6H_4Cl, C_6H_4).

Anal. Calcd for $C_{18}H_{16}Cl_2N_2O$: C, 62.3; H, 4.6; Cl, 20.4; N, 8.1. Found: C, 62.0; H, 4.9; Cl, 20.2; N, 8.0.

2-(Pyrrolidinomethyl)benzhydrylamine (14). A. From Lithium Hydride Reduction of 5e.—Following the procedure for **6a** 50.0

g (0.14 mol) of **5e**, 16.4 g (0.43 mol) of lithium aluminum hydride, and 1500 ml of diethyl ether (refluxed 56 hr) gave 40.3 g of oil. The oil was taken up in CH_2Cl_2 and washed with 2 *N* HCl (200 ml, twice). The acid layer was made alkaline with 50% NaOH, extracted with $CHCl_3$, dried ($MgSO_4$), filtered, and concentrated to give 33.0 g (83%) of **14** as an oil: R_f 0.2 ($CHCl_3$–CH_3OH, 95:5); ir (CH_2Cl_2) 2.87, 2.98 μ (NH_2); nmr $CDCl_3$) δ 1.67 (2 H, m, CCH_2CH_2C), 2.18 (2 H, D_2O exchangeable, NH_2) 2.42 (4 H, m, CH_2NCH_2), 3.32 (H_A), 3.72 (H_B, q, J = 12.0 cps, $ArCH_2N$), 5.52 (1 H, s, ArCHAr'), 7.00–7.32 (8 H, m, C_6H_4, C_6H_4Cl).

A solution of **14** in anhydrous THF was treated with dry HCl to give the dehydrochloride **14** of mp 220° (hygroscopic).

Anal. Calcd for $C_{18}H_{23}Cl_3N_2$: C, 57.8; H, 6.1; Cl, 28.6; N, 7.5. Found: C, 58.1; H, 6.4; Cl, 28.3; N, 7.2.

B. From Lithium Aluminum Hydride Reduction of 16 Oxime.—A mixture of 7.0 g (0.023 mol) of **16**, 7.0 g (0.10 mol) of hydroxylamine hydrochloride, 5.6 g (0.10 mol) of potassium hydroxide, and 200 ml of 95% ethanol was stirred and refluxed for 6 hr. The solvent was removed *in vacuo* and the residue treated with 50 ml of water and 150 ml of methylene chloride. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give 6.5 g of crude **16** oxime as an oil: R_f 0.15 ($CHCl_3$–CH_3OH; 95:5; 22 R_f 0.85); ir (CH_2Cl_2) no C=O band.

Anal. Calcd: N, 4.6. Found: N, 4.7.

Following the procedure given in A, 6.5 g (0.023 mol) of crude **16** oxime, 1.75 g (0.046 mol) of lithium aluminum hydride, and 200 ml of diethyl ether (refluxed 14 hr) gave 2.8 g of **14**. Comparison of the ir and nmr spectrum of **14** prepared from **5e** showed them to be identical.

2-*p*-Chlorophenyl-2-*o*-tolyl-1,3-dioxolane (15).—A mixture of 50.0 g (0.22 mol) of 2-*p*-chlorobenzoyltoluene, 26.8 g (0.43 mol) of ethylene glycol, 5.0 g of *p*-toluenesulfonic acid, and 300 ml of benzene was stirred and refluxed in a flask equipped with a Dean–Stark tube until (25 hr) the "water layer" (19 ml) in the side arm remained constant. The solution was washed with 150 ml of 2 *N* NaOH, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue gave 43.0 g (71%) of **15**: bp 135–137° (0.10 mm); $n^{20}D$ 1.5842; nmr ($CHCl_3$) δ 2.17 (3 H, s, CH_3), 4.02 (4 H, A_2B_2, OCH_2CH_2O), 7.05–7.88 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{16}H_{15}ClO_2$: C, 69.9; H, 5.5; Cl, 12.9. Found: C, 69.7; H, 5.4; Cl, 12.8.

4-Chloro-2′-pyrrolidinomethylbenzophenone (16).—To a stirred refluxing mixture of 82.5 g (0.30 mol) of **15**, 34.8 g (0.42 mol) of anhydrous $NaHCO_3$, and 500 ml of carbon tetrachloride, irradiated with a high-intensity light source, there was added a solution of 48 g (0.30 mol) of bromine and 200 ml of carbon tetrachloride at such a rate that the bromine color faded rapidly. After 1 additional hr of reflux the mixture was cooled to *ca.* 30° and treated with a solution of 42.6 g (0.60 mol) of pyrrolidine in 200 ml of carbon tetrachloride. After 18 hr the salts were filtered off and the filtrate was saturated with anhydrous HCl. The solvent was decanted and the oily residue (59.7 g, crude ketal amine) was refluxed for 20 hr in a solution of 300 ml of methanol, 30 ml of water, and 60 ml of concentrated hydrochloric acid. The cooled solution was made basic with 2 *N* Na_2CO_3, extracted with methylene chloride, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue gave 22.8 g (25%) of **16**: mp 69–71° (CH_3OH–H_2O); ir (CH_2Cl_2) 5.98 (C=O); nmr ($CDCl_3$) δ 1.45 (4 H, m, CCH_2CH_2C), 2.21 (4 H, m, CH_2NCH_2), 3.60 (2 H, s, $ArCH_2N$), 7.32 (4 H, s, C_6H_4Cl), 7.50 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{18}H_{18}ClNO$: C, 72.1; H, 6.1; Cl, 11.8; N, 4.7; O, 5.3. Found: C, 72.0; H, 6.1; Cl, 11.7; N, 4.6; O, 5.6.

A solution of **16** in diethyl ether–methylene chloride was treated with anhydrous HCl to give the hydrochloride of **16**, mp 201–204°.

Anal. Calcd for $C_{18}H_{19}Cl_2NO$: C, 64.3; H, 5.7; Cl, 21.1; N, 4.2. Found: C, 64.2; H, 5.7; Cl, 20.9; N, 4.2.

7H,12H-Phthalazino[2,3-*b*]phthalazine-5,14-dione (17).—Following the procedure of Hatt and Stephenson,[9] α,α'-dibromo-*o*-xylene and phthalazine-1,4-dione gave **17**: mp 195–196° (lit.[9] mp 196.5–197.5°); uv λ_{max}^{EtOH} 232 mμ (ϵ 11,250), 236 (11,100), 308 (5900); nmr ($CDCl_3$) δ 5.32 (4 H, s, CH_2NNCH_2), 7.32 (4 H, s, C_6H_4), 7.75 and 8.23 (4 H, A_2B_2, COC_6H_4CO).

5,7,12,14-Tetrahydrophthalazino[2,3-*b*]phthalazine (18).—Following the procedure used to prepare **7a** a mixture of 6.0 g (0.023 mol) of **17**, 1.7 g (0.035 mol) of lithium aluminum hydride, and absolute tetrahydrofuran (24 hr reflux) gave 2.5 g (46%) of **18**: mp 127–129° (lit.[10] mp 132–133°); uv maxima 252 mμ (ϵ 575), 258 (690) 266 (895), 273 (975); nmr[11] ($CDCl_3$) δ 3.98 [8 H, s, $(CH_2)_2NN(CH_2)_2$], 7.09 (8 H, A_2B_2, C_6H_4, C_6H_4). The mass spectrum exhibits a molecular ion peak at *m/e* 236 ($C_{16}H_{16}N_2$) with abundant fragment peaks at *m/e* 132 ($M^+ - CH_2C_6H_4CH_2$), 118 ($CH_2C_6H_4CH_2N$), and 104 ($CH_2C_6H_4CH_2$).

Treatment of **18** in dry THF with anhydrous HBr gave the hydrobromide of **18**, mp 253–256° (CH_2Cl_2–ether).

Anal. Calcd for $C_{16}H_{17}BrN_2$: C, 60.6; H, 5.4; Br, 25.2; N, 8.8. Found: C, 60.1; H, 5.5; Br, 25.2; N, 8.5.

6-Methyl-5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazinium Iodide (19) and 1,2,3′,4′-Tetrahydrospiro[isoindoline-2,2′-(1′H)-phthalazinium] Bromide (20). A. From 18 and Methyl Bromide.—A solution of 5.0 g of **18** in 50 ml of dry THF was cooled in an ice bath and treated with a stream of methyl bromide gas for 0.3 hr. After stirring 18 hr at room temperature the resultant solid was filtered off to give 5.9 g of **19**: mp 218–219°; nmr (C_2D_6SO) δ 3.52 (3 H, s, NC^+H_3) 4.32 ($2H_A$), 4.72 ($2H_B$, q, J = 8.0 cps, $ArCH_AH_BNCH_ACH_BAr$), 5.15 (4 H, s, $ArCH_2N^+CH_2Ar$), 7.10–7.56 (8 H, m, C_6H_4, C_6H_4).

Anal. Calcd for $C_{17}H_{19}BrN_2$: C, 61.6; H, 5.8; Br, 24.1; N, 8.5. Found: C, 61.5; H, 5.9; Br, 23.9; N, 8.4.

B. From 21 and α,α'-Dibromo-*o*-xylene.—A mixture of 10.7 g (0.075 mol) of **21**, 19.2 g (0.072 mol) of α,α'-dibromo-*o*-xylene, 20.0 g (0.15 mol) of anhydrous K_2CO_3, and 100 ml of acetone was stirred and refluxed for 52 hr. The acetone was decanted off and the remaining solid was treated with about 100 ml of water and 100 ml of $CHCl_3$ and then stirred for 2 hr. The insoluble material was filtered off to give 7.5 g (31%) of **19**: mp 215–217°; nmr identical with **19** obtained in procedure A. On standing for about 48 hr there was obtained 4.7 g of solid, mp 157–165°. Recrystallization (CH_2Cl_2–ether) gave 4.2 g (18%) of **20**: mp 142° dec; nmr (C_2D_6SO) δ 3.08 (3 H, s, NCH_3), 4.12 (2 H, s), 4.32 (2 H, s, $ArCH_2N$), 5.12 (2 H, s, CH_2N^+), 7.00–8.00 (8 H, m, C_6H_4, C_6H_4).

Anal. Calcd for $C_{17}H_{19}BrN_2$: C, 61.6; H, 5.8; Br, 24.1; N, 8.5. Found: C, 61.5; H, 5.8; Br, 24.2; N, 8.9.

2-Methyl-1,2,3,4-tetrahydrophthalazine (21).—From 60 g (0.40 mol) of 2-carboxybenzaldehyde, 23 g (0.50 mol) of methylhydrazine, and toluene there was obtained 50 g (81%) of 2-methylphthalazine-1(2H)-one (**5f**): mp 110–111° (toluene, lit.[12] mp 113–115°); uv maxima, 225 mμ (ϵ 14,855), 244 (5905), 253 (5905), 287 (6855), 313 (3045); nmr ($CHCl_3$) δ 3.80 (3 H, s, CH_3), 6.28 (4 H, m, C_6H_4), 8.08 (1 H, s, CH=N).

Following the procedure given to prepare **7a** a mixture of 35.0 g (0.22 mol) of **5f**, 10.0 g (0.22 mol) of lithium aluminum hydride, and ether (1200 ml) gave 28.6 g (92%) of **21**: bp 140–141° (25 mm); $n^{20}D$ 1.5613; nmr ($CHCl_3$) δ 2.40 (1 H, D_2O exchangeable, NH), 2.55 (3 H, s, CH_3), 3.57 (2 H, s, CH_2NMe), 4.06 (2 H, s, CH_2N), 7.06 (4 H, m, C_6H_4). Th3 hydrochloride of **21** prepared in the usual manner had mp 160–162° (CH_2Cl_2–ether).

Anal. Calcd for $C_9H_{13}ClN_2$: C, 58.5; H, 7.1; Cl, 19.1; N, 15.2. Found: C, 58.7; H, 7.1; Cl, 18.9; N, 14.9.

6-Methyl-5,6,7,14-tetrahydrodibenzo[*c*,*h*][1,6]diazecine (22).—To a freshly prepared solution of 1.5 g (0.065 mol) of sodium in 40 ml of dry methanol maintained under a nitrogen atmosphere there was added 7.0 g (0.021 mol) of **19** in 50 ml of dry methanol. The solution was refluxed for 192 hr and the solvent was removed *in vacuo*. The residue was treated with 100 ml of water and 100 ml of chloroform. The chloroform layer was washed with 2 *N* HCl (100 ml, twice) and the acid layer was made basic (2 *N* NaOH), extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 4.3 g (85%) of **22**: mp 219–222° (CH_2Cl_2–CH_3OH); ir (KBr) 6.12 μ (C=N); uv maxima 250 mμ (ϵ 9800); nmr ($CDCl_3$–C_2D_6SO) δ 1.92 (3 H, s, CH_3N), 4.34 (2 H, s, CH_2N), 4.38 (2 H, s, CH_2N), 4.48 (2 H, s, $=NCH_2$), 7.21–7.44 (7 H, m, C_6H_4, C_6H_3), 8.08 (1 H, m, HC=CC=N), 8.81 (1 H, s, CH=N).

Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.6; H, 7.3; N, 11.2. Found: C, 81.1; H, 7.3; N, 11.2.

6-Methyl-5,6,7,12,13,14-hexahydrodibenzo[*c*,*h*][1,6]diazecine (23).—A mixture of 1.0 g of **22**, 0.1 g of platinum oxide, and 50 ml of acetic acid was hydrogenated as in the preparation of **11** to give 0.80 g (79%) of **23**: mp 162–164° (CH_3OH); ir (CH_2Cl_2) 3.03 μ (NH); nmr ($CDCl_3$) δ 1.92 (3 H, s, NCH_3), 3.03 (1 H,

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D_2O exchangeable, NH), 3.61 (4 H, s, CH_2NCH_2), 3.83 (4 H, s, CH_2NCH_2), 7.13–7.50 (8 H, m, C_6H_4, C_6H_4).

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.9; H, 8.0; N, 11.1. Found: C, 80.9; H, 8.2; N, 11.1.

Registry No.—**5a**, 20072-33-7; **5b**, 20072-34-8; **5c**, 20072-35-9; **5d**, 4725-83-1; **5e**, 20072-37-1; **6a**, 20072-38-2; **6b**, 20072-39-3; **7a**, 20072-40-6; **7** hydrochloride, 20072-41-7; **8a**, 20072-42-8; **9**, 20072-43-9; **10**, 20072-44-0; **10**, dihydrochloride, 20072-45-1; **11**, 20072-46-2; **12a**, 20072-47-3; **12b**, 20072-48-4; **13a** 20126-04-9; **13b**, 20072-49-5; **14**, 20072-50-8; **14**, dihydrochloride, 20072-51-9; **15**, 20072-52-0; **16**, 20072-53-1; **16** hydrochloride, 20072-54-2; **17**, 13152-91-5; **18**, hydrobromide, 20126-05-0; **19**, 20072-56-4; **20**, 20126-06-1; **21**, 20072-57-5; **21** hydrochloride, 20072-58-6; **22**, 20072-59-7; **23**, 20072-60-0.

Acknowledgment.—The authors thank Messrs. Urs Stoeckli and Alvin Schneider for instrumental and synthetic assistance.

A Novel N-CH_2-N Bridging Reaction[1a]

PAUL AEBERLI[1b] AND WILLIAM J. HOULIHAN[1c]

Sandoz Pharmaceuticals, Hanover, New Jersey 07936

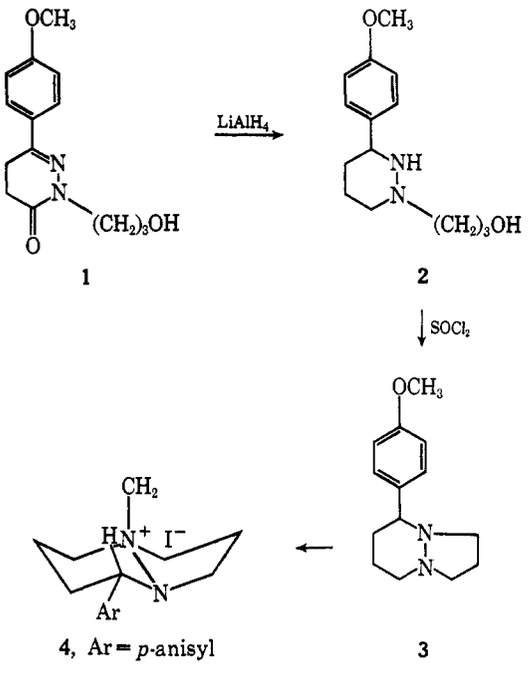
Received December 30, 1968

Treatment of the methyl iodide salts (**4** and **10**) of the bridgehead hydrazines, 2-*p*-anisyl-1,6-diazabicyclo[4.3.0]nonane (**3**) and 2-*p*-anisyl-1,6-diazabicyclo[4.4.0]decane (**9**), with refluxing sodium methoxide–methanol resulted in the formation of the N-CH_2-N bridged derivatives 2-*p*-anisyl-1,6-diaza[4.3.1]decane (**12**) and 2-*p*-anisyl-1,6-diaza[4.4.1]undecane (**14**). The same hydrazine salts when treated with sodium–ammonia gave the medium-sized ring compounds 6-*p*-anisyl-1-methyl-1,5-diazacyclononane (**13**) and 5-*p*-anisyl-1-methyl-1,6-diazacyclodecane (**15**). The formation of the NCH_2N derivatives is postulated to occur by a 1,2 shift (**17**) analogous to a Stevens rearrangement.

In the preceding paper[2] from our laboratories it was reported that the 2,6-benzodiazonine and dibenzo[*c*,*h*]-[1,6]diazecine ring systems could be prepared by the base elimination of the appropriate bridgehead hydrazine quaternary salts from 2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazine and 5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazine. The present work reports our findings in the attempt to extend the synthetic usefulness of this reaction to the preparation of 1,5-diazacyclononane and 1,6-diazacyclodecane ring systems from the appropriate bridgehead hydrazine quaternary salts.

The synthesis of the required bridgehead hydrazine intermediates **3** and **9** are given in Schemes I and II. When **3** was allowed to react with methyl iodide it gave a sharp melting quaternary salt in nearly quantitative yield. The nmr of this compound gave a single methyl signal (δ 3.62) indicating that the methylation had occurred stereoselectively. Recent findings on the quaternization of piperidine[3a] and other cyclic nitrogen derivatives[3b] have shown that the methylation of these systems occurs stereoselectively with the incoming methyl group occupying an axial position. By analogy with this work we have assigned structure **4**, with an axial methyl group and an equatorial anisyl group, as the most probable conformational form.[4] Additional support for the methyl assignments will be given below.

SCHEME I



1 **2** **3** **4**, Ar = *p*-anisyl

When the mixed anhydride from 3-*p*-anisylpropionic acid (**5**) and ethyl chloroformate was allowed to react with hexahydropyridazine it gave a hydrazide that could be represented by **6** or its ring tautomer (**6a**). The ir of this compound gave carbonyl bands at 5.97 and 6.10 μ and a uv maximum at 228 mμ indicating that the tautomeric form **6** predominates. Treatment of a toluene solution of **6** with acid gave the unsaturated lactam **7**. The position of the double bond was determined from uv and nmr data. Catalytic hydrogenation of **7** afforded **8** which on further reduction with lithium aluminum hydride gave **9**. Reaction of **9** with methyl iodide gave a quaternary salt that gave a nmr spectrum with a single methyl signal (δ 3.62). By ar-

(1) (a) Portions of this paper were presented by W. J. Houlihan and R. E. Manning at the First International Congress of Heterocyclic Chemistry, The University of New Mexico, Albuquerque, N. M., June 1967. (b) Sandoz Ltd., Basel, Switzerland. (c) To whom inquiries should be sent.

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(4) We have presumed that the indicated chair conformations (transfused) predominate in all compounds containing a six-membered ring since inspection of models reveals no apparent reason why the usual order of stability (chair > boat) should be reversed.