

avoid air oxidation) to another centrifuge tube containing methyl iodide (2 ml.), mixed, and centrifuged for 1 min. to remove a yellow oil. From the last supernatant, colorless needle clusters separated which were collected after 1 hr. at room temperature.

Acknowledgments.—We are indebted to Mr. Joseph Sizensky and Mr. Paul Goodyer for valuable technical assistance.

Synthesis of A New Class of Antishock Agents^{1a}

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Antishock activity has been found in a series of octahydro- and decahydrobenzo[*a*]cyclopenta[*f*]quinolizines. Methods of synthesis of such compounds and the relative antishock activities are described. From the data available, no structure-activity relationship is evident.

The cardiovascular, and, in particular, the potent antishock properties of 2,3,3a,5,6,11,12,12a-octahydro-8-hydroxy-1H-benzo[*a*]cyclopenta[*f*]quinolizinium bromide (VIIa, R₁, R₃ = H; R₂ = OH) have been described by Osborne.^{1b} For the same compound, Detar² has reported a positive inotropic effect on the cat papillary muscle preparation. In view of the interest in this and related products as representatives of a new class of antishock agents, a preliminary discussion of their synthesis is presented in this paper. Although a

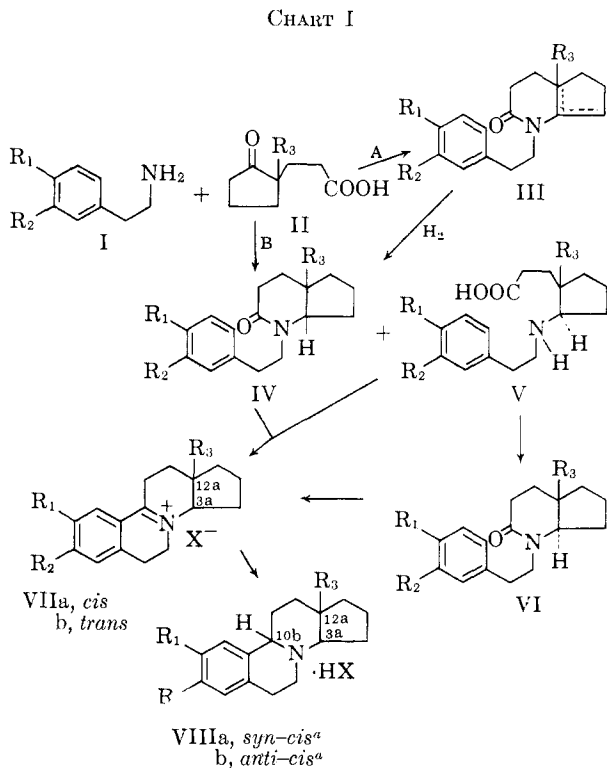
representative number of such products have been prepared, no structure-activity relationship has yet been uncovered. This work, however, is still in progress, and a subsequent report will be presented at a later time to delineate the scope of this activity.

Two procedures have been used for the preparation of these compounds, as indicated by routes A and B shown in Chart I.

According to route A, the starting substituted phenethylamine (I, R₁ and R₂ = H or OMe) and cyclopentanone-2-propionic acid (II, R₃ = H or Me) were condensed in refluxing xylene to afford moderate (50–70%) yields of the unsaturated lactam (III). This product underwent stereospecific reduction over palladium-carbon catalyst to give the *cis* lactam (IV). According to route B, IV was obtained directly in ca. 65% yield by a reductive condensation of the two starting materials in ethanol over palladium-carbon. This procedure also gave a 25% yield of the *trans* amino acid (V), which cyclized at its melting point to the *trans* lactam (VI). Ring closures on either of the lactams IV or VI or the amino acid V were carried out in high yields with phosphorus oxychloride in benzene. The resulting *cis* and *trans* quaternary salts (VIIa and b, R₁ and R₂ = H or OMe) were then demethylated directly with hydrobromic acid to afford the corresponding phenolic salts.

Tentative assignments of the *cis* and *trans* configurations to IV and V, respectively, were made initially by consideration of the relative ease of lactam formation from the initially formed amino acid mixture. Inspection of molecular models of the *cis* and *trans* forms of amino acid V supported the contention that the more easily formed lactam was the *cis*. Chemical proof of these assignments was obtained by the reaction sequence outlined in Chart II for the series where R₁ = R₃ = H and R₂ = OMe.

The isomeric lactams IV and VI were reduced with lithium aluminum hydride to the corresponding isomeric tertiary bases, IXa and b, characterized as their crystalline hydrobromide salts. There were then prepared samples of the known³ *cis* (Xa) and *trans* (Xb) octahydro-1-pyridines, and these two bases reacted with *m*-methoxyphenylacetyl chloride to give the oily amides (XIa, XIb). Reduction of XIa and XIb with lithium



^a *syn-anti* refers to the 10b-12a relationship; *cis-trans* refers to the 12a-13a ring fusion.

(1) (a) This work was presented in part before the Division of Organic Chemistry, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, Abstracts, p. 39M; (b) M. W. Osborne, M. M. Winbury, and W. M. Govier, *Federation Proc.*, **22**, 308 (1963).

(2) R. L. Detar, G. C. Boxill, and M. M. Winbury, *Ann. Soc. for Pharmacol. Exptl. Therapeutics*, Paper 034, Pharmacology Meeting, August, 1963, San Francisco, Calif.

(3) T. Henshall and E. W. Farnell, *J. Chem. Soc.*, 661 (1962).

TABLE I
 OCTAHYDROBENZO[*a*]CYCLOPENTA[*f*]QUINOLIZINIUM SALTS (VII)

	R ₁	R ₂	R ₃	X	3a-12a stereo.	M.p., °C.	% calcd.			% found			Activity
							C	H	X	C	H	X	
1	OMe	OMe	H	Br	<i>cis</i>	199-201	59.02	6.60	21.82	59.18	6.83	21.67	—
2	HO	HO	H	Br	<i>cis</i>	222-224	56.81	5.96	23.63	56.62	6.20	23.56	±
3	H	OMe	H	Br	<i>cis</i>	210-212	60.71	6.60	23.77	60.54	6.88	23.86	— — —
4	H	OH	H	Br	<i>cis</i>	274-276	59.63	6.26	24.80	59.68	6.04	24.81	+++
5	OMe	OMe	Me	I	<i>cis</i>	212-213	53.40	6.13	29.70	53.68	6.30	29.66	— —
6	OH	OH	Me	Br	<i>cis</i>	243-244	57.96	6.30	22.69	57.93	6.60	22.80	+
7	H	OH	H	Br	<i>trans</i>	276-278	59.63	6.26	24.80	59.57	6.33	25.05	—

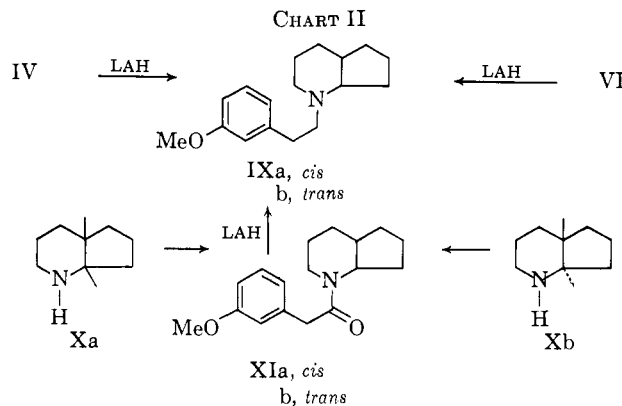
aluminum hydride gave two bases identical in every respect with those prepared from IV and VI.

Saturated derivatives were obtained by reduction of the quaternary salts (VIIa, VIIb) followed by demethylation. Hydrogenation of the *cis* salt VIIa afforded both of the possible epimers of the tertiary base (VIIIa, VIIIb), whereas the *trans* salt VIIb gave only one saturated product (VIIIc). Configurational assignments to the tertiary hydrogens introduced during these hydrogenations are tentative and are based on considerations of reduction product ratios formed under various conditions and on examination of molecular models. Thus, one component of the mixture of *cis* bases is formed predominantly by reduction with sodium in liquid ammonia while metal-acid reduction conditions (Zn-HClO₄) lead solely to the other epimer. These conditions have been equated in related systems⁴ with formation of the more stable and less stable epimers, respectively. Since molecular models show significantly less destabilizing, nonbonded interactions in the *syn-cis* configuration (VIIIa) than in the *anti-cis* structure (VIIIb), the predominant epimer from the sodium reduction was assigned the more stable *syn-cis* configuration, and the product from zinc-perchloric acid reduction was assigned the less stable *anti-cis* configuration.

Reduction of the *trans* salt VIIb gave only one product regardless of the conditions used. This product was assigned the *anti-trans* configuration (VIIIc), rather than the epimeric *syn-trans* configuration on the basis of molecular models which show far less nonbonded interactions in the former configuration.

Infrared and n.m.r. spectra have been obtained on products VIIIa, b, and c. The n.m.r. spectra did not furnish any further data because the tertiary protons at position 10b were lost under the broad methylene peaks. The infrared spectra of products VIIIa and VIIIc, but not of VIIIb, when taken in chloroform solution, showed distinct absorption bands in the 2800-cm.⁻¹ region. These bands are indicative of a *trans* conformation of the quinolizidine ring fusion in the former two products and a *cis* conformation in the latter product. This conclusion is supported by the relative rates of reoxidation of the saturated bases to the quaternary salts with mercuric acetate (more rapid attack by the reagent on the axial hydrogen of VIIIa and VIIIc than on the equatorial hydrogen of VIIIb). Such conformational arguments, however, do not furnish any further information concerning the configurations of the C_{10b} hydrogens since, for each product, both *cis*- and *trans*-quinolizidine conformations are possible.

(4) (a) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954); (b) G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **79**, 495 (1957); (c) A. R. Battersby and S. Garratt, *J. Chem. Soc.*, 3512 (1959); (d) S. De Groot and J. Stratling, *Rec. Trav. Chim.*, **80**, 121 (1961).



Comparison of the results as illustrated in Tables I and II points up the lack of structure-activity relationships evident from the limited number of compounds thus far tested. For example, reduction of the azomethine linkage resulted in loss of activity in the case of phenols (compare compounds 4 and 10, and 2 and 11), but increase in activity for the methyl ethers (3 and 8, and 1 and 9). The effect due to demethylation likewise was ambivalent, increasing activity in the quaternary salts (3 and 4, and 1 and 6) but decreasing it in the reduced bases (8 and 10, and 9 and 11). Introduction of an angular methyl group increased activity in the case of the phenolic quaternary salts (2 and 6), had no effect in the case of the quaternary methyl ethers (1 and 5), and decreased activity in the case of the saturated methyl ethers (9 and 12).

Experimental⁶

Methods.—Antishock activity was determined in anesthetized dogs. Blood pressure was sensed and recorded by usual means. Shock was induced by epinephrine infusions⁵ at the rate of 10 γ /kg./min. for 1 hr. duration. Termination of the infusion produced a rapid fall in blood pressure followed by a stabilization period at low blood pressure levels. Two test substances were administered 30 min. apart at a dose of 500 γ /kg. during this stabilization period. (This was a consistently effective dose of compound 4.) A compound was considered to have activity if it produced an increase in pulse pressure and a rise in blood pressure toward control values. The experiments were terminated by administering compound 4 for a comparative potency evaluation. If it did not prove effective, the animal preparation was considered unresponsive and the data discarded.

A system of scoring was devised with compound 4 indicated as maximally active and given a score of +++. The scoring system is as follows: (a) +++ maximum substance (compound 4); (b) ++ activity approaches reference substance but it not as potent; (c) + mild-moderate activity; (d) \pm questionable activity; (e) — no activity; (f) — — produces further animal deterioration; (g) — — — appears to have a toxic effect on this type of preparation.

(5) R. N. Lewis and M. D. Nickerson, *Proc. Soc. Exptl. Biol. Med.*, **51**, 389 (1942).

TABLE II
 DECAHYDROBENZO[*a*]CYCLOPENTA[*f*]QUINOLIZINE SALTS (VIII)

	R ₁	R ₂	R ₃	X	10b-12a, 3a-12a stereo.	M.p., °C.	% calcd.			% found			Activity
							C	H	N	C	H	N	
8	H	OMe	H	Br	<i>syn-cis</i>	260-262	60.35	7.15	23.62	60.42	7.23	23.91	+
9	OMe	OMe	H	Br	<i>syn-cis</i>	284			21.70			21.64	+
10	H	OH	H	Br	<i>syn-cis</i>	272-274	59.26	6.84	24.65	59.28	6.99	24.85	-
11	HO	HO	H	Br	<i>syn-cis</i>	286-287	56.47	6.52	23.49	56.75	6.67	23.55	- - -
12	OMe	OMe	Me	Br	<i>syn-cis</i>	255-257	59.68	7.38	20.90	59.68	7.48	20.90	- - -
13	H	OMe	H	Br	<i>anti-cis</i>	233-234	60.35	7.15	23.62	60.07	7.32	23.71	+
14	H	OH	H	Br	<i>anti-trans</i>	307-309	59.26	6.84	24.65	59.08	7.03	24.86	+

Cyclopentanone-2-propionic Acid.—Cyclopentanone pyrrolidine enamine and methyl acrylate were condensed according to the procedure of Stork,⁷ and the crude adduct hydrolyzed with dilute hydrochloric acid. The acid, b.p. 111-113° (0.05 mm.), slowly crystallized to a low-melting, waxy solid.

2-Methylcyclopentanone-2-propionic Acid.—2-Methylcyclopentanone⁸ and acrylonitrile were condensed according to the procedure of Frank and Pierle⁹ for 2-methylcyclohexanone. The adduct, b.p. 152-154° (17 mm.), was obtained in 80% yield. Hydrolysis to the acid was carried out by refluxing with 10% NaOH for 4 hr. The acid, b.p. 132-135° (0.2 mm.), was obtained in 70% yield.

Homoveratrylamine was obtained commercially (Eli Lilly and Co.).

***m*-Methoxyphenethylamine.**—*m*-Methoxyphenylacetic acid (Sterling-Winthrop) was converted to the amide by the procedure of Rahman,¹⁰ and this was reduced with lithium aluminum hydride. The amine distilled at 80° (0.25 mm.), *n*_D²⁰ 1.5367.

General Procedure for Preparation of Unsaturated Lactams (III).—A mixture of 0.2 mole each of the amine and the keto acid in 200 ml. of xylene was refluxed under a Dean-Stark trap for 6 hr. The xylene was removed under reduced pressure, and the dark oil was taken up in 200 ml. of chloroform. The chloroform solution was washed with water, 5% sodium bicarbonate solution, 2 *N* hydrochloric acid, and water. It was dried over magnesium sulfate; the chloroform was removed; the residue was distilled.

1,3,4,4a,5,6-Hexahydro-1-(*m*-methoxyphenethyl)-4a-methyl-2H-1-pyridine-2-one (III, R₁ = H; R₂ = OMe; R₃ = Me), b.p. 192-195° (0.08 mm.). This material was cyclized directly.

1,3,4,5,6,7-Hexahydro-1-(3,4-dimethoxyphenethyl)-2H-1-pyridine-2-one (III, R₁ = R₂ = OMe; R₃ = H), b.p. 220-230° (0.75 mm.), m.p. 104-105°.

Anal. Calcd. for C₁₈H₂₃NO₃: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.59; H, 7.94; N, 4.86.

1,3,4,5,6,7-Hexahydro-1-(*m*-methoxyphenethyl)-2H-1-pyridine-2-one (III, R₁ = R₃ = H; R₂ = OMe), b.p. 199-202° (0.25 mm.).

Anal. Calcd. for C₁₇H₂₁NO₂: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.04; H, 8.02; N, 5.07.

General Procedure for Catalytic Hydrogenation of III to IV.—Twenty grams of the unsaturated lactam (III) in 200 ml. of ethanol was shaken over 2.0 g. of 10% palladium-on-carbon catalyst at 3.5 kg./cm.² of hydrogen at room temperature until hydrogen absorption ceased (usually overnight, uptake of hydrogen was ca. 90% of theory). The catalyst and solvent were removed and the residue was used directly for cyclization.

General Procedure for Reductive Condensations B.—A mixture of 0.05 mole each of the amine and of the keto acid in 200 ml. of ethanol was hydrogenated at room temperature and 3.5 kg./cm.² pressure over 3 g. of 10% palladium-on-carbon catalyst. Hydrogen absorption was rapid at first but slowed down later. The reactions were allowed to proceed overnight. Total hy-

drogen uptake was usually 85-90% of theory. The catalyst was filtered and the ethanol was removed under reduced pressure. The residue consisted mostly of the *cis* lactam (IV) and the *trans* amino acid (V), but also contained a small amount of the *cis* amino acid. For this reason, the total residue was taken up in 200 ml. of hot acetonitrile and the solution was refluxed for 15 min. to complete the cyclization of the *cis* amino acid to the lactam. The solution was then cooled in ice and the pure *trans* amino acid was filtered. The filtrate was evaporated to dryness, and the oily residue was partitioned between water and ether. The ether layer was dried and evaporated to obtain the pure *cis* lactam.

***cis*-Octahydro-1-(*m*-methoxyphenethyl)-2H-1-pyridine-2-one (IV, R₁ = R₃ = H; R₂ = OMe).** Crystals from isopropyl ether, m.p. 52°, yield, 62%.

***trans*-2-(β-Carboxyethyl)-N-(*m*-methoxyphenethyl)cyclopentylamine (V, R₁ = R₃ = H; R₂ = OMe).** Crystals from 2-propanol, m.p. 144-145°, yield 25%.

***cis*-Octahydro-1-(3,4-dimethoxyphenethyl)-2H-1-pyridine-2-one (IV, R₁ = R₂ = OMe; R₃ = H).** Crystals from isopropyl ether, m.p. 74-75°, yield, 64%.

***trans*-2-(β-Carboxyethyl)-N-(3,4-dimethoxyphenethyl)cyclopentylamine (V, R₁ = R₂ = OMe; R₃ = H).** Crystals from ethanol, m.p. 153-154°, yield, 22%.

***trans*-Octahydro-1-(*m*-methoxyphenethyl)-2H-1-pyridine-2-one (VI, R₁ = R₃ = H; R₂ = OMe).**—The *trans* amino acid described above, m.p. 144-145°, was melted under N₂ (bath temperature 160°), and maintained above its melting point for ca. 10 min. On cooling, it solidified and melted at 81°. The melting point did not change on recrystallization from isopropyl ether.

General Procedure for Cyclization Reactions (IV, V, VI → VII).—A solution or suspension of the lactam or amino acid in benzene (ca. 10% by weight) was treated with 3 parts by weight of phosphorus oxychloride. The solution was refluxed for 1-2 hr. during which time the solution turned yellow and an oil precipitated. The solvent was evaporated to give an oil which was dissolved in water by warming. The yellow aqueous solution was poured slowly into a mixture of ice-NaOH (5%) solution. The gummy precipitated base was extracted with ether. The dried ether solution was treated with dry hydrogen bromide, and the gummy precipitate was recrystallized from alcohol. The quaternary salts thus prepared are listed in Table I.

General Procedure for Catalytic Reductions (VII → VIII).—A 10% solution of quaternary salt VII in ethanol was hydrogenated over 0.2 g. of platinum oxide at room temperature and 3.5 kg./cm.² pressure. Hydrogen absorption was complete in 5-10 min. The catalyst and solvent were removed to leave a white solid residue. If the starting quaternary salt (VII) was *trans*, this product was homogeneous and was recrystallized directly from methanol to give VIIIc in high yield. If the starting salt was *cis*, the reduction product consisted of mixed VIIIa and VIIIb. In this case, recrystallization of the mixed salt from methanol afforded almost pure VIIIa. After removal of the VIIIa, the filtrate was evaporated to dryness, and the residue was taken up in a small volume of hot ethanol. A small second crop of VIIIa was filtered from the hot solution. On cooling of the ethanol filtrate in a freezer, VIIIb separated slowly. A second recrystallization of the two *cis* salts from methanol and ethanol, respectively, afforded the two epimers in pure form.

Reductions carried out in this way on *cis* quaternary bromides afforded the *syn-cis* and *anti-cis* epimers in ca. 3:1 ratio. If the quaternary perchlorates were used, the ratio was ca. 1:1. The saturated bases thus obtained are listed in Table II.

Zinc Perchloric Acid Reduction of VIIa. Quaternary perchlor-

(6) Melting points were taken on a Fisher-Johns block. Infrared spectra were determined on a Baird Model 455 instrument. Isomeric purities were determined by thin layer chromatography on silica gel using iodine as developing agent. A 1-butanol-acetic acid-water solvent system (5:4:1.5, equilibrated for 48 hr. before use) was used for the basic products; ethyl acetate-acetone mixtures were used for the lactams; and acetone-methanol mixtures for the amino acids.

(7) G. Stork, A. Brizzolara, H. Landesman, J. Szmanski, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(8) J. B. Umland and M. L. Jeffrain, *ibid.*, **78**, 2788 (1956).

(9) R. L. Frank and R. C. Pierle, *ibid.*, **73**, 724 (1951).

(10) A. Rahman, M. Medrano, and O. P. Mittal, *Rec. Trav. Chim.*, **79**, 188 (1950).

ate (2 g., VIIa, $R_1 = R_3 = H$; $R_2 = OMe$, prepared by treating an aqueous solution of the bromide with 10% perchloric acid and recrystallizing the precipitate from ethanol, m.p. 174–175°) was dissolved in 200 ml. of water, and treated over the course of 2 hr. at 90° with 10 g. of zinc dust and 15 ml. of 60% perchloric acid in small portions. The yellow color of the solution faded to a final water-white. Excess zinc was removed by filtration and the filtrate was cooled. The precipitated white solid was filtered, dissolved in a small volume of methanol, and poured into 5% NaOH solution. The base was extracted with ether. The dried ether solution was treated with dry hydrogen bromide and the precipitated salt was recrystallized from ethanol to give 0.5 g. of VIIIb, m.p. 225–228°. This material, by thin layer chromatography, contains none of the higher melting, less soluble *syn-cis* epimer VIIIa.

Sodium-Liquid Ammonia Reduction of VIIa.—A solution of 0.5 g. of quaternary bromide VIIa ($R_1 = R_3 = H$; $R_2 = OMe$) in 10 ml. of methanol was poured into a mixture of ice and 5% NaOH solution. The precipitated base was extracted with 100 ml. of ether, and the dried ether layer was added to a mixture of 400 ml. of liquid ammonia and 10 ml. of *t*-butyl alcohol. The resulting clear solution was treated with stirring at reflux (–33°) with very small pieces of clean sodium until the solution turned blue (3 min.). Methanol (5 ml.) was then added immediately to discharge the blue color (to avoid Birch reduction of the aromatic ring). The ammonia was allowed to evaporate, 20 ml. of water was added, and the ether phase was separated and dried. Thin layer chromatography of this solution showed a major spot for the *syn-cis* epimer VIIIa, R_f 0.40, and a very weak spot (R_f 0.44) corresponding to the *anti-cis* epimer VIIIb.

***cis*- and *trans*-1-(*m*-Methoxyphenylacetyl)-octahydro-1-pyridine (XI).**—A solution of 13.65 g. (0.075 mole) of *m*-methoxyphenylacetic acid and 20 ml. of thionyl chloride in 200 ml. of benzene was refluxed for 1 hr., then concentrated to a yellow oil under reduced pressure. The oil was dissolved in 50 ml. of benzene and added dropwise at 0° with rapid stirring to a mixture of 7.5 g. (.059 mole) of the octahydro-1-pyridine, 45 ml. of benzene and 48 ml. of 12% NaOH solution. After stirring overnight at room temperature, the benzene layer was separated, washed with

5% NaOH solution, water, 2 *N* HCl, and water. The solution was dried and concentrated to 16 g. of an orange oil.

Prepared as above from reportedly "pure" *cis*- and *trans*-octahydro-1-pyridines, the total crude XIa and XIb both showed 2 clear spots by thin layer chromatography (R_f 0.8 and 0.9; solvent ethyl acetate), the faster of which was the major spot in the *trans* compound and the slower of which was the major spot in the *cis* compound. Extensive chromatography on alumina (Merck neutral) afforded pure samples of both amides. Both products were eluted with ether, the *trans* compound came off the column first. From this work, it was estimated that the reportedly pure *trans*-octahydro-1-pyridine actually contained ca. 10% of the *cis*, and the reportedly pure *cis* base contained ca. 25% of the *trans* isomer.

Lithium Aluminum Hydride Reductions of Amides IV, VI, XIa, and XIb.—The amide in ether was treated with excess lithium aluminum hydride and the mixture was stirred overnight. The reaction mixture was decomposed cautiously by the slow addition of the minimum amount of water. After stirring for several hours, the granular white slurry was filtered, and the filtrate was treated with dry hydrogen bromide. The precipitated salt was filtered and recrystallized from 2-propanol. The IXa hydrobromides (*cis*) prepared from IV and Xa were identical by melting point (153–154°), infrared spectrum, and thin layer chromatography. The IXb hydrobromides (*trans*) prepared from VI and Xb were identical by the same criteria (m.p. 169–170°).

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Notes

Reaction of 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-Oxide with Dimethylamine

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The reaction of 2-chloromethyl-4-phenylquinazoline 3-oxides with amines has been the subject of considerable recent study.^{1–5} Both Sternbach, *et al.*,² and Bell⁵ have reported that reaction of 2-chloromethyl-4-phenylquinazoline 3-oxides with secondary amines gives only the "normal" quinazoline product in which the chloro atom was replaced by the secondary amine. We have confirmed this simple replacement when 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide was allowed to react with either diethylamine or piperidine. On the other hand, when the secondary amine employed was dimethylamine, two reaction products

were obtained. The simple replacement product, 6-chloro-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide (II),¹ and the rearranged product, 7-chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide, (III) were both obtained.

To prove the structure of III, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IV)¹ was methylated with sodium hydride and methyl iodide; III resulted in 83% yield.

A similar alkylation procedure converted 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (V)¹ to 7-chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine (VI). The latter compound was also prepared by deoxygenation of III. The spectral properties of III were markedly similar to IV but dissimilar to I and II.^{2,6}

N-Alkylation of IV was also carried out with sodium hydride and benzyl chloride, allyl bromide, and methoxymethyl chloride. Cyclohexyl bromide, cyclohexyl iodide, propargyl bromide, ethyl bromoacetate, and ethyl chloroacetate failed to give the desired N-alkylated product.

(1) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

(2) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(3) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *ibid.*, **26**, 4488 (1961).

(4) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(5) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).

(6) The ultraviolet spectrum of IV as reported⁷ could be reproduced in 95% ethanol. It was found that the six-membered ring structure could be differentiated from the seven-membered ring structure easily if the spectra were determined by solution of the compound in 5 ml. of 95% ethanol diluted to 50 ml. with 0.1 *N* HCl.

(7) L. H. Sternbach, B. A. Koehlin, and E. Reeder, *J. Org. Chem.*, **27**, 4671 (1962).