action mixture was not hydrolyzed. Instead, the volatile materials were removed by a high vacuum trap-to-trap distillation and analyzed by glpc. A 78% yield (*cis/trans* ratio = 2.2) of 7-bromonorcarane was obtained. In still another such experiment carried out on a 0.05-mole scale the reaction mixture was quenched with D_2O. Trap-to-trap distillation at reduced pressure of the dried organic layer followed. The 7-bromonorcarane isomers (*cis/trans* ratio = 2.32) obtained in 73.3% yield were isolated by glpc. Their infrared spectra showed no bands attributable to C–D bonds, and analysis for deuterium content by the falling-drop method (J. Nemeth, Urbana, Ill.) showed that no deuterium had been incorporated. A similar reaction mixture was quenched with trimethylchlorosilane and hydrolyzed with saturated ammonium chloride. Distillation and glpc analysis of the organic layer showed the presence of only two components, *cis*- and *trans*-7-bromonorcarane (2.4:1 ratio) in 78% yield. No higher boiling organosilicon compounds could be detected.

Reaction of 7,7-Dibromonorcarane with CD_3MgI in THF.—The Grignard reagent was prepared from 0.036 mole of trideuteriomethyl iodide[13] in 25 ml of THF under argon. 7,7-Dibromonorcarane (0.036 mole) was added with vigorous stirring. The reaction mixture was stirred at room temperature (after the initial exotherm) for 2.5 hr and then was quenched with D_2O. The usual work-up procedure gave 7-bromonorcarane in 75% yield, $n^{25}D$ 1.5094, *cis/trans* ratio = 2.44. Infrared analysis showed no C–D bands, and analysis for deuterium by the falling-drop method demonstrated that no deuterium had been introduced.

Preparation of 1-Bromo-2-*n*-amylcyclopropane.—1,1-Dibromo-2-*n*-amylcyclopropane (13.5 g, 0.05 mole) was added slowly with stirring to 0.05 mole of CH_3MgBr in 30 ml of THF at room temperature under a nitrogen atmosphere. Some 15 min after completion of the addition, a vigorous, exothermic reaction occurred and solid was precipitated. The reaction mixture was stirred at room temperature for 2 hr, then was hydrolyzed with 10% hydrochloric acid. The dried organic layer was distilled *in vacuo* into a receiver at −78° and analyzed by glpc (isothermal, 20% SE-30 on Chromosorb W, at 172°, 15 psi of helium, *n*-dodecane external standard). The presence of 1-bromo-2-*n*-amylcyclopropane (75.3%) was demonstrated. The *cis/trans* ratio was 2.6. The combined isomers were analyzed.

Anal. Calcd for $C_8H_{15}Br$: C, 50.26; H, 7.85; Br, 41.88. Found: C, 50.42; H, 7.80; Br, 41.70.

trans-1-Bromo-2-*n*-amylcyclopropane, $n^{25}D$ 1.4579, had the shorter glpc retention time. Its nmr spectrum (CCl_4) showed a complex multiplet from 0.91 to 1.35 ppm and a quintet (J = 4.0 cps) centered at 2.5 ppm.

cis-1-Bromo-2-*n*-amylcyclopropane, $n^{25}D$ 1.4636, showed doublets at 0.98 and 1.4 ppm and a sextet (J = 7.5 cps) centered at 3.0 ppm.

Acknowledgments.—The authors are grateful to the National Science Foundation and to the Alfred P. Sloan Foundation for generous support of this work.

(13) F. A. Cotton, J. H. Fassnacht, W. D. Horrocks, Jr., and N. A. Nelson, *J. Chem. Soc.*, 4138 (1959).

Cyclic Aminimides

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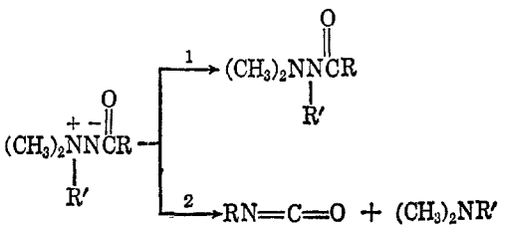
Received December 2, 1965

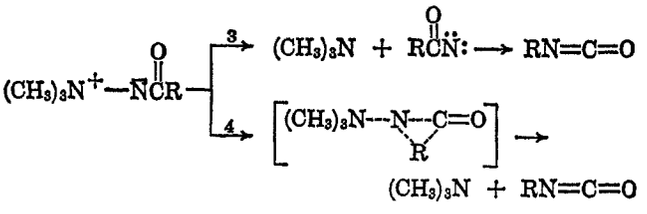
The preparation and reactions of cyclic aminimides of the type shown (A) are described. When R is benzyl a Wawzonek rearrangement takes place with the benzyl group migrating to the adjacent nitrogen atom. However, when R is methyl neither migration nor a Curtius N–N cleavage as observed in the acyclic case occurs. The possible implications of this result as applied to the mechanism of isocyanate formation is briefly discussed.

Recently aminimides which have their negative charge delocalized by means of an adjacent carbonyl group have been investigated and found to possess unusual chemical properties. Wawzonek and Yeakey[1] have found that compounds of this class, where R′ is benzyl or allyl, when heated undergo a Stevens-type rearrangement (1). Gibson and Murray,[2] on the other hand, have shown that when R′ is an alkyl group other than benzyl or allyl, N–N bond cleavage results to yield an isocyanate and tertiary amine (2), a result

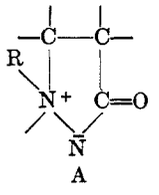


which has recently been confirmed by Wawzonek and Gueldner.[3] Isocyanate formation is of particular interest and can be assumed like the Curtius rearrangement to proceed by either a nitrene (3) or concerted pathway (4).

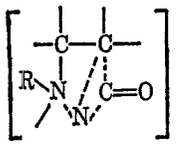
(1) S. Wawzonek and E. Yeakey, *J. Am. Chem. Soc.*, **82**, 5718 (1960).
(2) M. S. Gibson and A. W. Murray, *J. Chem. Soc.*, 880 (1965).
(3) S. Wawzonek and R. C. Gueldner, *J. Org. Chem.*, **30**, 3031 (1965).



A cyclic aminimide (structure A designated below)



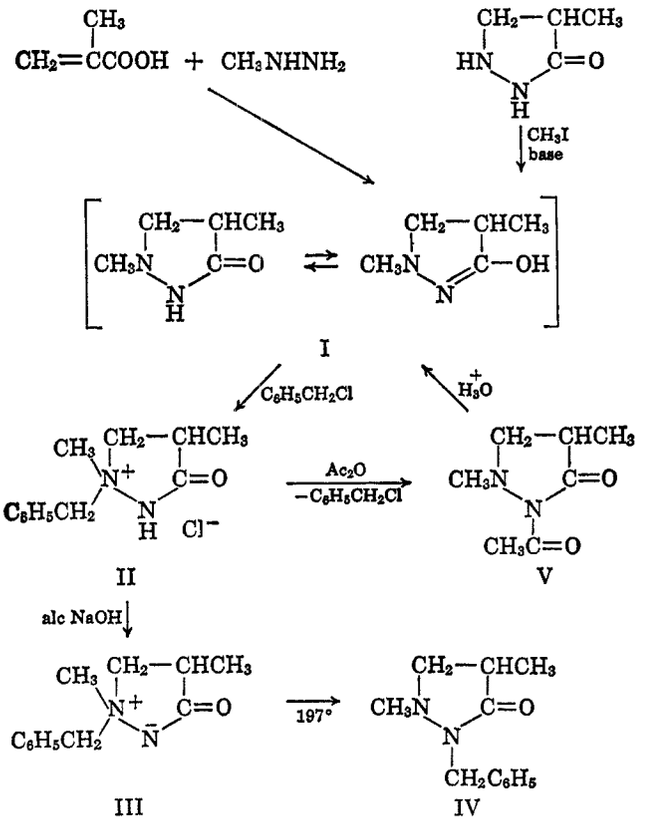
would be expected to give similar rearrangements, a Wawzonek rearrangement if a benzylic substituent is present, and, if nitrene is an intermediate and R is methyl, a β-amino isocyanate. If on the other hand, nitrene is not an intermediate in isocyanate formation, it is doubtful that isocyanate would be formed in the cyclic case. A bicyclic transition state (i) would be required for a concerted mechanism which in all probability would possess a high energy of activation. To test these hypotheses, a cyclic aminimide (III) was



i

prepared by quaternizing 1,4-dimethyl-3-pyrazolidinone (I) with benzyl chloride followed by treatment with alcoholic NaOH (Scheme I).

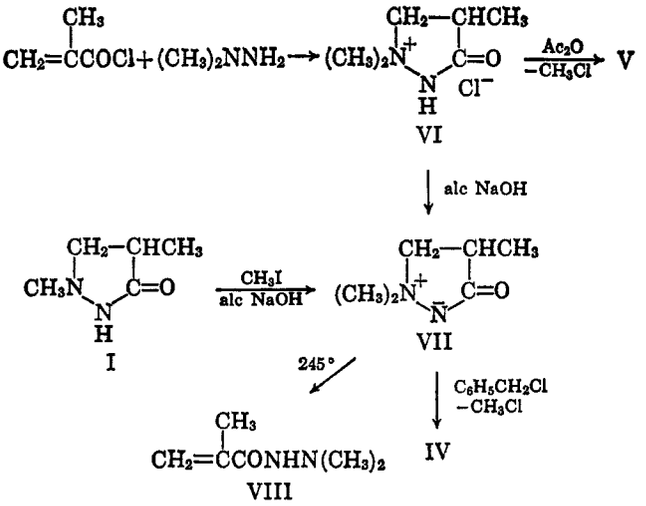
SCHEME I



The previously unreported precursor I was prepared by heating methacrylic acid with methylhydrazine. An identical product was obtained by methylating 4-methyl-3-pyrazolidinone, a result which indicated that the 1-methyl isomer and not the 2-methyl isomer was obtained from the methacrylic acid–methylhydrazine reaction. The infrared spectrum of I showed a strong and broad OH band at 3150 cm^{-1}, a strong band at 1670 cm^{-1}, and no absorption between 1490 and 1590 cm^{-1}, characteristic of monosubstituted amides, evidence which indicates that I exists primarily in the enol form. The intermediate chloride II, when warmed with acetic anhydride, smoothly underwent dealkylation with the loss of benzyl chloride. The product, 2-acetyl-1,4-dimethyl-3-pyrazolidinone (V), is undoubtedly an excellent leaving group as evidenced by its complete lack of basicity. When III was heated just above its melting point (197°) a smooth Wawzonek rearrangement took place to give a nearly quantitative yield of 1,4-dimethyl-2-benzyl-3-pyrazolidinone (IV). The infrared spectrum of the crude product indicated the absence of isocyanate.

In a further attempt to apply the isocyanate synthesis to a cyclic system, the cyclic aminimide VII was prepared (Scheme II). The quaternization of 1,4-dimethyl-3-pyrazolidinone (I) with methyl iodide

SCHEME II



followed by base gave VII. A more efficient procedure consisted of treating methacrylyl chloride with *unsym*-dimethylhydrazine in alcohol followed by neutralization, a variation of a previously reported procedure in which the product was erroneously reported as 1-dimethylamino-3-methylazetidin-2-one, a β-lactam.[4] The hydrochloride of 1-methacrylyl-2,2-dimethylhydrazine (VIII) was obtained as a by-product. Treatment of VII with benzyl chloride gave concurrent loss of methyl chloride to give IV, the product obtained previously from the Wawzonek rearrangement. Upon warming with acetic anhydride, the chloride salt VI smoothly lost methyl chloride to yield V. The cyclic aminimide VII when heated above its melting point (245°) did not undergo N–N cleavage to an isocyanate as in the noncyclic case, but underwent ring opening to give VIII in an essentially quantitative yield.

The anomalous result, lack of isocyanate formation, in the case of the cyclic aminimide VII gives support to the possibility that isocyanate formation with noncyclic aminimides proceeds *via* a concerted mechanism and not *via* a nitrene. In this regard it has been recently suggested that the Curtius rearrangement of pivaloyl azide when carried out thermally does not proceed *via* a nitrene.[5]

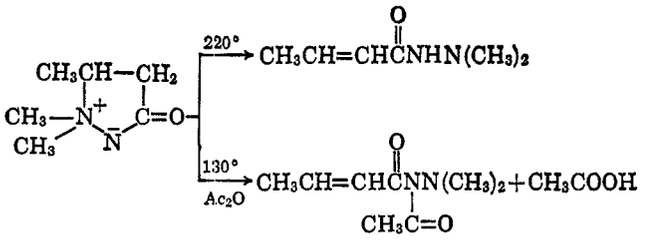
The addition of crotonyl chloride to an alcoholic solution of *unsym*-dimethylhydrazine also gave a cyclic salt from which a cyclic aminimide (IX) could be isolated by treatment of the salt with base. As in the previous case, ring opening occurred when IX was heated above its melting point. Ring opening was strongly catalyzed by benzaldehyde probably due to initial addition of aldehyde to the negatively charged nitrogen atom followed by proton elimination at the 4 position. No reaction took place when a 25% solution of IX in dimethylformamide was heated to 180°. A similar pathway would account for the products which resulted when IX was warmed with acetic anhydride (Scheme III).

Experimental Section[6]

1,4-Dimethyl-3-pyrazolidinone.—Methacrylic acid (17.2 g) was added slowly to methylhydrazine (9.2 g) with stirring. After the

(4) T. A. Sokolova and L. A. Ovsyannikoua, *Dokl. Akad. Nauk SSSR*, **143**, 140 (1962).
(5) W. Lwowski and G. T. Tisue, *J. Am. Chem. Soc.*, **87**, 4022 (1965).
(6) Melting points are corrected and boiling points are not.

SCHEME III



initial exotherm had subsided, the mixture was distilled to give 19.50 g of slightly yellow liquid, bp 138° (15 mm). The infrared spectrum showed a broad band at 3200 cm^{-1} and carbonyl absorption at 1690 cm^{-1}. There was no absorption between 1460 and 1600 cm^{-1}.

Anal. Calcd for $C_6H_{10}N_2O$: C, 52.63; H, 8.77; N, 24.56. Found: C, 52.35; H, 8.61; N, 24.74.

4-Methyl-3-pyrazolidinone[7] (10 g) was treated with excess methyl iodide. After standing overnight a gummy precipitate had formed which was dissolved in water. The aqueous solution was made basic with dilute NaOH and stripped under reduced pressure. The semicrystalline residue was distilled to give 7.4 g of straw yellow liquid, bp 138° (15 mm). The infrared spectrum of the distillate was identical with that of 1,4-dimethyl-3-pyrazolidinone obtained from methacrylic acid and methylhydrazine.

1-Benzyl-1,4-dimethyl-3-oxopyrazolidinium Hydroxide Inner Salt (III).—Benzyl chloride (25.2 g) was added slowly with stirring to 1,4-dimethyl-3-pyrazolidinone (22.8 g). The addition which was exothermic required ice-bath cooling. The dark semicrystalline mixture was recrystallized twice from ethanol to give a white crystalline product (19.6 g). The acidity, pK_a = 2.8, of the salt (half-neutralization pH) was typical of that generally found for quaternized 1-alkyl-3-pyrazolidinones. The salt was dissolved in 100 ml of methanol and the solution was treated with a saturated solution of sodium hydroxide in methanol until just basic. The mixture was filtered and solvent was removed from the filtrate to give a crystalline residue which was recrystallized twice from acetonitrile (10.2 g), mp 183–184°. The infrared spectrum showed a broad band at 1580 cm^{-1} which is typical of aminimides.[3]

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.58; H, 7.84; N, 13.72. Found: C, 70.39; H, 7.92; N, 13.61.

2-Acetyl-1,4-dimethyl-3-pyrazolidinone (V).—A mixture of the quaternary salt II (18.5 g) and acetic anhydride (20.4 g) was heated with stirring at 135° for 2 hr. The solution which resulted gave upon distillation benzyl chloride (3.5 g) and a colorless liquid product (8.7 g), bp 128° (15 mm). The product could not be titrated with 0.1 *N* perchloric acid in glacial acetic acid using glacial acetic acid as solvent. The infrared spectrum showed strong carbonyl absorption at 1700 and 1740 cm^{-1}.

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.84; H, 7.69; N, 17.94. Found: C, 53.66; H, 7.63; N, 18.08.

A portion of the liquid product (5.0 g) was added to 10 ml of concentrated HCl and the mixture refluxed for 12 hr. After neutralization with aqueous NaOH and removal of solvent, a liquid product, bp 138° (15 mm), 2.15 g, was obtained having an infrared spectrum identical with that of 1,4-dimethyl-3-pyrazolidinone.

2-Benzyl-1,4-dimethyl-3-pyrazolidinone (IV).—The cyclic aminimide III (5.0 g) was heated at 190° for 6 hr. The liquid product when distilled gave a colorless liquid (4.8 g), bp 110° (0.2 mm). The infrared spectrum showed strong carbonyl absorption at 1680 and a medium band at 1600 cm^{-1}. There was no NH or OH absorption.

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.72. Found: C, 70.63; H, 7.93; N, 13.59.

1,1,4-Trimethyl-3-oxopyrazolidinium Hydroxide Inner Salt (VII).—Methyl iodide (28.2 g) dissolved in 50 ml of benzene was added to a solution of 1,4-dimethyl-3-pyrazolidinone dissolved in 100 ml of benzene. The solution while standing for 12 hr slowly deposited a crystalline precipitate which after isolation was recrystallized from ethanol (24.83 g), pK_a = 3.0. The salt was dispersed in 100 ml of methanol, and the mixture was treated with a saturated solution of sodium hydroxide in methanol until just basic. The crystalline residue obtained by stripping the solution under reduced pressure was recrystallized twice from acetonitrile to give a white hygroscopic crystalline product (10.2 g), mp 245°. The infrared spectrum showed strong absorption at 1580 cm^{-1}.

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.31; H, 9.37; N, 21.85. Found: C, 56.07; H, 9.20; N, 21.88.

The salt, in this case the hydrochloride, from which the aminimide VII could also be prepared was formed by adding methacrylyl chloride (52.5 g) to an alcoholic solution of *unsym*-dimethylhydrazine at 40–50°. During the addition the hydrochloride VI precipitated and was removed by filtration (52 g). The cyclic aminimide was prepared from the salt exactly as described above for the iodide. The alcoholic filtrate obtained by removal of the salt was treated with a saturated solution of sodium hydroxide in methanol until basic and suction filtered, and the filtrate was stripped at reduced pressure to give a gummy residue which crystallized on standing. The product was recrystallized twice from dimethylformamide to give 1,1-dimethyl-2-methacrylylhydrazine[4] (13.5 g), mp 70–71°. The infrared spectrum showed carbonyl absorption at 1670, double-bond absorption at 1630, and amide absorption at 3200 and 1540 cm^{-1}.

2-Acetyl-1,4-dimethyl-3-pyrazolidinone from VI.—A mixture of the chloride VI (8.2 g) and acetic anhydride (10.2 g) when gently refluxed evolved methyl chloride which was condensed in a trap placed in a Dry Ice–acetone bath. The identity of the methyl chloride was established by comparing its infrared spectrum to that of an authentic sample. After a 2-hr reflux period the acetic anhydride solution was distilled to give a clear liquid distillate (4.9 g), bp 128° (15 mm). The infrared spectrum of the distillate was identical with that of 2-acetyl-1,4-dimethyl-3-pyrazolidinone.

2-Benzyl-1,4-dimethyl-3-pyrazolidinone from VII.—The cyclic aminimide VII (12.8 g) and benzyl chloride (12.6 g) were added together and the mixture was heated at 130° for 48 hr. The evolved gas which proved *via* infrared to be methyl chloride was collected in a trap placed in a Dry Ice–acetone bath. After the heating period the mixture was distilled to give a colorless liquid (6.0 g), bp 110° (0.2 mm). The identity of the product was established from its infrared spectrum. A viscous black residue remained from the distillation.

Pyrolysis of Cyclic Aminimide VII.—The cyclic aminimide VII (10 g) when heated at 260° at 30 mm gave a distillate (7.8 g) which solidified on cooling. The product which was recrystallized from dimethylformamide, mp 70–71°, gave an infrared spectrum identical with that of 1,1-dimethyl-2-methacrylylhydrazine. A mixture melting point was undepressed.

1,1,5-Trimethyl-3-oxopyrazolidinium Hydroxide Inner Salt (IX).—Crotonyl chloride (52.25 g) was added dropwise at 30–40° to a solution of *unsym*-dimethylhydrazine dissolved in 100 ml of ethanol. The precipitate was removed by filtration and recrystallized from ethanol yielding 53.45 g. Titration of a portion of the product with 0.1 *N* NaOH gave an equivalent weight of 163 (calcd 164), pK_a = 2.8.

The salt (16.4 g) was placed in 50 ml of methanol and the slurry was treated with a saturated solution of NaOH in methanol until just basic. The mixture was filtered and the filtrate was stripped under reduced pressure to give a white crystalline product which was recrystallized from acetonitrile, 6.8 g, mp 220°. The infrared spectrum showed typical aminimide absorption at 1580 cm^{-1}.

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.31; H, 9.37; N, 21.85. Found: C, 56.12; H, 9.40; N, 21.60.

1,1-Dimethyl-2-crotonylhydrazine.—The cyclic aminimide IX (12.8 g) was heated at 225° until it had become a homogeneous liquid. The crystalline product obtained upon cooling was recrystallized from *n*-hexane to give a white crystalline product (10.5 g), mp 70–71°. The infrared spectrum showed medium to strong characteristic absorption at 3120, 1670, 1620, and 1540 cm^{-1}.

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.31; H, 9.37; N, 21.85. Found: C, 56.35; H, 9.41; N, 21.96.

The identical product, *via* infrared, was obtained by heating IX (12.8 g) with benzaldehyde (10.6 g) at 130° for 24 hr. Removal of the benzaldehyde at reduced pressure gave a viscous residue which crystallized on standing. The product was recrystallized from *n*-hexane to give a white crystalline product (8.0 g), mp 70–71°, mixture melting point undepressed.

1,1-Dimethyl-2-acetyl-2-crotonylhydrazine.—The cyclic aminimide IX (12.8 g) was added to acetic anhydride (10.2 g) and the mixture was heated at 120° for 48 hr. The homogeneous solu-

(7) T. Lieser and K. Kemmner, *Chem. Ber.*, **84**, 4 (1951).

tion which resulted was distilled after removal of volatile by-products to give a colorless liquid (8.30 g), bp 88–90° (13 mm). An identical product (2.2 g), *via* infrared, was obtained by warming at 110° for 5 hr a mixture of 1,1-dimethyl-2-crotonylhydrazine (2.56 g) and acetic anhydride (2.04 g). The infrared spectrum showed no NH absorption, strong absorption at 1700, and medium absorption at 1620 cm^{-1}. The diacylhydrazine was nonbasic, a characteristic of this class of compounds.

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.47; H, 8.23; N, 16.47. Found: C, 56.51; H, 8.21; N, 16.29.

Hydrobenzo[*b*]quinolizines. I. The Synthesis and Stereochemistry of Perhydrobenzo[*b*]quinolizines and Related Compounds[1,2]

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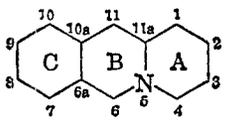
Received December 10, 1965

An approach to the synthesis of perhydrobenzo[*b*]quinolizine derivatives which starts from tricyclic aromatic compounds is described. Birch reduction of **9** afforded diene **8**, and strong acid hydrolysis gave a monophenol (**10**). Methylation of the phenol gave a methyl ether (**11**), and oxidation of the methyl ether yielded 4-methoxyphthalic acid. The latter sequence and nonidentity of the monophenol with **16** supported assignment of structure **10**. Mild acid hydrolysis of **8** gave a mixture of unsaturated ketones (**13** and **18**), and hydrogenation of the mixture afforded the diol monoether **19**. Birch reduction of **17** gave diene **20**, and mild acid hydrolysis afforded ketones **21** and **24**. Hydrogenation of the ketone mixture gave alcohol **22** and chromium trioxide oxidation of the alcohol gave the saturated ketone **25**. Birch reduction of **26** gave the diene **27**. Catalytic hydrogenation of **27** yielded **29**, and hydroxylation of the latter compound with 1 molar equiv of hydrogen peroxide in formic acid gave the diol **30**. An alternate preparation of **30** consisted of prior hydroxylation of **27** to **31**, followed by hydrogenation. Hydroxylation of **27** with excess hydrogen peroxide in formic acid yielded the tetrol **28**.

The perhydrobenzo[*b*]quinolizine (1,3,4,6,6a,7,8,9,10,-10a,11,11a-dodecahydro-2H-benzo[*b*]quinolizine) ring system (**1**) occurs in clinically useful hypotensive alkaloids of both the *Veratrum* [*e.g.*, protoveratrine A (**2**)] and *Rauwolfia* [*e.g.*, reserpine (**3**)] series. In each alkaloidal type, the ring designated C in **1** bears several oxygenated substituents. Only two simple derivatives of system **1** appear to have been described to date: **4**, synthesized as a model compound for the construction of the C–D–E ring skeleton of yohimbine,[3] and **5**, synthesized as a precursor of *dl*-alloyohimbane.[4]



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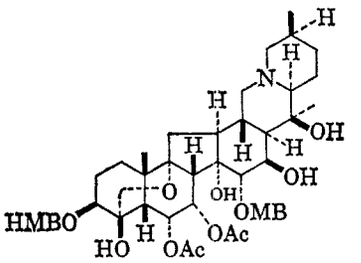
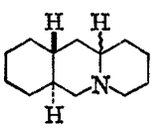


HMB = (+)-2-hydroxy-2-methylbutyryl
MB = (−)-2-methylbutyryl

2



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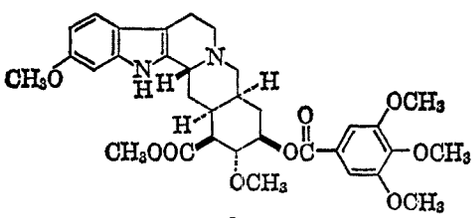

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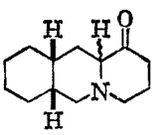

5

We describe herewith the first of a series of studies of synthetic approaches to perhydrobenzo[*b*]quinolizine derivatives. It is hoped that such synthetic sequences may lead ultimately to alkaloid analogs with enhanced or more specific pharmacological properties.

In the present work, an approach to derivatives of **1** which starts from known tricyclic aromatic compounds was selected. It was anticipated that selection of suitably substituted aromatic precursors might allow for the control of the stereochemistry during the reduction steps and facilitate the introduction of desired substituent groups. Several routes for the synthesis of 1,3,4,6,11,11a-hexahydro-8,9-dimethoxy-2H-benzo[*b*]-quinolizine (**9**) have been described previously.[5–7] Sugimoto proceeded *via* 2-pyridyl-3,4-dimethoxyphenylcarbinol, prepared by treatment of 3,4-dimethoxybenzaldehyde with 2-pyridylmagnesium bromide.[4] We found that a better yield of the carbinol (65%) could be obtained by use of 2-pyridyllithium in place of the Grignard reagent. Reduction of the carbinol to 2-piperidyl-3,4-dimethoxyphenylmethane was accomplished best with sodium and 1-butanol, and conversion to **9** was effected by treatment of the hydrochloride with formaldehyde under Pictet–Spengler reaction conditions. A modification of the approach of Bradsher and Dutta[7] *via* 8,9-dimethoxyacridizinium bromide (**7**) proved to be more satisfactory for the large-

(1) This investigation was supported, in part, by Public Health Service Research Grant No. HE-02275 from the National Heart Institute. The work was presented, in part, at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 9–13, 1963, Abstracts, p 35-O.

(2) All asymmetric synthetic products described are racemic mixtures. Only one optical antipode for each is drawn for convenience of representation and discussion. In the representation of the quinolizidine derivatives, the electron pair on nitrogen is understood to project downward, and a heavy-line bond to the 11a hydrogen indicates the *trans*-quinolizidine configuration.

(3) E. E. van Tamelen, D. L. Hughes, and C. W. Taylor, *J. Am. Chem. Soc.*, **78**, 4625 (1956).

(4) R. T. Rapala, E. R. Lavagnino, E. R. Shepard, and R. Farkas, *ibid.*, **79**, 3770 (1957).

(5) N. Sugimoto, *J. Pharm. Soc. Japan*, **76**, 1045 (1956).

(6) C. Tani and K. Ishibashi, *ibid.*, **76**, 1064 (1956).

(7) C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960).