disproportionation reaction and R_2Mg as the active reducing agent. Under these assumptions, reduction by RMgOR′ is minor under the usual preparative conditions for the Grignard reaction. If the rate of the "first stage" reaction (equation 5) is very rapid with respect to the "second stage" reaction (equation 6), then the speed of the disproportionation reaction needs to be fast only with respect to the over-all time of the reaction in order to explain the data in Table I.

The present conclusions apply only to the *reduction reaction* of the Grignard and dialkylmagnesium reagents and are in accord with our previous finding[8] that the nature of the halogen atom in the Grignard reagent has only a slight effect on the reduction reaction. The extent to which these ideas apply to the Grignard *addition reaction* is not known. Anteunis[9] has concluded that R_2Mg cannot be the active species in the addition reaction of the methyl Grignard reagent to benzophenone because of the observed kinetics and because only one of the two methyl groups in the dimethylmagnesium reacted. Because of the variations in the yields of addition products with different halogens of the Grignard reagent, we had previous postulated[8] that the Grignard addition reaction involved the halogen atom in the transition state. Addition takes place with pure dialkylmagnesium even more rapidly than with the Grignard reagent[9,10] and thus it would appear that there may be more than one mechanism for the addition reaction. In any event prior conclusions must be re-evaluated in the light of this postulated disproportionation reaction (equation 7).

This postulated disproportionation reaction (equation 7) adds another parameter to the variables in the Grignard reaction. It is possible that magnesium halide acts as a catalyst for this reaction which probably varies widely with the nature of the Grignard reagent. An application of this disproportionation concept may be able to rationalize the $R_2Mg \cdot MgX_2$ structure for the Grignard reaction with the many facts of the Grignard reaction now known.

(8) D. O. Cowan and H. S. Mosher, *J. Org. Chem.*, **27**, 1 (1962).
(9) M. Anteunis, *ibid.*, **27**, 596 (1962).
(10) J. G. Aston and S. A. Bernhard, *Nature*, **165**, 485 (1950).
(11) B. F. Landrum and C. Lester, *J. Am. Chem. Soc.*, **74**, 4954 (1952).
(12) R. H. Eastman, *ibid.*, **79**, 4243 (1957).

Experimental

Grignard from (+)-2-Methylbutyl Chloride.—The Grignard reagent from 123 g. (1.2 moles) of (+)-2-methyl-1-chlorobutane, $\alpha^{25}D$ +1.40° (1 dm., neat, 97% optically pure) and 31.6 g. (1.3 moles) of magnesium was prepared in 1 l. of anhydrous ether. The solution was allowed to settle and then decanted under nitrogen into a storage flask; titration indicated at 94% yield.

(+)-Di(2-methylbutyl)magnesium.—To 600 ml. (0.66 mole) of the Grignard reagent, prepared from the same (+)-2-methylbutyl chloride in ether, was added with stirring 76 g. (0.86 mole) of dioxane over a period of 4 hr. under a nitrogen atmosphere. After stirring for 24 hr. the mixture was transferred under nitrogen to centrifuge tubes which were capped and centrifuged. The supernatant solution was transferred to a graduated storage vessel; titration indicated an 80% yield of dialkylmagnesium compound.

Reaction of (+)-Di(2-methylbutyl)mgnesium with Methyl *t*-Butyl Ketone and Acetaldehyde.—To 275 ml. of an ether solution containing 0.205 equivalent (0.75 *N*) of (+)-di(2-methylbutyl)-magnesium was added over a 45-min. period 10 g. (0.1 mole) of methyl *t*-butyl ketone in 45 ml. of ether. After stirring for 6 hr. at room temperature 4.4 g. (0.1 mole) of freshly distilled acetaldehyde dissolved in 45 ml. of ether was added over a 45-min. period. After standing overnight the slightly turbid reaction mixture was hydrolyzed by the slow addition of a minimum amount of water. The ether solution was decanted from the crystalline precipitate of magnesium salts[11] and most of the ether removed by distillation through a 15-plate column. The residue was chromatographed using an Aerograph A-90-C gas chromatograph. The 150-cm. column was packed with Ucon Polar on firebrick. Each component was identified by comparison of retention times with authentic samples and by infrared spectrometric analysis of fractions trapped at the proper time from the effluent of the chromatograph. The percentage yields, 16% enolization, 28% reduction, and 56% condensation, were calculated from weight per cent as determined from the chromatogram.[12]

The reduction and condensation products were isolated using a Beckman Megachrome preparative gas chromatograph. The high boiling material proved to be the condensation product, 2,2,5,6,6-pentamethyl-4-hepten-3-one, $n^{20}D$ 1.4469, 2,4-dinitrophenylhydrazone; m.p. 147–148.5°. 2,2,5,6,6-Pentamethyl-4-hepten-3-one is reported to have the following properties, $n^{23}D$ 1.4500, 2,4-DNP, m.p. 147–148°.[13] The reduction product, methyl-*t*-butylcarbinol had the properties, $\alpha^{20}D$ +0.70 (1 dm., neat), acid phthalate $[\alpha]^{20}D$ 8.02° ($\alpha^{20}D$ +0.80°, *c* 9.97, $CHCl_3$, l = 1 dm.), m.p. 84.1–85.8°.

A second reaction, conducted exactly as the first except that the order of adding methyl *t*-butyl ketone and acetaldehyde was reversed, gave the results summarized in Table I. A third and fourth reaction using the Grignard reagent instead of the dialkylmagnesium compound, were carried out in the same manner with the results shown in Table I.

(13) P. D. Bartlett, *ibid.*, **76**, 2349 (1954).

Ambelline

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Degradative evidence is presented to show that ambelline possesses the stereo structure III (R = OH, R′ = H).

In one of our earliest isolation studies, we reported the occurrence of ambelline in *Amaryllis belladonna*.[2] Since that time, it has been detected in several other genera of the Amaryllidaceae, particularly in the *Nerine* spp.[3–5] Ambelline was characterized as a tertiary base, $C_{18}H_{21}NO_5$, with the oxygen atoms contained in two methoxyl groups, one methylenedioxy group, and one hydroxyl. Catalytic hydrogenation provided a single dihydro derivative.[2,6] One

(1) (a) Visiting Fellow, National Heart Institute, 1962; (b) Visiting Scientist, National Heart Institute, 1958–1959; (c) present address: Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa.

(2) L. H. Mason, E. R. Puschett, and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 1253 (1955).

(3) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 2093 (1956); **90**, 369 (1957).

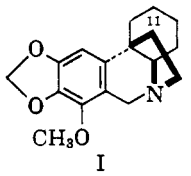
(4) H.-G. Boit, *ibid.*, **89**, 1129 (1956).

(5) R. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 2620 (1959).

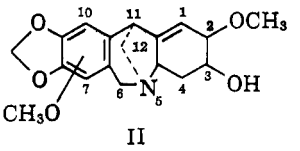
(6) An identical characterization was reported by J. Renz, D. Stauffacher, and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955), for traces of ambelline isolated from *Buphane fischeri* Baker.

methoxyl could be assigned to the aromatic ring because of strong infrared absorption at 1623 cm.$^{-1}$ and ultraviolet absorption of ambelline and its derivatives at 288 mμ.[7] This was confirmed by the chemical degradations discussed below.

Ambelline was recovered unchanged after treatment with 10% hydrochloric acid at room temperature for two hours. At elevated temperatures, this reaction mixture gave rise to a crude oil which was oxidized by manganese dioxide suspended in chloroform. The infrared absorption spectrum of the product showed a moderate band at 1675 cm.$^{-1}$. This provided the first clue that an allylic methyl ether might be present. Neither 90% formic acid nor 10% ethanolic potassium hydroxide at reflux temperature for two hours had any effect. Ambelline was stable to both ethanolic selenium dioxide and a suspension of manganexe dioxide in chloroform at room temperature for seventeen hours. Chemical reduction (lithium aluminum hydride in refluxing tetrahydrofuran) was unsuccessful and ambelline was recovered in 68% yield. Catalytic reduction with palladium on charcoal in either glacial acetic acid or ethanol, as well as platinum in glacial acetic acid, gave a single dihydro product. These chemical data permitted us to eliminate five of the seven basic ring systems known to occur in the Amaryllidaceae. Ambelline could be derived from the powellane (I)[8-10] or methoxymontanine (II)[11,12] or another, yet undiscovered, ring system.



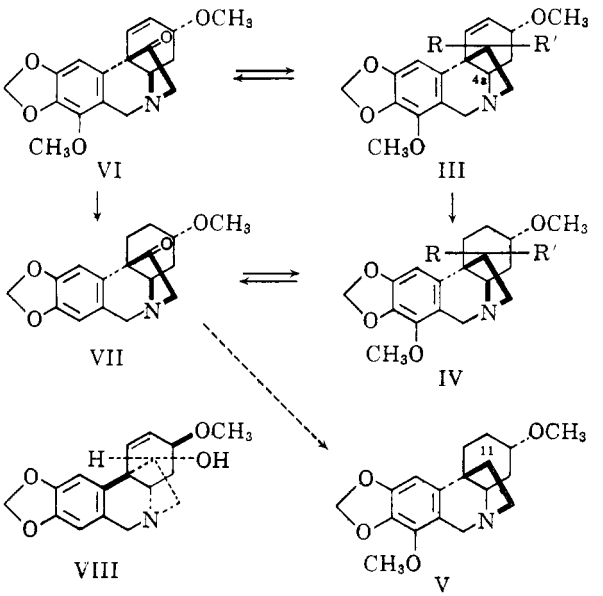
I



II

Several methods were found to convert the alcohol group of ambelline and its dihydro derivative to the corresponding ketone. Although an attempted oxidation of dihydroambelline utilizing fluorenone as an oxidant at room temperature was unsuccessful, the reaction was accomplished with cyclohexanone at reflux temperature. The product, oxodihydroambelline, also could be obtained by the prolonged oxidation of dihydroambelline with activated manganese dioxide. The preferred method used the pyridine-chromic oxide reagent.[13] Under these conditions, 76 and 78% yields of oxoambelline and oxodihydroambelline could be realized from ambelline and dihydroambelline, respectively. Oxoambelline and oxodihydroambelline showed carbonyl absorption at 1748 cm.$^{-1}$ and 1750 cm.$^{-1}$, respectively. Although neither ketone showed an ultraviolet absorption spectrum characteristic of a ketone conjugated with unsaturation, the multiple bands near 292 and 315 mμ suggested π-electron overlap between the carbonyl group and the aromatic ring. Such an effect had been noted earlier in the haemanthamine and crinamine series.[14] These data provided no preference between ring systems I and II because a C-11 ketone in I or a C-12 ketone in II would be compatible with our observations.

Because our earlier work had provided a large number of reference compounds in the powellane (I) series, it seemed advantageous to attempt to convert dihydroambelline to a deshydroxy compound which might be identical with dihydrobuphanidrine (V). As was found to be the case in the haemanthamine series,[14] Wolff–Kishner and Clemmensen conditions were not effective in converting the ketone to a methylene group. Reduction of ambelline tosylate with lithium aluminum hydride regenerated ambelline. Following the procedure which was successful for the conversion



of haemanthamine to (+)-dihydrobuphanisine,[14] dihydroambelline was treated with thionyl chloride and then lithium aluminum hydride. Only dihydroambelline was recovered. At this point we examined the hydroxyl stretching frequencies of ambelline and dihydroambelline at high dilution in carbon tetrachloride. Both compounds showed strongly bonded absorption (3564 and 3565 cm.$^{-1}$, respectively). The frequency of this absorption, when considered with our previous data on the anomalous ultraviolet absorption of the ketones, indicated that the hydroxyl group of ambelline and its dihydro derivative must be oriented in a direction toward the aromatic ring. The condition can be fulfilled either by a C-11 hydroxyl in I or a C-12 hydroxyl in II. This deduction would have the support of two negative results that were mentioned earlier. In dilute refluxing hydrochloric acid, haemanthamine (VIII) forms easily a cyclic ether between C-11 and C-3; epihaemanthamine (epimeric at C-11) affords the same ether in very poor yield. The observation that allylic methoxyl cleavage occurs in preference to ether formation when ambelline is heated with acid can be explained in terms of the epimeric hydroxyl configurations in the two alkaloids. Finally, it had been observed that epidihydrohaemanthamine could not be converted to dihydrobuphani-

(7) W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **77**, 4807 (1955).

(8) H. M. Fales and W. C. Wildman, *ibid.*, **82**, 3368 (1960).

(9) W. C. Wildman, *ibid.*, **80**, 2567 (1958).

(10) H. A. Lloyd, E. A. Kielar, R. J. Highet, S. Uyeo, H. M. Fales, and W. C. Wildman, *J. Org. Chem.*, **27**, 373 (1962).

(11) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *ibid.*, **25**, 2153 (1960).

(12) For reactions characteristic of each Amaryllidaceae ring system, see W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, ed., Academic Press, Inc., New York, N. Y., 1960, p. 289.

(13) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 427 (1953).

(14) H. M. Fales and W. C. Wildman, *ibid.*, **82**, 197 (1960).

sine by successive treatment with thionyl chloride and lithium aluminum hydride.

To prepare the desired epidihydroambelline, we examined the sodium borohydride reduction of oxodihydroambelline. In methanolic solution, this reduction afforded a mixture of dihydroambelline (44%), an uninvestigated organoboron compound, and the desired epidihydroambelline (40%). Treatment of the latter compound, first with thionyl chloride and then lithium aluminum hydride, gave a homogeneous oily product possessing the same retention time by gas phase chromatography and infrared spectrum (liquid film) as dihydrobuphanidrine (V).[8-10] The picrate of deoxydihydroambelline had the same melting point and optical rotation as dihydrobuphanidrine picrate, and a mixture melting point determination showed no depression. The optical rotatory dispersion curves of the product and dihydrobuphanidrine were identical within experimental error. These reactions show that dihydroambelline is 11-hydroxydihydrobuphanidrine (IV. R = OH, R′ = H). In turn, oxodihydroambelline is VII.

To be consistent with the chemical reactivity of ambelline and oxoambelline, the isolated double bond can be only at C-1–C-2 or C-4–C-4a. A C-1–C-2 assignment could be anticipated by analogy with many other alkaloids of this ring system and was proven by several physical methods.

In contrast with the sodium borohydride reduction of VII, which provided nearly equal amounts of the two alcohols epimeric at C-11 (IV), oxoambelline afforded ambelline in over 90% yield. The filtrates from the ambelline recrystallization could be shown to contain traces of epiambelline (III. R = H, R′ = OH) by spectral methods. In dilute carbon tetrachloride solution these filtrates showed two peaks in the hydroxyl stretching region, 3603 and 3565 cm.$^{-1}$. Pure ambelline shows only one at 3565 cm.$^{-1}$. The 3603-cm.$^{-1}$ absorption is that predicted for epiambelline by analogy with haemanthamine (VIII) which shows absorption at 3598 cm.$^{-1}$. Hydrogenation of this mixture shifted the 3603 cm.$^{-1}$ band to 3630 cm.$^{-1}$, the frequency found for epidihydroambelline and other unbonded secondary alcohols. The 3565-cm.$^{-1}$ absorption, which is due to OH bonded to the π-electrons of the aromatic ring is unaffected by the reduction. If the double bond of ambelline were at C-4–C-4a, a far less favorable condition would exist for hydrogen bonding to the isolated double bond and the OH absorption would be higher than 3610 cm.$^{-1}$.

A close parallel exists between the pK_a values of ambelline and dihydroambelline (6.90 and 7.70, respectively) and haemanthamine and dihydrohaemanthamine (6.93 and 7.55, respectively). If the double bond of ambelline were C-4–C-4a, a much lower pK_a would be expected for it. The n.m.r. spectrum of oxoambelline shows two singlets for the lone aromatic proton at C-10 and the methylenedioxy protons (δ = 6.58 and 5.88, respectively). Between them, there is an *AB* pattern of *two* olefinic protons (δ = 6.52 and 6.18; J = 10). The proton at higher field is further split by coupling to a single proton (J = 5). These data give unequivocal evidence of C-1–C-2 saturation.

Our continuing interest in the biosynthesis of Amaryllidaceae alkaloids made it desirable to carry out one additional degradative sequence for future use. Oxohaemanthamine methiodide in refluxing alkali was converted to N-(6-phenylpiperonyl)sarcosine which could be hydrogenolyzed to sarcosine and 2-methyl-4,5-methylenedioxybiphenyl.[15] By identical reactions, oxoambelline methiodide gave 3-methoxy-2-methyl-4,5-methylenedioxybiphenyl and sarcosine.

Experimental[16]

Ambelline.—The principal sources of ambelline were *Nerine bowdenii* W. Wats.,[5] and an *Amaryllis belladonna* hybrid.[17] Preliminary characterization of the alkaloid was reported in an earlier paper.[2]

Dihydroambelline (IV. R = OH, R′ = H).—Prepared by the method described earlier,[2] the product was crystallized from ethyl acetate and sublimed at 170° (0.03 mm.), m.p. 195–197°; $[\alpha]_{589}^{25}$ −16°, $[\alpha]_{436}^{25}$ −42° (*c* 0.675); λ_{max} 287 mμ (log ϵ 3.19)[18]; OH band at 3565 cm.$^{-1}$. Catalytic reduction of ambelline in acetic acid at atmospheric pressure with either platinum or palladium also gave dihydroambelline.

Oxoambelline (VI).—To a solution of 2.5 g. of ambelline (m.p. 260°) in 100 ml. of dry pyridine was added a slurry of 4 g. of chromic acid anhydride in 50 ml. of pyridine. After stirring for 20 hr. at room temperature, the solution was poured on ice, and the excess of oxidizing agent was reduced by sodium sulfite. The solution was made basic with sodium carbonate and extracted four times with chloroform. The chloroform extracts were washed with water, dried with magnesium sulfate, and evaporated. The resulting viscous brown oil (2.2 g.) was chromatographed on 100 g. of Florisil. Benzene–ethyl acetate mixtures eluted 1.9 g. of colorless oil which crystallized from ether–hexane. Two further crystallizations from the same mixture gave a product melting at 118–119°; $[\alpha]_{589}^{25}$ −123°, $[\alpha]_{436}^{25}$ −442° (*c* 0.47); λ_{max} 292 mμ (log ϵ 3.31), 315 mμ (log ϵ 3.24). The optical rotatory dispersion curve shows a negative Cotton effect at 445 mμ (−2350°). The crystalline product was sublimed at 110° (0.03 mm.) and the resulting colorless glass was analyzed.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.41; H, 5.77; N, 4.39.

Oxoambelline also could be obtained by oxidation of ambelline with cyclohexanone and aluminum *t*-butoxide in toluene solution at 111°. The best yield by this method was 60%.

The hydrochloride was prepared in ether solution with gaseous hydrogen chloride. The precipitate was washed twice with ether, m.p. 222–224° (evac. cap.). Two recrystallizations from chloroform–ethyl acetate gave fine white crystals, m.p. 227–228° (evac. cap.); $[\alpha]_{589}^{22}$ −29° (*c* 0.70); λ_{max} 298 mμ (log ϵ 3.38), 308 mμ (log ϵ 3.41). The product is quite soluble in chloroform.

Anal. Calcd. for $C_{18}H_{20}NO_5Cl$: C, 59.10; H, 5.51; N, 3.83; 2OCH$_3$, 16.96. Found: C, 59.33; H, 5.41; N, 3.95; OCH$_3$, 16.96.

The picrate was prepared in ethanol and recrystallized seven times from chloroform–ethanol, m.p. 225–228° dec. The analytical sample was dried overnight *in vacuo* at 75°.

(15) W. C. Wildman, H. M. Fales, and A. R. Battersby, *J. Am. Chem. Soc.*, **84**, 681 (1962); *ibid.*, **83**, 4098 (1961).

(16) Physical measurements of melting points, infrared and ultraviolet spectra, and optical rotations were performed on the instruments used in our previous papers. Hydroxyl stretching frequencies were determined at high dilution in carbon tetrachloride on a Beckman IR-7 infrared spectrophotometer. Unless noted to the contrary, all infrared spectra and optical rotations were determined in chloroform solution and all ultraviolet spectra in absolute ethanol. Gas phase chromatographs were obtained on a Barber–Colman Model 15 apparatus equipped with an argon ionization detector. The column was a 6 ft. × 4.3 mm. U-tube packed with 3/4% SE-30 on Chromosorb W, 80–100 mesh. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J. We are indebted to Dr. E. D. Becker and Mr. R. B. Bradley of the National Institute of Arthritis and Metabolic Diseases, and Dr. Roy King, Iowa State University of Science and Technology, for the nuclear magnetic resonance spectra which were obtained on a Varian A-60 analytical nuclear magnetic resonance spectrometer operating at 60 Mc. Frequencies were obtained relative to tetramethylsilane as an internal standard by interpolation using the audio sideband technique.

(17) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 1472 (1960).

(18) Contrary to our previous report,[2] no maximum is present at 245 mμ.

Anal. Calcd. for $C_{24}H_{22}N_4O_{12}$: C, 51.61; H, 3.97; N, 10.03. Found: C, 51.67; H, 4.12; N, 10.02.

The treatment of oxoambelline in acetone solution with methyl iodide at room temperature yielded a methiodide which was recrystallized from ethanol, m.p. 250–254° dec.; $[\alpha]^{24}_{589}$ −83°, $[\alpha]^{24}_{436}$ −284° (*c* 0.41; dimethylformamide–water, 1:1).

Anal. Calcd. for $C_{19}H_{22}NO_5I$: C, 48.42; H, 4.67; N, 2.97. Found: C, 48.41; H, 4.53; N, 3.19.

Oxodihydroambelline (VII).—Dihydroambelline (800 mg.) was oxidized and worked up by the method described for oxoambelline The resulting 750 mg. of brown oil was chromatographed on 40 g. of Florisil. Benzyl–ethyl acetate mixtures eluted 620 mg. of viscous, colorless oil which could be crystallized from methanol, m.p. 163–164°; $[\alpha]^{24}_{589}$ −247°, $[\alpha]^{24}_{436}$ −732° (*c* 0.30); λ_{max} 292 mμ (log ε 3.36), 313 mμ (log ε 3.24), λ_{inf} 250 mμ (log ε 3.70); in 1% hydrochloric acid–ethanol: λ_{max} 297 mμ (log ε 3.45), 305 mμ (log ε 3.46); λ_{inf} 253 mμ (log ε 3.58).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.05; H, 6.39; N, 4.34.

The picrate was prepared in ethanolic solution. Three recrystallizations from chloroform–ethanol gave the analytical sample, m.p. 249–250° dec.

Anal. Calcd. for $C_{24}H_{24}N_4O_{12}$: C, 51.43; H, 4.32; N, 9.99. Found: C, 51.55; H, 4.48; N, 9.95.

The methiodide was obtained by refluxing oxodihydroambelline with an excess of methyl iodide in acetone solution for 10 min. The crystals were filtered and recrystallized twice from water–ethanol to give the analytical sample, m.p. 275° dec.

Anal. Calcd. for $C_{19}H_{24}NO_5I$: C, 48.22; H, 5.07; N, 2.96. Found: C, 47.90; H, 5.23; N, 2.84.

Oxodihydroambelline also was prepared by oxidation of dihydroambelline with manganese dioxide in chloroform solution at room temperature or by catalytic hydrogenation of oxoambelline with palladium on charcoal in ethanolic solution.

Epidihydroambelline (IV. R = H, R′ = OH).—To a solution of 325 mg. of oxodihydroambelline in 10 ml. of methanol was added 750 mg. of sodium borohydride. An additional 10 ml. of methanol and two 500-mg. portions of hydride were added after 15 and 30 min., respectively. The mixture was allowed to stand for 2 hr. at room temperature and then was heated on the steam bath for 15 min. It was poured into a cold solution of 0.5 *N* sulfuric acid and made basic with sodium hydroxide. Extraction with chloroform yielded 350 mg. of oily product which was chromatographed on 30 g. of Florisil. Benzene–ethyl acetate (9:1) eluted 60 mg. of an organoboron compound (white crystals from ether–hexane, m.p. 156–158°). Ethyl acetate gave 130 mg. of crystals, m.p. 233–238°; after two recrystallizations from ethyl acetate, the product melted 238–240°. Sublimation at 190° (0.05 mm.) gave the analytical sample, m.p. 239.5°; $[\alpha]^{24}_{589}$ −67°, $[\alpha]^{24}_{436}$ −130° (*c* 0.135); λ_{max} 287 mμ (log ε 3.26); OH band at 3630 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20; $2OCH_3$, 18.63. Found: C, 64.62; H, 6.88; N, 4.27; OCH_3, 19.11.

Further elution of the column with ethyl acetate–methanol mixtures afforded 142 mg. of crystalline dihydroambelline, m.p. 192°.

Refluxing the reaction mixture in acetic acid does not change the amount of boron-containing compound. Epidihydroambelline can be separated by gas chromatography from dihydroambelline. The latter has a considerably shorter retention time.

Epiambelline (III. R = H, R′ = OH).—A solution of 600 mg. of oxoambelline in 30 ml. of methanol containing a trace of boric acid was treated with 1 g. of sodium borohydride. The mixture was kept at room temperature for 2 hr. during which time two additional 500-mg. portions of hydride were added. The solution was heated on a steam bath for a few minutes. The reaction mixture was poured into cold 0.5 *N* sulfuric acid, made alkaline with 2 *N* sodium hydroxide, and extracted with chloroform. The resulting crude, crystalline product (580 mg.) was chromatographed on 20 g. of Florisil. Benzene–ethyl acetate mixtures eluted first a boron-containing compound which after recrystallization from methanol showed a melting range of 185–200°. Infrared analysis indicated that all subsequent fractions were ambelline, melting between 240 and 258°. One recrystallization of these combined fractions from chloroform–acetone gave 400 mg. of pure ambelline. The residue (110 mg.) in the mother liquors was rechromatographed on 5 g. of Florisil. All fractions were examined in the hydroxyl stretching region in dilute carbon tetrachloride. The first few fractions which were eluted with benzene–ethyl acetate (19:1) showed two bands at 3603 and 3565 cm.$^{-1}$. The band at 3565 cm.$^{-1}$ could be assigned to the hydroxyl group of ambelline, while the absorption at 3603 cm.$^{-1}$ is that predicted for epiambelline. After recrystallization of these fractions from chloroform–ethyl acetate, the product melted at 245–248° but had a much lower positive optical rotation than pure ambelline. Gas phase chromatography showed that the material was largely ambelline, but a second compound was eluted 0.5 min. later. The mixture could not be separated by chromatography on Florisil or recrystallization. It was hydrogenated catalytically with palladium on charcoal (10%) in ethanolic solution. The product showed the expected shift of one hydroxyl band to 3630 cm.$^{-1}$ (as in epidihydroambelline) with the other band remaining at 3565 cm.$^{-1}$ (as in pure ambelline and dihydroambelline). The yield of the epi compound in this reaction is estimated to be 3–5%.

Conversion of IV (R′ = OH) to Dihydrobuphaniedrine.—A solution of 75 mg. of epidihydroambelline in 10 ml. of freshly distilled thionyl chloride was refluxed for 2 hr. and then evaporated to dryness. Twenty-five milliliters of dry tetrahydrofuran was added and the solution was refluxed with 700 mg. of lithium aluminum hydride overnight. The cooled mixture was hydrolyzed with a saturated solution of sodium potassium tartrate and extracted thoroughly with chloroform. The resulting 65 mg. of crude, oily product was chromatographed on 3 g. of Florisil. A clear, liquid product (45 mg.) was eluted with ethyl acetate and ethyl acetate–ethanol mixtures.

The picrate was prepared in ethanol and recrystallized four times from chloroform–ethanol, m.p. 277–280° dec. It did not depress the melting point of pure dihydrobuphanidrine picrate, $[\alpha]^{25}_{589}$ +16°, $[\alpha]^{25}_{500}$ +37° (*c* 0.51); authentic dihydrobuphanidrine picrate, $[\alpha]^{24}_{589}$ +11°, $[\alpha]^{24}_{500}$ +27° (*c* 0.50).

Anal. Calcd. for $C_{24}H_{26}N_4O_{11}$: C, 52.74; H, 4.80; N, 10.02. Found: C, 52.41; H, 4.88; N, 10.46.

The picrate was dissolved in chloroform and passed through a column of Merck alumina. The eluted oil, b.p. 145° (0.01 mm.), was pure by gas phase chromatography and possessed the same retention time as dihydrobuphanidrine. Infrared spectra (liquid film) of the product and dihydrobuphanidrine were identical as were the optical rotatory dispersion curves, within experimental error.

N-(2-Methoxy-6-phenylpiperonyl)sarcosine Hydrochloride.—To a solution of 700 mg. of oxoambelline methiodide in 10 ml. of hot water was added 3 ml. of 50% sodium hydroxide. The solution was heated on the steam bath for 1 hr. The brown, gummy layer that formed was freed from excess alkali by decantation and dissolved in cold 6 *N* hydrochloric acid. The solution was saturated with sodium chloride and extracted five times with chloroform. The solvent was evaporated and the remaining oil was dissolved in a little hot acetone. A fine, crystalline precipitate formed, 450 mg., m.p. 182–185°. The product was recrystallized several times from methanol–acetone to give the analytical sample, m.p. 185.5–187°; λ_{max} 224 mμ (log ε 4.54); λ_{inf} 252 mμ (log ε 3.79), 288 mμ (log ε 3.35).

Anal. Calcd. for $C_{18}H_{20}NO_5Cl$: C, 59.10; H, 5.47; N, 3.83; Cl, 9.71. Found: C, 59.24; H, 5.50; N, 3.61; Cl, 9.55.

3-Methoxy-2-methyl-4,5-methylenedioxybiphenyl.—A solution of 200 mg. of N-(2-methoxy-6-phenylpiperonyl)sarcosine hydrochloride in 35 ml. of ethanol and 0.5 ml. of acetic acid was hydrogenated with 800 mg. of pre-equilibrated palladium on charcoal (10%). The reduction stopped after an uptake of 1.7 equivalents of hydrogen. The solution was filtered, diluted with water, and extracted with ether. The ether solution was washed three times with water, dried with magnesium sulfate, and evaporated to leave 90 mg. of a slightly yellow oil that was distilled at 120–130° (0.07 mm.); λ_{max} 258 mμ (log ε 3.25); λ_{max} 218 mμ (log ε 4.39), 287 mμ (log ε 2.90). The purity of the distillate was established by gas phase chromatography.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.51; H, 6.02.

The aqueous raffinate was concentrated to half volume and made basic with 2 *N* sodium hydroxide. A solution of 2 g. of *p*-toluenesulfonyl chloride in 60 ml. of benzene was added, and the emulsion was stirred for 24 hr. The layers were separated, and the alkaline aqueous layer was extracted with ether. The aqueous solution was acidified with 2 *N* hydrochloric acid and extracted four times with chloroform. Evaporation of the dried chloroform solution gave 80 mg. (60%) of crude N-tosylsarcosine,

m.p. 147–149°.[19] After recrystallization from acetone–hexane and ethyl acetate–hexane, the product was sublimed at 125° (0.07 mm.) to give the analytical sample, m.p. 151–152°.

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Anal. Calcd. for $C_{10}H_{13}NO_4S$: C, 49.40; H, 5.36; N, 5.77; S, 13.21. Found: C, 49.33; H, 5.42; N, 5.79; S, 13.19.

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Beckmann Rearrangements in Alicyclic Systems. V. Evidence for Carbonium Ion Intermediates in Acid-catalyzed Oxime Rearrangements[1,2]

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The Beckmann reactions of several 1,1-disubstituted 2-tetralone oximes in phosphorus pentachloride are shown to result in the formation in high yield of unsaturated nitriles from typical α-trisubstituted oxime fragmentation. Rearrangement of these oximes in polyphosphoric acid and the cyclization of the unsaturated nitriles in this medium are shown to proceed in such a fashion as to yield identical products, the expected lactam and α,β-unsaturated ketone. In each case studied, the ratio of lactam to unsaturated ketone was found to be identical to that obtained from the independent nitrile cyclizations under comparable conditions of temperature and time. It is concluded from these data that the lactam, although the expected product of Beckmann rearrangement, is produced *via* a Ritter cyclization of the nitrile intermediate from initial fragmentation of the oxime. These data support a mechanism for these reactions involving ionic intermediates in α-trisubstituted oxime rearrangements.

Recently,[3] the Beckmann rearrangements of 2,2-disubstituted 1-indanone oximes and related tetralone and benzosuberone oximes were reported to rearrange in the normal fashion to 3,3-disubstituted hydrocarbostyrils and homologous products. These reactions did not follow the same course of rearrangement as previously observed in other spiro-[4] and 2,2-disubstituted cycloalkanone oximes.[5] The literature indicates that the cleavage of an oxime which is completely substituted at the α-carbon is a rather general process.[6,7] Compounds of this class, together with certain bridged bicyclic ketoximes[8] and compounds bearing a β-hetero atom adjacent to the oximino group[9] follow the cleavage reaction rather than the normal course of rearrangement to an amide or a lactam. The structural features of these systems, in general, indicate that this process involves the ejection of a positive fragment from the β-position of an electron-deficient intermediate. Our interest in these processes has been centered about the examination of the rearrangement behavior of α-trisubstituted oximes, particularly, in cyclic systems. These studies have indicated that it may be possible to have more than one mechanistic route followed in the rearrangement of hindered ketoximes. In extending these studies, it was of interest to investigate model systems potentially capable of fragmentation but in which the previously reported α,β-unsaturated ketone formation from the unsaturated nitrile intermediate would compete with a second potential cyclization reaction through the Ritter reaction[10] involving the nitrile addition to the double bond to form an amide, identical in type to the expected product of Beckmann rearrangement. This second route would yield the normal Beckmann rearrangement product, but, *via* a reaction course which would be expected to proceed through such intermediate carbonium ion steps as to yield, in the case of an asymmetric α-carbon, a racemic product.[11] It is the purpose of this paper to show that this second mechanistic route is followed, at least, with a number of hindered ketoximes. This observation together with previous observations in rearrangements in cyclic systems adds additional information to the fundamental mechanistic processes involved in group migration from carbon to nitrogen and also indicates a similarity to analogous carbon–carbon rearrangement processes.

One of the most frequently quoted exceptions[12] to the generality of oxime fragmentation in the α-trisubstituted class of oximes is the polyphosphoric acid rearrangement of 1,1,4,4-tetramethyl-2-tetralone oxime. This oxime has been reported to rearrange normally to the expected lactam in 24% yield. The remaining products of the reaction were not characterized. Since the course of reaction in this case could follow either normal rearrangement or a fragmentation–recombination route, it was of interest to examine carefully the

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