was washed with two 200-ml portions of water, dried (K_2CO_3), and evaporated to a crude oil (3.5 g, 52%) which was distilled to give pure 2-oxo-3-*t*-butyl-1,2,3-tetrahydrooxathiazine (**18**), bp 60–65° (0.02 mm).

Anal. Calcd for $C_7H_{15}NSO_2$: C, 47.47; H, 8.53; N, 7.90. Found: C, 47.58; H, 8.49; N, 7.94.

Acid Hydrolysis of *cis*-2-Oxo-3-*t*-butyl-5-phenyl-1,2,3-oxathiazolidine (15a).—The oxathiazolidine **15a** (100 mg, 0.42 mmol) and hydrochloric acid (0.5 g, 5.2 mmol) were dissolved in 10 ml of tetrahydrofuran and 10 ml of water. After stirring overnight, the reaction mixture was made basic with sodium hydroxide and evaporated to yield a solid which was extracted with 20 ml of carbon tetrachloride and 10 ml of water. The organic layer was dried (K_2CO_3) and evaporated to a solid (60 mg, 75%) which was identified as 1-phenyl-2-*t*-butylaminoethanol (**6**) by analysis of the nmr spectrum and comparison with the nmr spectrum of an authentic sample.

Acid Hydrolysis of 17.—The oxathiazolidine **17** (300 mg, 0.81 mmol) was dissolved in 7 ml of EtOH and 3 ml of water, and 2 ml of concentrated hydrochloric acid added. This mixture was allowed to stand at room temperature for 1 week. It was evaporated and, after basification, extracted into chloroform. The dried chloroform extracts were evaporated to give 126 mg (47%) of solid which was identical by thin layer and nmr spectral comparison with **9**.

Attempted Base Hydrolysis of *cis*-2-Oxo-*t*-butyl-5-phenyl-1,2,3-oxathiazolidine (15a).—Oxathiazolidine **15a** (320 mg, 1.34 mmol) and sodium hydroxide (0.20 g, 5.0 mmol) were dissolved in 10 ml of tetrahydrofuran and 10 ml of water. After stirring overnight at room temperature, the reaction mixture was evaporated to a paste and extracted with 20 ml of ether and 10 ml of water. The ether layer was dried (K_2CO_3) and evaporated to give the starting oxathiazolidine **15a** (by analysis of the nmr spectrum) as a solid (240 mg, 75% recovery). The recovered oxathiazolidine **15a** (190 mg, 0.79 mmol) and sodium hydroxide (0.40 g, 10 mmol) were dissolved in 10 ml of tetrahydrofuran and 10 ml of water. After refluxing overnight, the reaction mixture was flash evaporated to a paste and extracted with 20 ml of ether and 15 ml of water. The ether layer was dried (K_2CO_3) and evaporated to give the starting oxathiazolidine **15a** (by analysis of the nmr spectrum) as a solid (125 mg, 66% recovery).

Attempted Base Hydrolysis of *cis*-2-Oxo-3-*t*-butyl-4-phenyl-1,2,3-oxathiazolidine (14a).—Oxathiazolidine **14a** (100 mg, 0.42 mmol) and sodium hydroxide (0.35 g, 8.8 mmol) were dissolved in 10 ml of tetrahydrofuran and 10 ml of water and stirred for 12 hr at room temperature. The reaction mixture was evaporated to a paste which was extracted with 10 ml of water and 20 ml of carbon tetrachloride. The carbon tetrachloride layer was dried (K_2CO_3) and evaporated to solids (100 mg, 100% recovery) which gave an nmr spectrum identical with that of the starting oxathiazolidine.

Registry No.—**3**, 4620-70-6; **4**, 18366-38-6; **5**, 18366-39-7; **6**, 18366-40-0; **7**, 18366-41-1; **8**, 6071-99-4; **9**, 18366-43-3; **10**, 18366-44-4; **11**, 18366-45-5; **12a**, 18366-46-6; **12b**, 18366-79-5; **13a**, 18366-80-8; **13b**, 18366-81-9; **14a**, 18366-82-0; **14b**, 18366-83-1; **15a**, 18366-84-2; **15b**, 18366-85-3; **16**, 18366-47-7; **17**, 18366-86-4; **18**, 18366-48-8; **21**, 18366-49-9; ethyl 2-*t*-butylaminopropionate, 18366-50-2; methyl 3-*t*-butylaminobutyrate, 18366-51-3; methyl 2-*t*-butylamino-2-phenylacetate, 18366-52-4.

1,5-Benzodiazocines

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The syntheses of 2-(3-aminopropylamino)-5-chlorobenzophenones **2** and **9** and their intramolecular dehydrations to give 8-chloro-1,2,3,4-tetrahydro-6-phenyl-1,5-benzodiazocines **3** and **10** were effected. A procedure purported to yield a 8-chloro-3,4-dihydro-1,5-benzodiazocin-2-one has been found in fact to give a dimer. This procedure has been successfully utilized in the synthesis of 8-chloro-3,4-dihydro-1-methyl-6-phenyl-1,5-benzodiazocin-2(1H)-one **19**, which has been structurally related to **10**. A rationale for the anomalous results of this reaction is offered.

As a result of our continuing interest in the syntheses of medium-sized heterocycles, we wish to report the preparation of some 1,5-benzodiazocines. Although the syntheses of 1,6- and 2,5-benzodiazocines have by now been well documented,[1] the recorded examples of the 1,5 system are limited to the hexahydrobenzodiazocines of Shiotani and Mitsuhashi[2] and the 3,4-dihydro-1,5-benzodiazocin-2-one claimed by Sulkowski.[3]

Of particular interest was the 6-phenyl-2,3,4,5-tetrahydro-1,5-benzodiazocine system, exemplified by compound **3** (Scheme I). As the result of another study,[4] 9-chloro-1,2,3,5-tetrahydro-7-phenylpyrimido[1,2-*a*]-[1,4]benzodiazepine (**1**) was available. Acid hydrolysis of **1** gave the desired substituted benzophenone **2** which was quite resistant to dehydration attempts, but was converted into a crystalline product on prolonged heating in pyridine. Intramolecular dehydration was inferred from the mass spectrum (*m/e* 270) and the elemental analysis. Since no transannular reaction would be anticipated and since the spectrophotometric results suggested the presence of both amine and imine moieties,[5] the 1,5-benzodiazocine structure **3** was assigned.

For practical reasons, an alternate synthetic procedure to **3** was desired. Compound **4**,[4] the precursor of **1**, was also available and was hydrolyzed in good yield to the substituted benzophenone **5a**. The reaction of **5a** with ethanolic ammonia gave a mixture which contained the open amine **2** as well as the cyclized product **3**. The high ratio of **3** to **2** resulting from these reaction conditions may be due to the addition of ammonia to the benzophenone carbonyl and increased susceptibility of the resultant quaternary carbon to nucleophilic attack,[6] or by actual formation of the

(1) See, for example, W. Schroth and B. Streckenbach, *Z. Chem.*, **3**, 465 (1963), and T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.*, **32**, 2180 (1967).

(2) S. Shiotani and K. Mitsuhashi, *Yakugaku Zasshi*, **84**, 656 (1964).

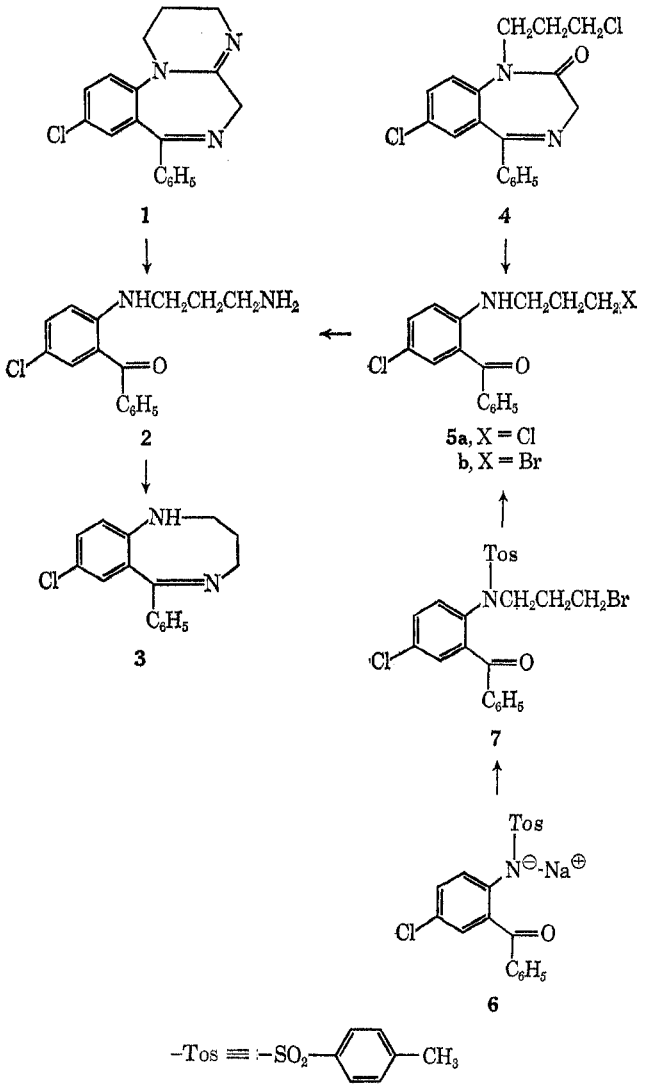
(3) T. S. Sulkowski, U. S. Patent 3,294,782 (1966).

(4) M. E. Derieg, R. I. Fryer, R. M. Schweininger, and L. H. Sternbach, *J. Med. Chem.*, **11**, 912 (1968).

(5) The ir absorptions (KBr) were at 3265 (NH) and 1610 cm^{-1} (>C=N—) and the uv maxima (2-propanol) were at 223 mμ (infl) (ε 22,500), 248 (17,300), 267 (infl) (13,500) and 365 (2700).

(6) For a discussion of the role of carbinolamine intermediates in the formation of Schiff bases, see R. L. Rieves in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1966, pp 608–614.

SCHEME I

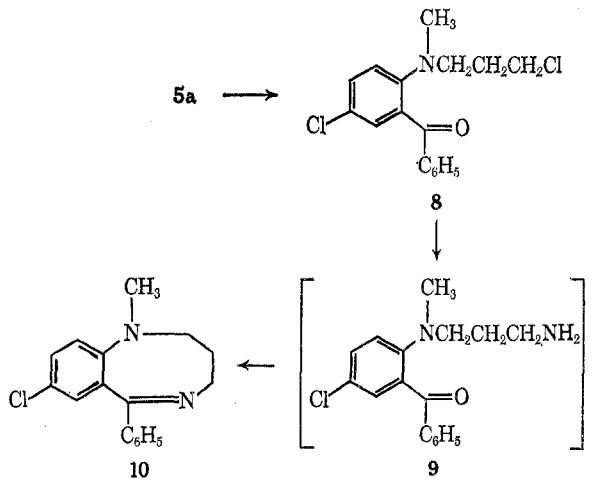


imine and the subsequent intramolecular transamination.[7]

The favored synthetic approach to **3** utilized the high yield alkylation of the sodium salt **6**[8] with 1,3-dibromopropane and the subsequent detosylation of **7** with sulfuric acid to give **5b** which, without isolation, was treated with ammonia as for **5a**.

The 1-methylbenzodiazocine **10** was of particular interest and since an attempt at the methylation of **3** had not proved encouraging, the appropriate modification of the fundamental reaction scheme was effected (Scheme II). Thus methylation of **5a** by means of the Eschweiler–Clarke method[9] afforded a high yield of **8** as a yellow oil. The crude reaction mixture was readily assayed on the basis of the carbonyl shift in the infrared spectrum ($CHCl_3$) from the intramolecular hydrogen bonded starting material **5a** (1620 cm^{-1}) to the normal benzophenone absorption of the product **8**

SCHEME II



(1655 cm^{-1}).[10] The amination of **8** in ethanolic ammonia afforded **10** in high yield, presumably by way of the unisolated intermediate **9**. The product **10** was compatible spectrophotometrically with the assigned structure and was shown to have the correct empirical formula and the predicted molecular weight of 284 by its mass spectrum. The yield of **10** under these reaction conditions was considerably higher than that of the unmethylated benzodiazocine **3**. Such a result was predictable from an examination of the Dreiding model of **2**. The formation of a six-membered ring involving the proton of the secondary aniline of **2** and the oxygen of the carbonyl group would place the aminopropyl side chain away from the carbonyl group and thus impair the desired condensation. In the case of the nonhydrogen-bonded intermediate **9**, no such structural rigidity is possible and, accordingly, cyclization is more facile.

During the course of these investigations, the synthesis of 8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocin-2-one (**13**) was reported by Sulkowski[3] (Scheme III). The hexahydrobenzodiazocine **16** and its 1-methyl analog **20** had been prepared by us as a part of our program of synthesizing derivatives of compounds **3** and **10**. Since it should be possible to convert the compound described as **13** into the structurally defined compounds **16** and **20** by way of reduction to the former, and methylation followed by reduction to the latter,[11] and since the physical character reported for **13** was incompatible with that anticipated for such a structure, the Sulkowski procedure was repeated. The product exhibited the reported melting point and elemental analysis as well as spectra (ir, uv, and nmr) compatible with the reported structure.

We were unable to complete the proposed structural relationship with **20** since the desired methylation of product **13** could not be effected. Furthermore, the treatment of the compound with lithium aluminum hydride afforded a new compound spectrophotometrically and by elemental analysis compatible but nonidentical with **16**. Mass spectral analysis demonstrated that both the original compound reported by Sulkowski and its reduction product were dimers of

(7) F. Weygand and M. Reckhaus, *Chem. Ber.*, **82**, 442 (1949); E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 826 (1962); B. A. Porai-Koshits and A. L. Remizov, *Sb. Statei Obshch. Khim., Acad. Nauk SSSR*, **2**, 1570 (1953); *Chem. Abstr.*, **49**, 5367 (1955).

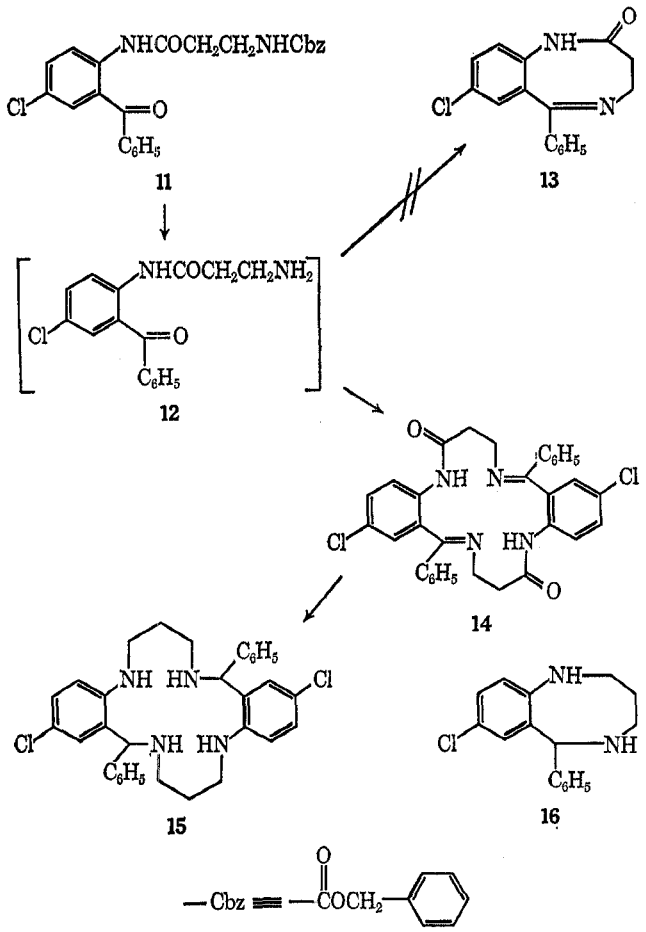
(8) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

(9) W. Eschweiler, *Ber.*, **38**, 880 (1905); H. I. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons Inc., New York, N. Y., 1962, pp 135 and 144.

(11) See for example L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

SCHEME III

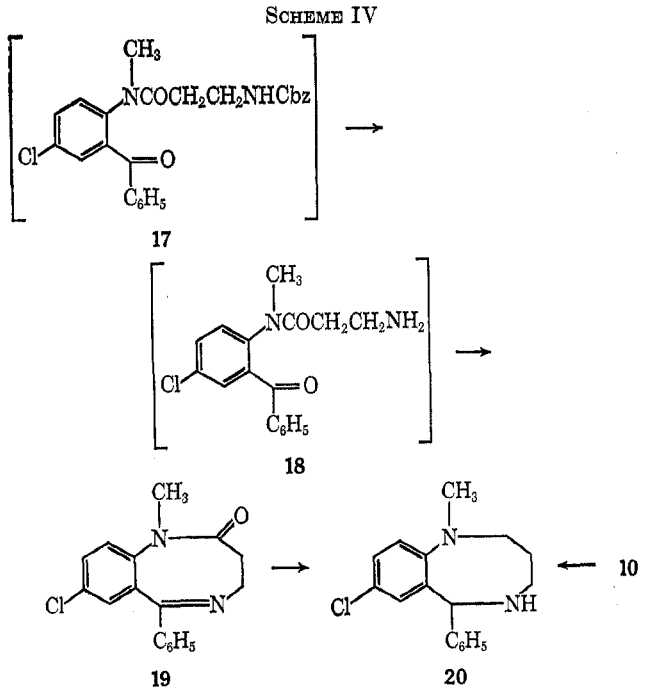


13 and 16, respectively, and, accordingly, the structures assigned were **14** and **15**.[12]

The 1,5,9,13-tetrazacyclohexadecane ring system was previously unknown. Although similar large ring dimers have been reported,[13] the synthesis of a dimeric sixteen-membered ring to the apparent exclusion of the eight-membered ring was curious. This phenomenon could, however, be explained by the hydrogen bonding noted in **5a** and observed again in **11** [ir ($CHCl_3$), 1640 cm^{-1} (C=O)]. The Dreiding model of the intramolecular hydrogen bonded compound **12** demonstrated that the primary amine could not effect intramolecular attack at the ketone carbonyl as a result of the molecular rigidity imparted by the formation of the new bonded ring. Accordingly, the intermolecular condensation to give **14** was credible. If, however, the amide was tertiary, such bonding would not exist and the eight-membered ring would be the anticipated product.

Thus the reaction of 5-chloro-2-methylaminobenzophenone[8] with carbobenzyloxy-β-alanyl chloride[9] gave **17** (Scheme IV) as an oil which was characterized by

SCHEME IV

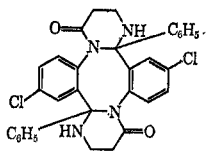


its infrared spectrum and which exhibited the unbonded carbonyl absorption at 1670 cm^{-1}. Cleavage of the blocking group with hydrogen bromide gave **18** as the hygroscopic hydrobromide. The free base of **18** was dehydrated in refluxing toluene to give a crystalline product in 23% yield. Preliminary assignment of the benzodiazocine structure **19** was based on spectral (ir, uv, nmr and mass) compatibility. In this case, no dimeric 16-membered ring was isolated. The structure of **19** was corroborated chemically by its reduction with lithium aluminum hydride to the hexahydrobenzodiazocine **20**, identical with that obtained by the lithium aluminum hydride reduction of **10**. The structural assignment of **19** was further substantiated by its comparison (ir and mixture melting point) with an authentic sample synthesized *via* an alternate procedure by Ott.[14] He had, in fact, synthesized the monomer **13**, which on methylation gave a derivative identical in all respects with our compound **19**.

Experimental Section[15]

2-(3-Aminopropylamino)-5-chlorobenzophenone Hydrochloride (2).—A solution of 5.0 g (16.2 mmol) of 9-chloro-1,2,3,5-tetra-

(12) It must be pointed out that although structure **14** is in accord with the physical character of the dimer of **13**, *i.e.*, ir (KBr) 1690 (secondary amide C=O), 1520 (amide II), 1615 cm^{-1} (C=N), uv max (2-propanol), 234 mμ (ε 72,000), 267 (30,000), 327 (10,000), a transannular condensation product such as i cannot be positively excluded. Accordingly, the structural assignment of **15** is also not irrefutable.



i

(13) See, for example, A. Muller, E. Srepel, E. Funder-Fritzsche, and F. Dicher, *Monatsh. Chem.*, **83**, 386 (1952); J. M. v. d. Zanden and G. Devries, *Rec. Trav. Chim. Pays-Bas*, **75**, 1159 (1956); M. Kumayai, *Nippon Kagaku Zasshi*, **81**, 489 (1960); *Chem. Abstr.*, **55**, 6487g (1961).

(14) After the completion of this work, we found by private communication that Dr. H. Ott, Sandoz, Inc., had also established that the dehydration of **12** under the published conditions gave a dimer.

(15) Melting points were determined microscopically on a hot stage and are corrected. The nmr spectra were determined on a Varian A-60 instrument, the ir spectra were determined on a Beckman IR-9 spectrophotometer, the uv spectra were determined on a Cary Model 14 spectrophotometer and the mass spectra were determined by means of a CEC 21-110B instrument at 70 eV by direct insertion. Excess lithium aluminum hydride (LAH) in reaction mixtures was decomposed as follows. For each 1 g of LAH used, the reaction mixture was carefully treated with 2.0 ml of water and then with 1.6 ml of 10 *N* sodium hydroxide and the reaction mixture was stirred 1 hr at reflux, dried and filtered to give a clear ethereal solution. All solutions were dried over anhydrous magnesium sulfate. Column chromatography over alumina utilized Woelm neutral alumina, activity grade I. The boiling point of the petroleum ether used is 30–60°.

hydro-7-phenylpyrimido[1,2-*a*][1,4]benzodiazepine (**1**)[4] in 25 ml of 3 *N* HCl in 25 ml of ethanol was stirred 18 hr at the reflux temperature. The reaction mixture was poured into an excess of ice and ammonium hydroxide and the basic mixture was extracted with methylene chloride. The organic extract was washed with water, dried and the solvent was removed *in vacuo* to give 4.0 g (85.7%) of a yellow gum. Crystallization from methylene chloride–cyclohexane–petroleum ether gave yellow prisms, mp 78–85°. The free base was converted into the hygroscopic hydrochloride in 88.5% conversion. Recrystallizations from isopropyl alcohol–ether gave yellow needles of pure **2** hydrochloride, mp 170°.

Anal. Calcd for $C_{16}H_{17}ClN_2O \cdot HCl$: C, 59.08; H, 5.58; Cl, 21.80. Found: C, 58.75; H, 5.84; Cl, 21.13.

8-Chloro-1,2,3,4-tetrahydro-6-phenyl-1,5-benzodiazocine (3).—A solution of 2.7 g (1 mmol) of **2** in 100 ml of pyridine was heated at reflux for 17 hr. The solvent was removed from the reaction mixture under reduced pressure. The residue was partitioned between methylene chloride and water and the organic layer was washed with water, dried and evaporated to a gum. This gum was chromatographed on alumina with benzene to give a total of 1.0 g (39.5%) of **3**, mp 146–150°. An analytical sample, mp 150–151°, was prepared by recrystallizations from cyclohexane–hexane.

Anal. Calcd for $C_{16}H_{15}ClN_2$: C, 70.97; H, 5.58; N, 10.35; Cl, 13.09. Found: C, 70.92; H, 5.77; N, 10.42; Cl, 13.00.

5-Chloro-2-(3-chloropropylamino)benzophenone (5a).—A solution of 17.4 g (50 mmol) of 7-chloro-1-(3-chloropropyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (**4**)[4] in 100 ml of 3 *N* HCl and 100 ml of ethanol was heated at reflux overnight. The reaction mixture was cooled, washed with ether, neutralized with ammonium hydroxide and extracted with ether. The organic phase was washed with water, dried and evaporated *in vacuo* to 14.1 g of yellow oil. Chromatography of the crude product on alumina with benzene gave 11.3 g (73.4%) of a pure yellow oil which crystallized on standing, mp 60–62°. Recrystallizations from hexane gave yellow prisms, mp 61.5–62°.

Anal. Calcd for $C_{16}H_{15}Cl_2NO$: C, 62.35; H, 4.90; Cl, 23.01. Found: C, 62.41; H, 5.12; Cl, 23.03.

5-Chloro-2-[N-(*p*-toluenesulfonyl)-3-bromopropylamino]benzophenone (7).—A solution of 244 g (0.6 mol) of the sodium salt of 2-tosylamido-5-chlorobenzophenone[5] in 2 l. of dry DMF was treated with 605.7 g (3.0 mol) of 1,3-dibromopropane and stirred overnight at 60°. The reaction mixture was poured into 2 l. of ice water and extracted with methylene chloride. The organic phase was washed with 10 *N* sodium hydroxide and with water. The solvent was removed *in vacuo* to give 295.7 g (97.2%) of tan oil. Standing three weeks in ether effected crystallization, mp 92–96°. An analytical sample was prepared by recrystallization from ether, mp 106–108°.

Anal. Calcd for $C_{23}H_{21}BrClNO_3S$: C, 54.50; H, 4.18; N, 2.76. Found: C, 55.16; H, 4.28; N, 2.97.

The detosylation of **7** was effected in near-quantitative yields by 17 hr of contact with 75% sulfuric acid at 75°. The crude product **5b** was utilized without further purification.

The Amination of 5.—A mixture of 9.0 g (29.2 mmol) of **5a**, 5.0 g (30 mmol) of potassium iodide and about 5 g of ammonia in 25 ml of ethanol was shaken at 121° under a pressure of 150 psi in a sealed container for about 6 hr. The reaction mixture was poured into ice and dilute sodium hydroxide and extracted with methylene chloride. The extract was dried and concentrated *in vacuo* to 8.5 g of a crude mixture of **2** and **3**. After chromatographic separation (ether over alumina) and recrystallization from ether, **3** was isolated in a yield of 45.7%. A similar reaction run at 102° for about 4 hr yielded 48.8% of **3** and 6.3% of **2**.

5-Chloro-2-(3-chloropropylmethylamino)benzophenone (8).—The yellow solution of 15.9 g (51.6 mmol) of **5a** in 100 ml of 98–100% formic acid was treated with 50 ml of a 37% solution of aqueous formaldehyde. The reaction mixture turned intense red and was refluxed 17 hr at which time the color had reverted to yellow. The reaction mixture was poured into ice water, made basic with sodium hydroxide and extracted with methylene chloride. The extract was chromatographed on alumina with hexane to give 10.9 g (65.3%) of pure **8**. An analytical sample was prepared by distillation, bp 191–193° (0.6 mm).

Anal. Calcd for $C_{17}H_{17}Cl_2NO$: C, 63.36; H, 5.32; N, 4.35. Found: C, 63.29; H, 5.31; N, 4.17.

8-Chloro-1,2,3,4-tetrahydro-1-methyl-6-phenyl-1,5-benzodiazocine (10).—A mixture of 5.7 g (17.7 mmol) of **8**, 3.32 g (20 mmol) of potassium iodide, 35 ml of ethanol and an excess of ammonia was shaken 6 hr at 90° under a pressure of 165 psi. The unreacted potassium iodide was removed by filtration, and the solvent was removed *in vacuo* from the filtrate. The residue was partitioned between 1 *N* sodium hydroxide and methylene chloride. The organic phase was separated, washed with water, dried and reduced *in vacuo* to an orange oil. The crude product was chromatographed on alumina with hexane and with ether to give a total of 3.7 g (73.8%) of **10**. An analytical sample, mp 111–113°, was prepared by recrystallization from petroleum ether.

Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02; N, 9.84. Found: C, 71.76; H, 6.05; N, 9.81.

2,12-Dichloro-10,20-diphenyldibenzo[*b*,*f*][1,5,9,13]tetraaza-9,19-cyclohexadecadiene-6,16-dione (14).—A solution of 37 mmol of 2-[2-aminopropionamido]-5-chlorobenzophenone (**12**)[3] in 100 ml of toluene was refluxed 8 hr into a Dean–Stark trap. The reaction mixture was allowed to cool and the precipitate was collected, giving 1.1 g (10%) of the product **14**, mp 310–318° (lit.[3] mp 310° dec). Recrystallizations from methylene chloride–hexane gave colorless prisms, mp 326–330°.

Anal. Calcd for $C_{32}H_{26}Cl_2N_4O_2$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.31; H, 4.41; N, 9.68.

2,12-Dichloro-5,6,7,8,9,10,15,16,17,18,19,20-dodecahydro-10,20-diphenyldibenzo[*b*,*j*][1,5,9,13]tetraazacyclohexadecane (15).—A mixture of 2.0 g (3.5 mmol) of **14**, 8.0 g of $LiAlH_4$ and 125 ml of anhydrous ether was stirred and refluxed for 72 hr. The reaction mixture was hydrolyzed[15] and the salts were removed by filtration. The filtrate was concentrated to 1.5 g (78.4%) of crude **15**. Recrystallizations from DMF–water gave colorless prisms, mp 240–242°.

Anal. Calcd for $C_{32}H_{34}Cl_2N_4$: C, 70.45; H, 6.28; N, 10.27. Found: C, 70.67; H, 6.43; N, 10.33.

8-Chloro-1,2,3,4,5,6-hexahydro-6-phenyl-1,5-benzodiazocine Dihydrochloride (16).—A mixture of 0.25 g (9.25×10^{-4} mol) of **3**, 1 g of $LiAlH_4$ and 300 ml of anhydrous ether was stirred and refluxed for 90 hr. The reaction mixture was hydrolyzed[15] and the ether solution separated and saturated with hydrogen chloride. Filtration yielded 300 mg (94.5%) of pale yellow dihydrochloride, mp 180°. Recrystallizations from methanol–ether gave colorless prisms, mp 218–225°.

Anal. Calcd for $C_{16}H_{17}ClN_2 \cdot 2HCl$: C, 55.59; H, 5.74; N, 8.10. Found: C, 55.86; H, 5.75; N, 8.23.

8-Chloro-3,4-dihydro-1-methyl-6-phenyl-1H-1,5-benzodiazocin-2-one (19).—A stirred suspension of 22.4 g (0.1 mol) of carbobenzyloxyalanine[3] in 300 ml of ether chilled to 0° with an external bath of ice and acetone was treated with 25 g (0.12 mol) of phosphorus pentachloride. The reaction mixture was stirred 1.5 hr and then the ether solution was decanted from the solids. The solution of acid chloride was added rapidly to 20 g (87 mmol) of 5-chloro-2-methylaminobenzophenone[8] dissolved in 150 ml of chloroform and the reaction mixture was stirred for 1 hr at room temperature. The reaction mixture was washed successively with water, 3 *N* sodium hydroxide, water, 3 *N* HCl and water, dried, and concentrated *in vacuo* to give a crude mixture of 2-(β-carbobenzyloxalanyl-N-methylamido)-5-chlorobenzophenone (**17**). Compound **17** was treated with 80 ml of 31% hydrogen bromide in acetic acid. The reaction mixture was stirred 2 hr at room temperature and was then treated with ether. The precipitate was separated and washed with several portions of ether. The hygroscopic precipitate formed a gum which was dissolved in 150 ml of water, made basic with ammonium hydroxide and extracted with toluene. The toluene solution of **18** was then refluxed overnight and the water formed was collected in a Dean–Stark trap. The reaction mixture was concentrated *in vacuo* to 16.8 g of a crude multicomponent gum which on crystallization from cyclohexane gave 5.1 g (23.4%) of colorless prisms, mp 170–171°.

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.53; H, 5.14; N, 9.27.

8-Chloro-1,2,3,4,5,6-hexahydro-1-methyl-6-phenyl-1,5-benzodiazocine (20). A. From 19.—A mixture of 2.2 g (7.3 mmol) of **19**, 8.5 g of $LiAlH_4$ and 125 ml of dry ether was stirred at the reflux temperature for 24 hr. The reaction mixture was hydrolyzed and the salts were removed by filtration. The filtrate was concentrated *in vacuo* to a residue which was crystallized from hexane to give 0.75 g (35.9%) of colorless crystals, mp 93–96°. Recrystallization from hexane gave the analytical sample, mp 100–101°.

Anal. Calcd for $C_{17}H_{19}ClN_2$: C, 71.19; H, 6.68; H, 9.77. Found: C, 71.35; H, 6.65; N, 9.74.

An ethereal solution of the free base was saturated with hydrogen chloride, forming the hydrochloride hydrate, mp 212–215°. Recrystallization from ethanol–ether gave colorless prisms, mp 223–225°.

Anal. Calcd for $C_{17}H_{19}ClN_2 \cdot HCl \cdot H_2O$: C, 59.88; H, 6.50; N, 8.21. Found: C, 59.45; H, 6.13; N, 7.95. (Acceptable analyses were not obtained due to the hygroscopic nature of the salt. However, the hydrochloride was quantitatively convertible into the base and exhibited mass spectrum identical with that of the base.)

B. From 10.—A mixture of 2.3 g (8 mmol) of **10**, 3.0 g of $LiAlH_4$ and 125 ml of anhydrous ether was stirred at reflux for 65 hr. The reaction mixture was hydrolyzed[15] and the salts were removed by filtration. The filtrate was concentrated *in vacuo* to 1.5 g (65.3%) of crude **20**, from which the pure product was isolated as the hydrochloride, spectrally (ir and mass) identical with that obtained from **19**.

Registry No.—**2**, 17953-79-6; **3**, 17953-82-1; **5a**, 17953-80-9; **7**, 17953-81-0; **8**, 17954-13-1; **10**, 17954-14-2; **14**, 17954-15-3; **15**, 17954-16-4; **16**, 17954-17-5; **19**, 17954-18-6; **20**, 17954-19-7; **20**·HCl, 17954-20-0.

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A Novel Synthesis of 1,5-Benzodiazocines

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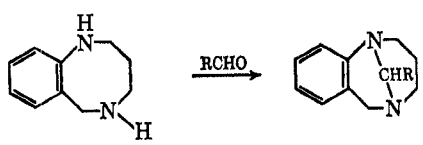
A novel synthetic route for the preparation of 1,5-benzodiazocines has been realized. It consists of bridging the two nitrogen atoms of a 1,2,3,4-tetrahydroquinazoline to a 1,5-methano-1,5-benzodiazocine followed by removal of the methylene bridge in **6** as formaldehyde or by hydrogenolytic cleavage of the 1,11 bond. This particular concept could conceivably be extended to the construction of larger rings containing two nitrogen atoms in the proper position. The bridgehead lactams **6** and **15** prepared from the corresponding amino acids by the mixed anhydride procedure exhibited ketone character as expected for such systems.

The 1,4-benzodiazepine ring system has received considerable interest since the advent of chlordiazepoxide and diazepam as tranquilizers.[1] The eight-membered-ring system (**1**) has, however, not been studied to any extent. Hexahydro-1,5-benzodiazocine (**1**) has been described for the first time by Shiotani and Mitsuhashi.[2] These authors bridged the two amino functions of **1** by condensation with aldehydes to obtain compounds of type **2** in excellent yields, a reaction which most probably is reversible. It was conceivable, therefore, to



1 **2**

build up the 1,5-benzodiazocine ring system by bridging the two nitrogen atoms in a properly substituted 1,2,3,-4-tetrahydroquinazoline by a three-carbon unit followed by expulsion of the methylene group between the two amino functions as formaldehyde. This novel approach toward the synthesis of 1,5-benzodiazocines has indeed been realized and is outlined in Scheme I.

As our point of departure we chose 6-chloro-4-phenyl-3,4-dihydroquinazoline[3] (**3**) which was most conveniently prepared by addition of phenyllithium across the 3,4 double bond[4] of 6-chloroquinazoline. The reaction sequence of Scheme I was also carried out with 4-phenyl-3,4-dihydroquinazoline and 4-(*p*-chlorophenyl)-3,4-dihydroquinazoline as starting materials.

β-Amino ester **4a** was obtained in almost quantitative yield on refluxing 3,4-dihydroquinazoline **3** with ethyl acrylate. As a cyclic amidine, **3** could theoretically react in its tautomeric 1,4-dihydro form. Armarego has pointed out[5] that 3,4-dihydroquinazoline always behaves as a 3,4-dihydro derivative though limited evidence to corroborate this fact seems to be available in the literature. Ir, uv,[6] or nmr spectra do not provide unambiguous proof for the obtained product **4a** but further chemical transformations leave no doubt about the correctness of this structural assignment.

Reduction of β-amino ester **4a** with sodium borohydride in refluxing ethanol led to a mixture of products from which 6-chloro-4-phenyl-1,2,3,4-tetrahydroquinazoline was isolated in approximately 50% yield. Hence the reduction of the carbon–nitrogen double bond was accompanied by a considerable amount of β elimination. Various attempts to suppress this β elimination by changing the reduction conditions were unsatisfactory. We therefore decided first to hydrolyze ethyl ester **4a** to acid **4b** under mild conditions followed by sodium borohydride reduction of its sodium salt. It was anticipated that the negative charge of the carboxylic ion would prevent the development of a second anionic center on the α-carbon atom and thereby impede the undesirable elimination of the propionic acid side chain. Both reactions have indeed been realized in high yield without detectable β elimination.

We now were ready to carry out what we considered to be the most critical step of our synthetic concept, namely, the lactamization of amino acid **5** to the bridgehead lactam **6**. Over the last 60 years many unsuccessful attempts toward the preparation of simple

(1) Trademarked as Librium and Valium, respectively.

(2) S. Shiotani and K. Mitsuhashi, *Yakugaku Zasshi*, **84**, 656 (1964); *Chem. Abstr.*, **61**, 10685*a* (1964).

(3) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(4) Nucleophilic additions of this type have been reported for quinazoline by T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960); *Chem. Abstr.*, **54**, 13125*e* (1960).

(5) W. L. F. Armarego, *Advan. Heterocycl. Chem.*, **1**, 285 (1960).

(6) For a comparison of the uv spectra of some 1,4- and 3,4-dihydroquinazolines, see A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 2689 (1961).