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.

Acknowledgment.—The authors are indebted to Dr. F. Vane, Dr. T. Williams, Dr. V. Toome, and Mr. S. Traiman for the spectral data and to Dr. Al Steyermark and Dr. F. Scheidl and their staff for the microanalyses. We also wish to thank Dr. H. Ott of Sandoz, Inc., Hanover, N. J., for providing us with a sample of compound **19** prepared by his procedure for comparative purposes.

A Novel Synthesis of 1,5-Benzodiazocines

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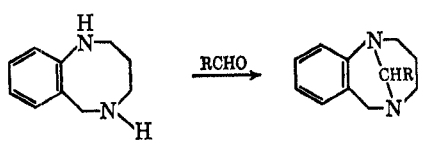
A novel synthetic route for the preparation of 1,5-benzodiazocines has been realized. It consists of bridging the two nitrogen atoms of a 1,2,3,4-tetrahydroquinazoline to a 1,5-methano-1,5-benzodiazocine followed by removal of the methylene bridge in **6** as formaldehyde or by hydrogenolytic cleavage 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).

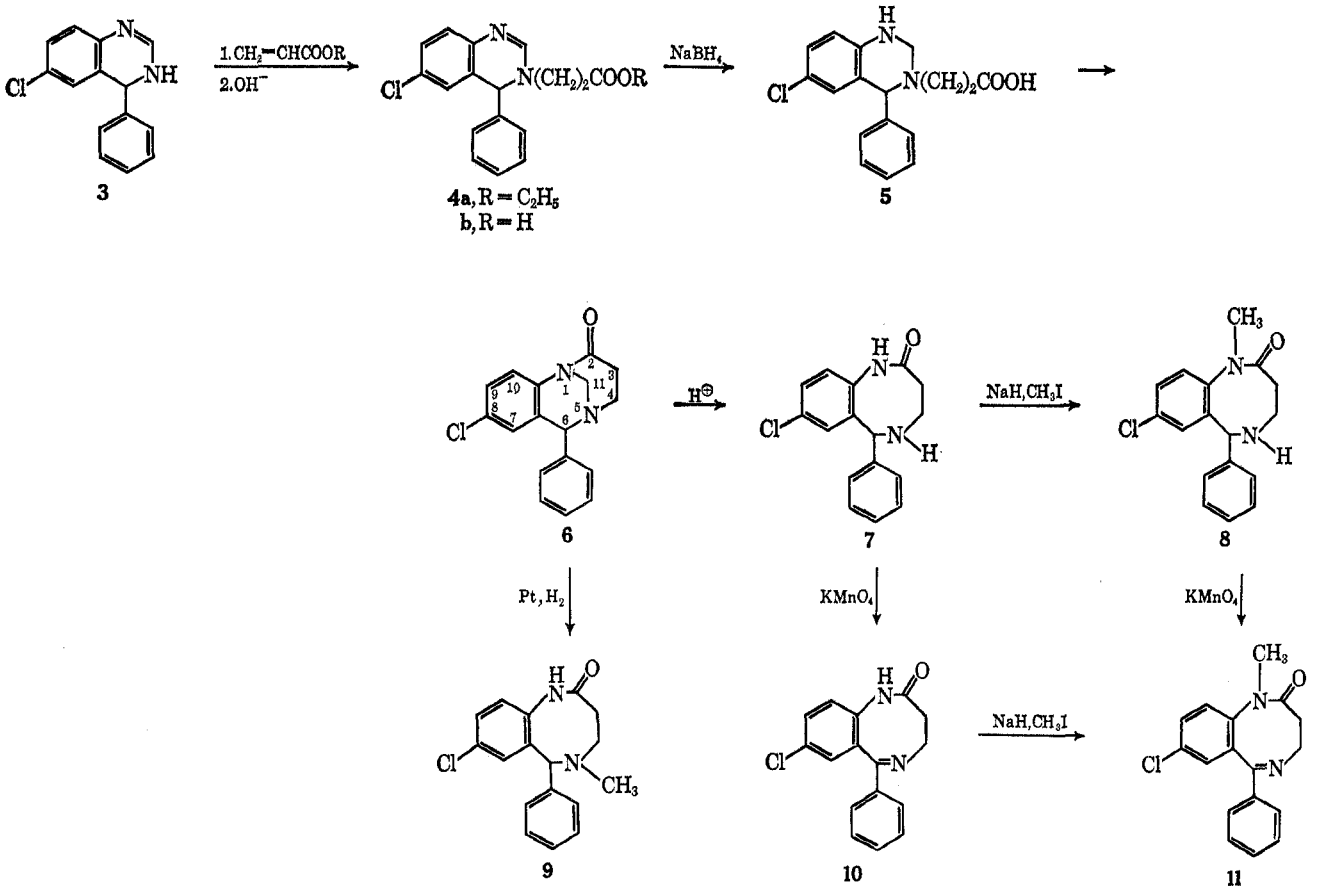
(3) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(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).

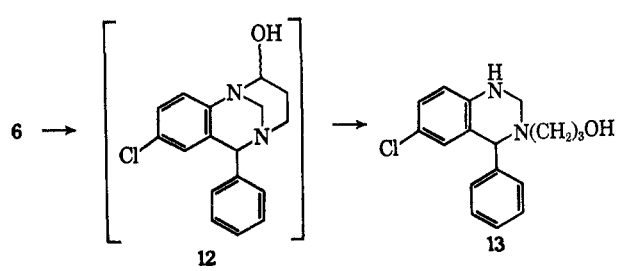
(6) For a comparison of the uv spectra of some 1,4- and 3,4-dihydroquinazolines, see A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 2689 (1961).

SCHEME I



bridgehead lactams (particularly 2-quinuclidones) have been reported,[7] but the first representatives of this type have been described[8] only in recent years. Bridgehead lactams are of considerable theoretical interest since their amide group cannot attain partial double bond character without violating Bredt's rule. Consequently normal amide resonance is inhibited and therefore the physicochemical and chemical properties of such lactams resemble rather those of isolated ketones than amides.

Our preliminary attempts of lactamization with thionyl chloride—the reagent used in the preparation of several 2-quinuclidones[8c,d]—led to a complicated reaction mixture. However, the mixed anhydride procedure[9] (used widely in peptide synthesis), *i.e.*, treatment of amino acid **5** with ethyl chlorocarbonate in the presence of triethylamine–absolute dioxane at room temperature proved very successful. The bridgehead lactam **6** was obtained in over 80% yield by exclusive intramolecular amide formation. We believe that this mixed anhydride procedure might be in general far superior to the acid chloride method in the preparation of bridgehead lactams due to the mild and nonacidic reaction conditions. Compound **6** exhibited a carbonyl absorption in the infrared spectrum at 1720 cm^{-1} which is in the frequency range of nonconjugated ketones as expected[8b-d] for such a bridgehead lactam. In the nmr spectrum the methylene bridge appeared as an AB pattern centered at δ 4.30 (J_{AB} = 12.5 cps) and the methine proton at C-6 as a singlet at δ 4.55. The preferred conformation of both substituents in position 3 and 4 of quinazolines **4** and **5** is, of course, equatorial while in the bridged quinazoline **6** the three-carbon bridge and consequently also the phenyl group are by necessity axial (the structural formula **6** represents arbitrarily one antipode). The Dreiding model of **6** does not imply substantial ring strain or steric crowding. The ketone character of the carbonyl group in lactam **6** could be demonstrated by sodium borohydride reduction. Amino alcohol **13** resulted presumably through carbinolamine **12** which was further reduced probably by way of its tautomeric aminoaldehyde form.[10]



When the bridgehead lactam **6** was treated with diluted hydrochloric acid or acetic acid at room temperature, 1,5-benzodiazocinone **7** resulted in essentially

(7) (a) P. Rabe, *Ann.*, **365**, 353 (1909); (b) R. Lukes, *Coll. Trav. Chim. Tchecoslov.*, **10**, 148 (1938); (c) W. v. E. Doering and J. D. Chanley, *J. Amer. Chem. Soc.*, **68**, 586 (1946); (d) H. K. Hall, Jr., *ibid.*, **80**, 6412 (1958); (e) R. Lukeš and M. Ferles, *Coll. Czech. Chem. Commun.*, **24**, 1297 (1959).

(8) (a) L. N. Jachontow and M. V. Rubzow, *Zh. Obshch. Khim.*, **27**, 83 (1957); (b) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, **80**, 2590 (1958); (c) H. Pracejus, *Ber.*, **92**, 988 (1959); (d) H. Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, *Tetrahedron*, **21**, 2257 (1965).

(9) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

(10) W. C. Wildman, *et al.*,[7b] obtained the stable carbinolamine haemanthidine by sodium borohydride reduction of the corresponding bridgehead lactam oxohaemanthidine.

quantitative yield. The formaldehyde generated in this reaction was identified as its dimedone derivative. One can speculate that the driving force of this reaction is the gain in resonance energy in the transformation of **6** into **7**. If substantial steric strain had been present in the bridged system **6**, hydrolytic cleavage of the lactam bond to regenerate amino acid **8** would have been expected at least to some extent. Such a pathway is well documented in the rapid acid hydrolysis of a few 2-quinuclidones.[8c,d] Structure **7** has been assigned on the basis of the microanalysis, the infrared spectrum (amide carbonyl at 1675 cm^{-1}), the nmr spectrum (lack of any signal for a methylene group) and further chemical transformations discussed below.

1,5-Benzodiazocinone **7** was methylated on N-1 to **8** (the N–CH_3 signal appeared at δ 3.42 in the nmr spectrum) by reacting its sodium salt in dimethylformamide with methyl iodide. On the other hand, hydrogenolysis of the bridgehead lactam **6** with platinum in glacial acetic acid led to 5-methyl-1,5-benzodiazocinone **9** (NCH_3 at δ 2.17) and none of the 1-methyl derivative **8** could be detected by thin layer chromatography. The 1,11 bond in the bridged lactam **6** is sterically less hindered (Dreiding model) than the 5,11 bond and the obtained result can therefore be explained on this ground.

In our preliminary attempts to oxidize **8** to **11** or **7** to **10** with selenium dioxide, silver oxide, or chromium trioxide, we invariably recovered starting material in high yields. Similar oxidations in the 1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one series[11] had been successful, provided the lactam nitrogen was not substituted.[11b]

We then found that aqueous potassium permanganate at room temperature provides an excellent way to introduce the 5,6-azomethine bond. 8-Chloro-1-methyl-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-one (**11**) was obtained in 36% yield while 8-chloro-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1-H)-one (**10**) resulted in 84% yield. Again as in the seven-membered ring series[11b] this oxidation proved more successful when N-1 was unsubstituted. The spectroscopic evidence (uv, ir, nmr) is compatible with structures **10** and **11**, respectively. Methylation of **10** at the lactam nitrogen atom was achieved under the usual conditions and led to **11** as well. Conclusive evidence for the structural assignment of **11** was provided by its comparison (ir and mixture melting point) with an authentic sample synthesized *via* an alternate route by Fryer and coworkers.[12]

After the completion of this work, the synthesis of 8-chloro-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-one (**10**) was claimed by Sulkowski.[13] The melting point of 310° for this product contrasts sharply with our melting point of 164–166° for **10**. We repeated Sulkowski's procedure to obtain a product with the reported melting point and the correct elemental analysis. The mass spectrum revealed, however, that the product under discussion was a dimer, the structure of which was tentatively established by Fryer.[12]

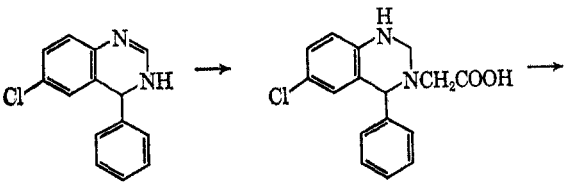
(11) (a) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **30**, 521 (1965); (b) R. I. Fryer, G. A. Archer, B. Brust, W. Zally, and L. H. Sternbach, *ibid.*, **30**, 1308 (1965).

(12) M. E. Derieg, R. M. Schweiniger, and R. I. Fryer, *ibid.*, **33**, 179 (1968).

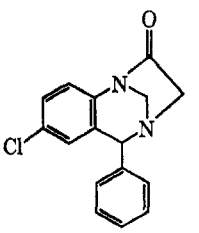
(13) T. S. Sulkowski, U. S. Patent 3,294,782 (1966).

The successful synthesis of the bridgehead lactam **6** and its further transformation to 1,5-benzodiazocines encouraged us to apply the same principle to build up the well-known 1,4-benzodiazepine ring system. Alkylation of **3** with ethyl bromoacetate, alkaline hydrolysis of the obtained amino ester to the corresponding acid, followed by sodium borohydride reduction, led to the crude 1,2,3,4-tetrahydroquinazoline **14** which could not be obtained in crystalline form, but was only characterized by thin layer chromatography (Scheme II). The ring closure to the rather strained lactam

SCHEME II



3 **14**



15

15 was again achieved by the mixed anhydride procedure (42% yield). To our knowledge, compound **15** represents the first bridgehead lactam reported so far bearing the amide carbonyl group in a five-membered ring. The structural assignment for **15** is based essentially on the extremely high carbonyl frequency (1780 cm^{-1} in CH_2Cl_2) in the infrared spectrum which reflects the substantial steric strain in this system as well as the lack of amide resonance. The bridgehead lactam **15** was even more sensitive toward hydrolysis than **6**. But in this case, cleavage of the amide bond to regenerate amino acid **11** among other water-soluble products seems to be the preferred pathway of hydrolysis. 7-Chloro-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one, the product expected from expulsion of formaldehyde, could not be detected.

In conclusion we wish to point out that the novel method for the synthesis of 1,5-benzodiazocines discussed in this paper could conceivably be expanded toward the construction of other medium-sized heterocycles bearing at least two nitrogen atoms in that ring.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus. Nmr spectra were determined in deuteriochloroform solution with internal tetramethylsilane as standard, on a Varian A-60 instrument. Ir spectra were measured on a Model 237 Perkin-Elmer spectrophotometer in methylene chloride; uv spectra on a Model 14 Cary spectrophotometer in alcoholic solution. Microanalyses were carried out in our analytical unit.

6-Chloro-4-phenyl-3,4-dihydroquinazoline (3).—To a suspension of 10.5 g (64 mmol) of 6-chloroquinazoline in 100 ml of dry ether was added dropwise 31 ml of a 2.1 *M* benzene–ether solution of phenyllithium (65 mmol) at 2–5°. The reaction mixture was stirred for an additional 30 min at room temperature, then diluted with 100 ml of ether and washed twice with 100 ml of

water. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*. On addition of ether to the residue 11.75 g (76%) of 6-chloro-4-phenyl-3,4-dihydroquinazoline (**3**) crystallized in white prisms, mp 172–173° (lit.[3] mp 173–174°).

Anal. Calcd for $C_{14}H_{11}ClN_2$: C, 69.3; H, 4.6; Cl, 14.6; N, 11.5. Found: C, 69.3; H, 4.9; Cl, 14.7; N, 11.4.

3-(2-Carbethoxyethyl)-6-chloro-4-phenyl-3,4-dihydroquinazoline (4a).—A solution of 3.8 g (15.6 mmol) of 6-chloro-4-phenyl-3,4-dihydroquinazoline in 50 ml of ethyl acrylate was refluxed for 4 hr. After thorough evaporation of excess ethyl acrylate *in vacuo*, 5.34 g (100%) of almost pure **4a** remained as a light brown oil. The product crystallized from ether in white prisms: mp 107–108°; ir (CH_2Cl_2) 1730 (ester C=O); nmr ($CDCl_3$) δ 2.50, 3.40 (complicated patter for side-chain methylene protons), 5.60 s (methine proton).

Anal. Calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.6; H, 5.6; O, 9.3. Found: C, 66.9; H, 5.8; O, 9.6.

Analogously prepared were the oils 3-(2-carbethoxyethyl)-4-phenyl-3,4-dihydroquinazoline and 3-(2-carbethoxyethyl)-4-(4-chlorophenyl)-3,4-dihydroquinazoline. Both products were practically pure in tlc and their ir and nmr spectra closely resembled the ir and nmr spectra of **4a**.

3-(2-Carboxyethyl)-6-chloro-4-phenyl-3,4-dihhdroquinazoline (4b).—A solution of 2.75 g (8 mmol) of 3-(2-carbethoxyethyl)-6-chloro-4-phenyl-3,4-dihydroquinazoline (**4a**) in 30 ml of ethanol and 12 ml of 2 *N* sodium hydroxide was kept at room temperature overnight. The clear solution was concentrated *in vacuo* to remove the ethanol. After addition of hydrochloric acid to obtain pH 6–7, the aqueous phase was extracted three times with methylene chloride, and the organic layers were combined, dried over anhydrous sodium sulfate and evaporated to dryness. From ethanol 2.26 g (90%) of 3-(2-carboxyethyl)-6-chloro-4-phenyl-3,4-dihydroquinazoline (**4b**) crystallized in white prisms: mp 166–167°; ir (KBr) 1710 (acid C=O).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.9; H, 4.8; N, 8.9; O, 10.2. Found: C, 64.6; H, 4.9; N, 8.6; O, 10.1.

Analogously prepared were 3-(2-carboxyethyl)-4-phenyl-3,4-dihydroquinazoline (amorphous), characterized by tlc and ir (KBr) 1710 (acid C=O), and 3-(2-carboxyethyl)-4-(4-chlorophenyl)-3,4-dihydroquinazoline (amorphous), characterized by tlc and ir (KBr) 1710 (acid C=O).

8-Chloro-1,5-methano-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one (6).—To a clear solution of 2.1 g (6.7 mmol) of 3-(2-carboxyethyl)-6-chloro-4-phenyl-3,4-dihydroquinazoline (**4b**) in 30 ml of ethanol and 5 ml of 2 *N* sodium hydroxide was added 0.6 g of sodium borohydride and the mixture was heated for 1.5 hr to 60°. The alkaline solution was neutralized with 2 *N* hydrochloric acid to pH 6–7 and extracted three times with methylene chloride. After the usual work-up 1.95 g (94%) of 3-(2-carboxyethyl)-6-chloro-4-phenyl-1,2,3,4-tetrahydroquinazoline (**5**) was obtained as a colorless oil, practically pure in tlc. This oil was dissolved in 20 ml of dry dioxane and 1.1 ml of triethylamine, and then 0.62 ml of ethyl chlorocarbonate was added dropwise at room temperature within 5 min. After standing an additional 15 min at room temperature the volatile parts were removed *in vacuo* at 20–30°. The crystalline residue was dissolved in methylene chloride and extracted twice with dilute sodium bicarbonate. The residue, after drying and evaporating the organic solvent (1.84 g), crystallized from ether (1.56 g, 78% over two steps) in prisms: mp 169–170°; ir (CH_2Cl_2) 1720 (C=O).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.3; H, 5.1; Cl, 11.9; O, 5.4. Found: C, 68.4; H, 5.3; Cl, 11.9; O, 5.4.

Analogously prepared were 1,5-methano-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one [mp 190–191°; ir (CH_2Cl_2) 1710 (C=O); yield 69% (*Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.5; H, 6.1; O, 6.1. Found: C, 77.4; H, 6.3; O, 6.3)] and 6-(4-chlorophenyl)-1,5-methano-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one [mp 160–161°; ir (CH_2Cl_2) 1715 (C=O); yield 67%].

8-Chloro-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one (7).—A solution of 12.0 g (40 mmol) of the bridgehead lactam **6** in 800 ml of dioxane, 800 ml of water and 200 ml of 1 *N* hydrochloric acid was kept at room temperature for 0.5 hr. After neutralization with sodium bicarbonate and concentration to a volume of approximately 1 l. *in vacuo*, 10.3 g (89%) of the product was filtered off: mp 208–210°; ir (CH_2Cl_2) 3390, 3350 (shoulder) and 1675 (amide C=O).

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.0; H, 5.3; Cl, 12.4; O, 5.6. Found: C, 66.8; H, 5.4; Cl, 12.5; O, 5.7.

The same product was obtained in essentially quantitative yield on standing of 1.0 g of **6** with 200 ml of water, 50 ml of dioxane, and 3 ml of acetic acid at room temperature for 1.5 hr.

Analogously prepared were 6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one [mp 187–189°; ir (CH_2Cl_2) 3375 (amide NH), 1670 (C=O); yield 80%] and 6-(4-chlorophenyl)-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one [mp 175°; ir (CH_2Cl_2) 3375 (amide NH), 1670 (C=O); yield 73%).

8-Chloro-1-methyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one (8).—8-Chloro-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one (**7**), 4.5 g (15.7 mmol), was dissolved in 110 ml of dry DMF and 1.0 g (20% excess) of sodium methoxide was added at room temperature. After 10 min, 2 ml of methyl iodide was added dropwise whereby a slight temperature raise was observed. The reaction mixture was evaporated *in vacuo* to a viscose oil, diluted with 10 ml of methylene chloride and extracted three times with water. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The reaction product (**8**) crystallized from ether: yield 3.64 g (77%) of white prisms; mp 151–153°; ir (CH_2Cl_2) 3340 (weak) and 1650 (amide C=O); nmr ($CDCl_3$) δ 1.50 s (NH), 3.42 s (NCH_3), 4.67 s (methine proton).

Anal. Calcd for $C_{17}H_{17}ClN_2O$: C, 67.9; H, 5.7; Cl, 11.8; O, 5.3. Found: C, 67.6; H, 5.8; Cl, 12.0; O, 5.5.

Analogously prepared was 1-methyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one [mp 140–141°; ir (CH_2Cl_2) 3325 (weak NH), 1650 (amide C=O) (*Anal.* Calcd for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.8; N, 10.5; O, 6.0. Found: C, 76.7; H, 7.1; N, 10.4; O, 6.2)].

5-Methyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one.—A solution of 2.64 g (10 mmol) of 1,5-methane-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one in 80 ml of glacial acetic acid was hydrogenated at room temperature in the presence of 300 mg of Adams platinum catalyst. The hydrogen uptake was complete within 0.5 hr. The catalyst was filtered off and the filtrate thoroughly evaporated to dryness *in vacuo*. From ethyl acetate 1.75 g (66%) of 5-methyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one crystallized in white prisms: mp 225–229°; ir (KBr) 3370 (amide NH), 1650 (amide C=O); nmr ($CDCl_3$, deuterated DMSO) δ 2.17 s (*n*-CH_3), 5.07 s (methine proton).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.8; N, 10.5. Found: C, 76.9; H, 6.7; N, 10.2.

Analogously prepared was 8-chloro-5-methyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one (**9**) (oil), characterized by tlc and nmr ($CDCl_3$, deuterated DMSO) δ 2.17 s (NCH_3), 5.11 s (methine proton).

8-Chloro-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-one (10).—To a solution of 4.5 g (15.7 mmol) of 8-chloro-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one (**7**) in 155 ml of dioxane (distilled over sodium) was rapidly added at room temperature 2.1 g of potassium permanganate in 40 ml of water under stirring. After 4 hr at room temperature, excess permanganate was destroyed by addition of a few drops of formic acid, the precipitate was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in methylene chloride and extracted three times with water. After drying and evaporating the organic phase, the residue (4.6 g) crystallized from ether to yield 3.74 g (84%) of 8-chloro-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-one (**10**): white prisms, mp 164–166°; ir (CH_2Cl_2) 3370 (sharp amide NH), 1670 (amide C=O) and 1620 (C=N); uv (ethanol) λ_{max} 240 mμ (ϵ 20,000); nmr ($CDCl_3$) δ 9.22 s (NH).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.5; H, 4.6; Cl, 12.5; O, 5.6. Found: C, 67.4; H, 4.8; Cl, 12.5; O, 5.7.

8-Chloro-1-methyl-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-one (11).—The amide N-methylation of 8-chloro-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-one (**10**) (4.22 g, 14.8 mmol) was carried out exactly as described for the preparation of **8**. The reaction product **11** crystallized from ether in pale yellow prisms: yield 3.11 g (70%); mp 167–168°; ir (CH_2Cl_2) 1660 (lactam) and 1620 (C=N); uv (ethanol) λ_{max} 245 mμ (ϵ 17,000); nmr ($CDCl_3$) δ 3.13 (NCH_3).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.3; H, 5.1; Cl, 11.9; O, 5.4. Found: C, 68.5; H, 5.3; Cl, 11.9; O, 5.7.

The same product was obtained in 36% yield when compound **8** was oxidized with potassium permanganate as described for the preparation of **10**.

Compound **11** was in every respect identical with an authentic sample of 8-chloro-1-methyl-6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-one provided by Fryer (Hoffmann-La Roche, Inc.).[12]

3-(3-Hydroxypropyl)-4-phenyl-1,2,3,4-tetrahydroquinazoline.—To a solution of 528 mg (2 mmol) of 1,5-methane-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one in 25 ml of 95% ethanol and 10 ml of methylene chloride was added at room temperature 200 mg of sodium borohydride. After standing for 1 hr the excess sodium borohydride was decomposed by addition of a few drops of acetic acid. The reaction mixture was concentrated *in vacuo* and distributed between methylene chloride and water. The organic phase was dried and evaporated and the residue crystallized from diethyl ether to yield 150 mg (28%) of 3-(3-hydroxypropyl)-4-phenyl-1,2,3,4-tetrahydroquinazoline in white prisms: mp 102–104°; nmr ($CDCl_3$) δ 4.78 s (methine hydrogen) multiplets for the methylene groups at δ 1.75, 2.80, 3.83.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.0; H, 7.5; N, 10.4; O, 6.0. Found: C, 75.8; H, 7.6; N, 10.4; O, 6.2.

Analogously prepared was 6-chloro-3-(3-hydroxypropyl)-4-phenyl-1,2,3,4-tetrahydroquinazoline (**13**) (oil), characterized by tlc and nmr (very similar to the nmr spectrum of the deschloro compound above).

7-Chloro-1,4-methano-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (15).—A mixture of 7.0 g (29 mmol) of 6-chloro-4-phenyl-3,4-dihydroquinazoline (**3**), 70 ml of ethanol, 7 ml of triethylamine and 4.1 ml of ethyl bromoacetate was refluxed for 1.5 hr. The volatile parts were thoroughly removed *in vacuo* and the obtained residue was distributed between methylene chloride and water. On drying and evaporating the solvent, 6-chloro-3-carbethoxymethyl-4-phenyl-3,4-dihydroquinazoline resulted as an oil (8 g, 85% of theory). This crude ester was dissolved in 100 ml of ethanol and 45 ml of 2 *N* sodium hydroxide and heated for 1.5 hr to 60°. After evaporation of the alcohol *in vacuo* the alkaline solution was extracted with ethyl acetate to remove nonacidic material. The aqueous layer was neutralized with 2 *N* hydrochloric acid to pH 6–7 and then extracted with methylene chloride to yield 5.0 g (68%) of crude 6-chloro-3-carboxymethyl-4-phenyl-3,4-dihydroquinazoline as a colorless oil. This crude amino acid was dissolved in 70 ml of ethanol and 20 ml of 2 *N* sodium hydroxide and reduced with 2.0 g of sodium borohydride at 60° within 1.5 hr. The excess sodium borohydride was decomposed with 2 *N* hydrochloric acid. The ethanol was removed *in vacuo*, the aqueous solution neutralized and extracted with methylene chloride. After drying and evaporating the organic solvent, 4.25 g (85%) of 6-chloro-3-carboxymethyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (**14**) resulted as a colorless oil, which was practically pure in tlc.

To a solution of 3.65 g of compound **14** in 50 ml of dry dioxane and 3.5 ml of triethylamine was dropwise added at 10° 2 ml of ethyl chloroacetate. After standing for 15 min at room temperature, the volatile parts were removed *in vacuo*, the resulting residue was dissolved in methylene chloride and this solution was extracted with dilute sodium bicarbonate and with water. The organic phase was dried over sodium sulfate and evaporated at 30° *in vacuo*. 7-Chloro-1,4-methano-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (**15**) crystallized from ether (1.43 g, 42%) in white prisms: mp 150–152°; ir (CH_2Cl_2) 1780 (C=O).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.5; H, 4.6; Cl, 12.5. Found: C, 67.0; H, 4.7; Cl, 12.2.

Registry No.—**3**, 17954-62-0; **4a**, 17954-63-1; **4b**, 17954-64-2; **6**, 17952-93-1; **7**, 17954-65-3; **8**, 17954-66-4; **10**, 14098-46-5; **11**, 17954-18-6; **15**, 17954-69-7; 1,5-methano-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one 17954-70-0; 6-(4-chlorophenyl)-1,5-methano-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one, 17954-71-1; 6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one, 17954-72-2; 6-(4-chlorophenyl)-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one, 17954-73-3; 1-methyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-one, 17954-74-4; 3-(3-hydroxypropyl)-4-phenyl-1,2,3,4-tetrahydroquinazoline, 17954-75-5.

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The Nitrosation of α,β-Unsaturated Oximes. IV. The Synthesis and Structure of 3,4-Diazacyclopentadienone Derivatives[1,2]

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β-Alkyl or aryl α,β-unsaturated oximes are converted by nitrous acid under oxygen or by a mixture of nitrous and nitric acids into 3,4-diazacyclopentadienone dioxides (**3**). Some negatively substituted methylene ketones are oxidized by nitrous acid to the same heterocycles. Nitrosation of the oximes under nitrogen produced the corresponding heterocyclic oxime. Nitrosation of 1-hydroxypyrazole 2-oxides (**10**) yielded 4-nitropyrazolenine 1,2-dioxides (**11**) that decomposed thermally to **3**. Reduction of the dioxides **3** with zinc in acetic acid furnishes a new and general route to 4-hydroxypyrazoles. Reduction of **3** with sodium dithionite yields 1,4-dhydroxypyrazoles, a new class of organic compounds. Oxidation of these latter compounds yields 3,4-diazacyclopentadienone oxides (**6**). A general mechanism for the nitrosation of α,β-unsaturated oximes is presented.

Nitrosation of β-aryl-α,β-unsaturated oximes produces a mixture of compounds which appear to be heterocyclic ketones and their corresponding oximes.[4] Since we have previously shown that mesityl oxide oxime is converted upon nitrosation into a pyrazolenine derivative[5] and, in an accompanying paper, that α-substituted α,β-unsaturated oximes yielded pyrazole derivatives,[6] we were led to suspect a five-ring structure for these compounds also.

Synthesis.—Previous investigators[4] reported that heterocyclic oximes were obtained from treatment of β-aryl-α,β-unsaturated oximes with nitrous acid while

(1) Part of these results have been described previously: paper III, J. P. Freeman and D. L. Surbey, *Tetrahedron Lett.*, 4917 (1967).

(2) Based in part on the Ph.D. dissertations of Donald L. Surbey and John J. Gannon. We are indebted to the donors of the Petroleum Research Fund, the Alfred P. Sloan Foundation, and the National Institutes of Health, National Cancer Institute, Grant No. CA 10742-01, for support of this research.

(3) Alfred P, Sloan Fellow, 1966–1968.

(4) (a) For some historical background on different structures proposed see ref 1. (b) Evidence for the presence of ketone and oxime functions is provided by G. Ponzio, *Gazz. Chim. Ital.*, **66**, 479 (1936), and G. Longo, *ibid.*, **66**, 815 (1936).

(5) Paper I, J. P. Freeman, *J. Org. Chem.*, **27**, 1309 (1962).

(6) J. P. Freeman and J. J. Gannon, *J. Org. Chem.*, **34**, 194 (1969). For a preliminary report, see J. P. Freeman and J. J. Gannon, *J. Heterocycl. Chem.*, **3**, 544 (1966).