material (charcoal) from chloroform–pentane mixtures gave 20 mg. of small shiny platelets (very slightly yellow), m.p. 144.5–146°.

Anal. Calcd. for $C_{16}H_{15}N_3SO_6$: C, 50.92; H, 4.01; mol. wt., 377. Found: C, 50.71; H, 4.12; mol. wt., 362 (Rast).

Reduction of Azirine (IIIA) with Sodium Borohydride in Acid Solution.—A solution of 1.5 g. of sodium borohydride (0.042 mole) in 80 ml. of pure methanol, and 50 ml. of 2 *N* aqueous hydrochloric acid solution (0.1 mole) were added *alternately* in small portions over a period of three minutes at room temperature to a stirred solution of 5.0 g. (0.0044 mole) of azirine (IIIA) in 325 ml. of pure methanol. The yellow solution warmed slightly and became orange. The acidity was reduced to a *p*H of 2–3 with aqueous 3% sodium bicarbonate solution. After stirring for ten minutes, the solution was made alkaline with more sodium bicarbonate, and the excess hydride was destroyed by adding 30 ml. of acetone. When concentrated under reduced pressure (temperature, 45–60°) the solution deposited brown crystals, wt. 4.1 g. After recrystallizing the crude product from hot methanol (carbon-treatment) a total of 3.0 g. (including mother liquor workup) of light yellow-tan needles was obtained, m.p. 156–158° (dec.). Several more recrystallizations from methanol gave very light yellow prisms, m.p. 158–159° (dec.) (compound XII or XIII).

Anal. Calcd. for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13. Found: C, 47.00; H, 5.48.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

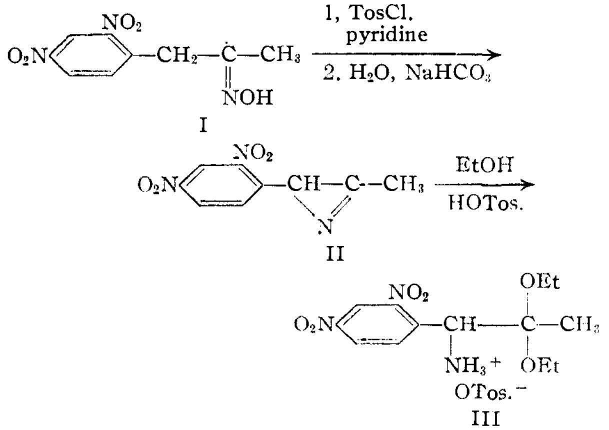
Observations on the Mechanism and Scope of the Neber Rearrangement

BY MELVIN J. HATCH[1] AND DONALD J. CRAM[2]

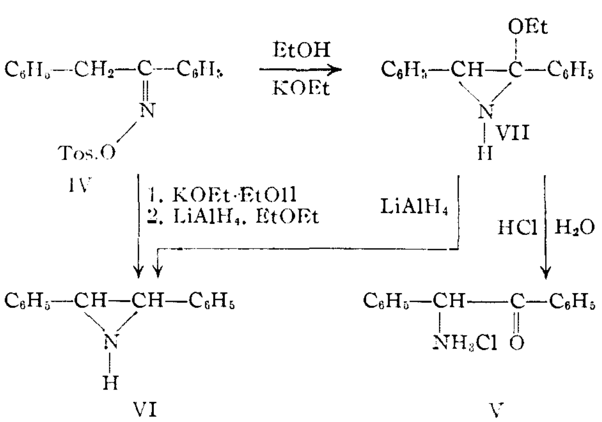
RECEIVED MARCH 26, 1952

In a further study of the Neber rearrangement, the *p*-toluenesulfonate of desoxybenzoinoxime (*syn*-benzyl) was treated with potassium ethoxide in ethanol to produce a new class of compound, the unstable 2,3-diphenyl-2-ethoxyethylenimine (VII), which when treated with lithium aluminum hydride gave *cis*-diphenylethylenimine. When hydrolyzed in aqueous acid, VII gave desylamine. Analogous reactions were demonstrated to occur in the *p,p'*-dichlorodesoxybenzoinoxime *p*-toluenesulfonate (*anti-p*-chlorobenzyl) system. These reactions constitute a new and simple means of synthesis of ethylenimines. The mechanism and scope of the Neber rearrangement are discussed.

The Neber[3] rearrangement can be classified as one of several "abnormal" rearrangements of ketoximes or their derivatives. When applied to the 2,4-dinitrophenylacetone system, the Neber rearrangement has been formulated[3c] as giving an azirine–pyridine hydrochloride complex which can be converted to azirine (II) and ultimately through hydrolysis to the amino ketal salt III. This reaction system represents a structural extreme, being atypical in two respects. (1) Due to the strong electron withdrawing ability of the nitro groups the hydrogen atoms on the benzyl carbon are acidic enough to allow the reaction to be initiated by pyridine instead of the usual sodium ethylate. (2) Again due to the nitro groups, the azirine itself (II)[4] would be expected to be far more resonance stabilized than in the usual systems submitted to the Neber reaction.[4] Therefore, the object of the present study has been to determine the nature of the reaction intermediates in more typical systems, and thereby to establish a more general framework for the over-all reaction mechanism.



The Neber Rearrangement in the Desoxybenzoin and *p,p'*-Dichlorodesoxybenzoin Systems.—Although the *p*-toluenesulfonate of desoxybenzoinoxime (IV) had previously been submitted to the Neber rearrangement to give desylamine hydrochloride[3d] (V), no intermediates were isolated. In the present investigation this ester (IV) was treated with potassium ethylate in ethanol, but aqueous acid was not added as usual to the filtered reaction mixture. Instead, ice-water was added to the solution, and the unstable solid that separated was dissolved in ether and reduced with lithium aluminum hydride to give *cis*-2,3-diphenylethylenimine (VI).



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[1] Parke, Davis Predoctoral Research Fellow, 1951–1952.

[2] Requests for reprints should be addressed to this author.

[3] (a) P. W. Neber and A. Friedolsheim, *Ann.*, **449**, 109 (1926); (b) P. W. Neber and A. Uber, *ibid.*, **467**, 52 (1928); (c) P. W. Neber and A. Burgard, *ibid.*, **493**, 281 (1932); (d) P. W. Neber and G. Huh, *ibid.*, **515**, 283 (1935); (e) P. W. Neber, A. Burgard and W. Thier, *ibid.*, **526**, 277 (1936).

[4] The structure of this intermediate has been discussed elsewhere [D. J. Cram and M. J. Hatch, THIS JOURNAL, **75**, 33 (1953)].

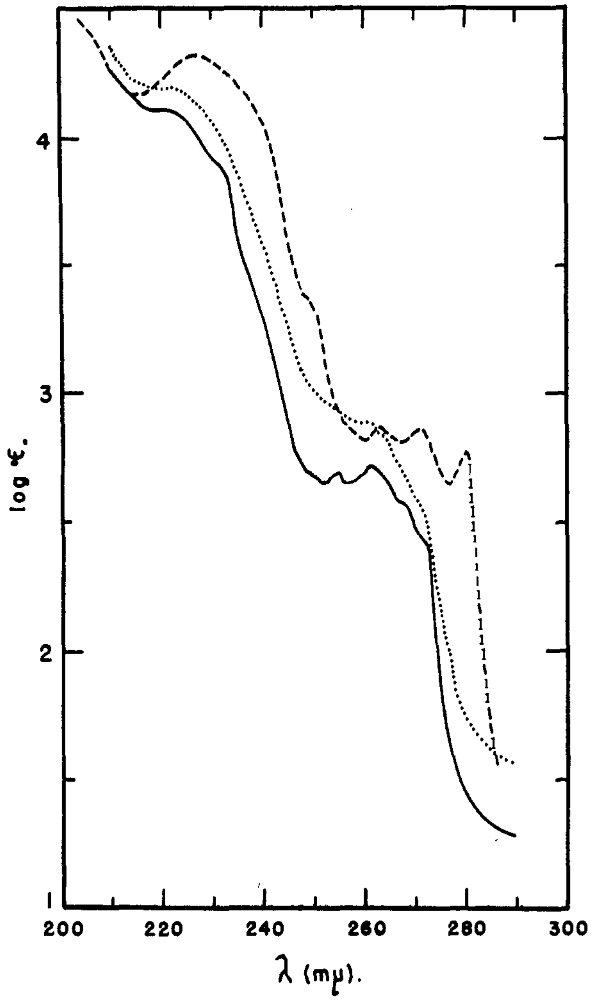

Fig. 1.—Ultraviolet absorption spectra (Cary spectrophotometer, model 11MPS) in cyclohexane: ....., 2,3-diphenyl-2-ethoxyethylenimine (VII); ----, 2,3-bis-(4′-chlorophenyl)-ethylenimine (XI); —, 2,3-diphenylethylenimine (VI).

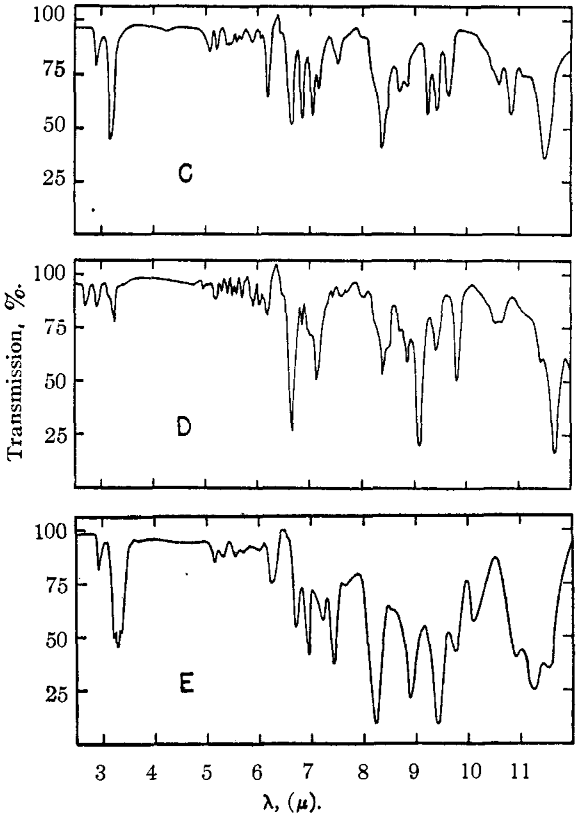

Fig. 2.—Infrared absorption spectra (Beckman IR2T spectrophotometer, NaCl prism): C, 10 wt. % of *cis*-2,3-diphenylethyleninine (VI) in carbon tetrachloride; D, 9 wt. % of 2,3-bis-(4′-chlorophenyl)-ethylenimine (XI) in carbon tetrachloride; E, 11 wt. % of 2,3-diphenyl-2-ethoxyethylenimine (VII) in carbon tetrachloride.

The identity of the product was established through comparison with authentic material.[5] This experiment indicates that in the rearrangement an intermediate does exist in which the nitrogen of the original oxime is bonded to two carbon atoms. This intermediate proved to be an *extremely unstable* substance which was isolated in a pure state only through the use of special low temperature or fractional crystallization techniques (see Experimental). The compound was demonstrated to be 2,3-diphenyl-2-ethoxyethylenimine (VII) and apparently represents the first known example of its structural class.[6]

Evidence for the assigned structure is as follows: (1) The molecule possesses a molecular formula of $C_{16}H_{17}NO$. (2) The substance contains one ethoxyl group. (3) When hydrolyzed by aqueous acid, the compound gave desylamine hydrochloride. (4) When reduced with lithium aluminum hydride, the compound gave *cis*-2,3-diphenylethylenimine (VI). (5) The ultraviolet absorption spectrum closely resembles that of *cis*-2,3-diphenylethyleneimine (see Fig. 1). (6) The band in the infrared spectrum (see Fig. 2) that occurs at 2.9 μ is evidence for an N-H bond in the molecule. The same band appears in the spectrum of *cis*-2,3-diphenylethylenimine (VI) and is undoubtedly due to an N-H stretching frequency.

In order to obtain further evidence regarding the intermediates in the Neber rearrangement, the *p*-toluenesulfonate of *p,p′*-dichlorodesoxybenzoin-oxime (VIII) was prepared and submitted to the usual rearrangement conditions. The ester underwent the Neber rearrangement in the ordinary manner to give the expected *p,p′*-dichlorodesylamine hydrochloride. It was hoped that the expected ethoxylethyleneimine (X) intermediate could be isolated. Although no ethoxyethylenimine was isolated, good evidence for its existence was obtained. When treated with lithium aluminum hydride, an ether solution of the reaction mixture gave a 61% yield of 2,3-*p,p′*-dichlorodiphenylethylenimine (XI). The structure (aside from configuration) of XI was proved by comparison with a sample of the compound synthesized by the indicated independent

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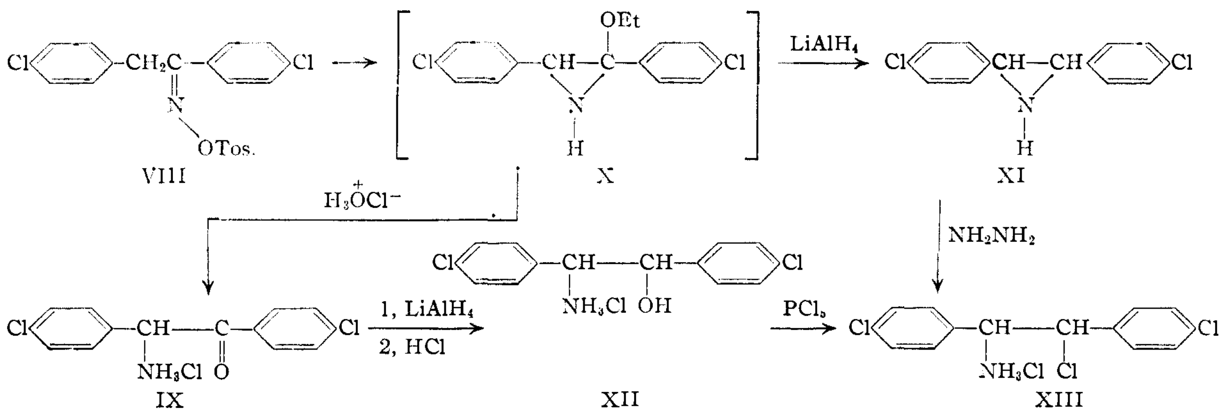
(5) A. Darapsky and H. Spannagel, *J. prakt. Chem.*, [2] **92**, 295 (1915).

(6) Recent reviews of the chemistry of ethylenimines make no mention of ethoxyethylenimines [J. S. Fruton in Elderfield's, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 61, and F. E. King, *J. Chem. Soc.*, 1318 (1949)]. The somewhat similar ethoxyethylenoxides are known [C. L. Stevens, W. Malik and R. Pratt, THIS JOURNAL, **72**, 4758 (1950)] and appear to be more stable.

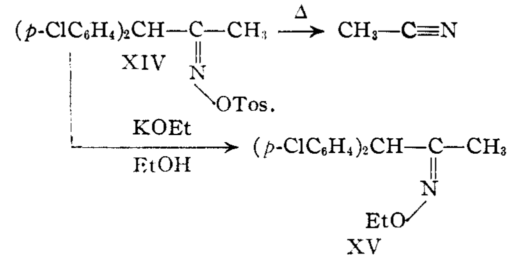


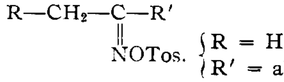
route. The reduction of IX to XII went in good yield (73%), and this fact allows the amino alcohol (XII) to be assigned the *erythro* configuration on the basis of the *Rule of Steric Control of Asymmetric Induction.*[7] Unfortunately the stereochemistry of the last two reactions in the synthesis are ambiguous, and hence the configuration of the imine X cannot be assigned.

Structural Features Necessary for the Neber Rearrangement.—The work of the original investigators[3] has rather definitely shown that in the Neber rearrangement no stereospecificity is present of the sort usually found in the Beckmann rearrangement. Neber's results can be generalized as follows. When two distinguishable α-methylene groups were available, the reaction proceeded in the direction which resulted in the substitution of the amino group for one of the more acidic hydrogens. In all of these cases except that where *o*-nitrophenylacetone-β-oxime tosylate was the starting material,[3] the reaction was *trans* in steric direction (the nitrogen seemingly migrated to the carbon atom *trans* to the tosylate group). When only one methylene group was available, the steric direction of the reaction was *cis* as far as can be determined (not all of the configurations of the oxime tosylates were assigned). Thus the configuration of the oximetosylate apparently has no important influence on the reaction direction. The only missing data in the historical evidence for the absence of configurational control of the reaction direction is an example to show that when the only available α-methylene group is *trans*, the reaction will proceed as usual. The Neber rearrangement of *p,p'*-dichlorodesoxybenzoinoxime tosylate (VIII) provides such an example. The hydroxyl and the *p*-chlorobenzyl groups in the parent oxime have been demonstrated to be *trans* to another,[8] and in the present work the tosylate was prepared under conditions which have not altered the configuration about the >C=N— bond in related oximes.[3,9]

All of the systems that have been submitted to the Neber rearrangement contain a methyl or methylene group alpha to a ketone function, and the question arises as to whether the reaction is limited to such structural types. Oxime tosylates of aldehydes when submitted to the reaction conditions of the Neber rearrangement give an E_2 reaction to form nitriles, and therefore any extension of the scope of the rearrangement could involve only α-methinylketoxime tosylates. Attempts were made to apply the Neber rearrangement to the oximetosylates of a number of such systems.

The tosylate of 1,1-bis-(*p*-chlorophenyl)-2-propanoneoxime (XIV) was prepared as shown in the diagram. This substance when heated underwent a second order Beckman rearrangement (fragmentation reaction) to give acetonitrile, and when subjected to the conditions normally used for the Neber rearrangement, the oximetosylate (XIV) produced a substance whose properties correspond to those of an *o*-ethyl ether of an oxime (XV). When the oximetosylate of 1,1-diphenylacetone was submitted to the action of hot pyridine, a Beckman rearrangement occurred to give N-acetylbenzhydrylamine. These results suggest that the Neber rearrangement is limited to systems represented by the general structure XVI (or equivalent cyclic systems).





$$\underset{\displaystyle \text{NOTos.}}{\text{R—CH}_2\text{—}\overset{}{\underset{\|}{\text{C}}}\text{—R}'}\quad \begin{cases}\text{R = H, alkyl or aryl group}\\ \text{R}' = \text{alkyl or aryl group}\end{cases}$$

XVI

The Mechanism of the Neber Rearrangement.—In view of the isolation of an ethoxyethylenimine

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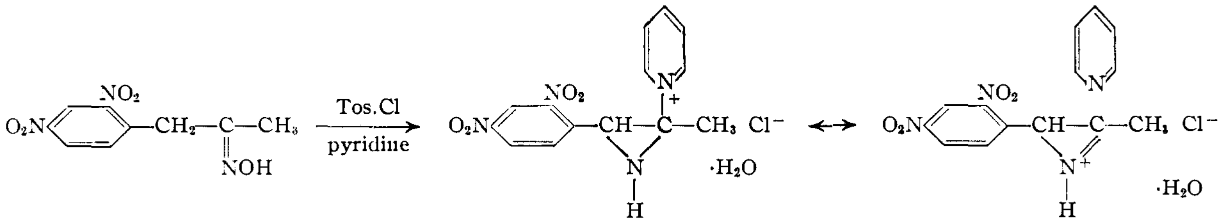
[7] D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, 74, 5828 (1952). In applying the rule, ClC$_6$H$_4$ > NH$_2$ > H in bulk.

[8] S. S. Jenkins, *ibid.*, 55, 703 (1933), and S. S. Jenkins and E. M. Richardson, *ibid.*, 55, 1618 (1933).

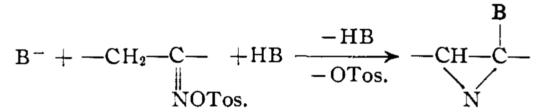
[9] P. Oxaley and W. F. Short, *J. Chem. Soc.*, 1514 (1948).



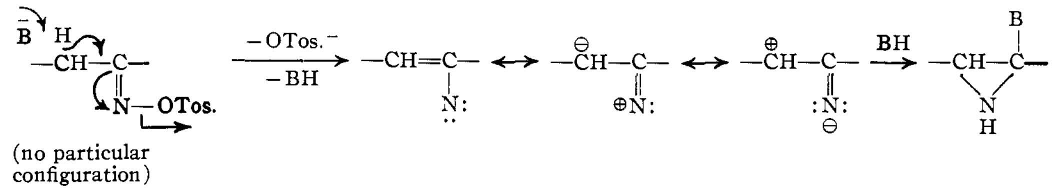
XVII

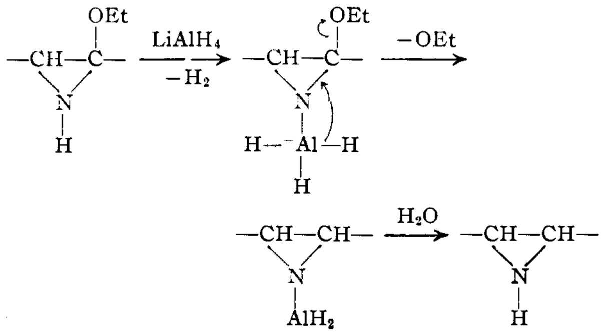
XVIII (resonance hybrid)

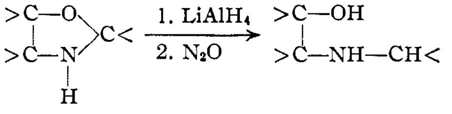
as an intermediate in the Neber rearrangement, a reasonable formulation for the structure of the azurine–pyridine hydrochloride complex prepared from 2,4-dinitrophenylacetoneoxime (XVII)[3c,4] is structure XVIII. The results obtained previously in this structurally extreme system are brought into close analogy with those obtained in more typical systems reported in this paper. The *first step* in the over-all reaction can therefore be generalized in terms of a base induced 1,3-elimination reaction (with ring closure) upon which has been superimposed a 1,2-addition reaction. This picture is essentially the same as the last one suggested by Neber.[3d].



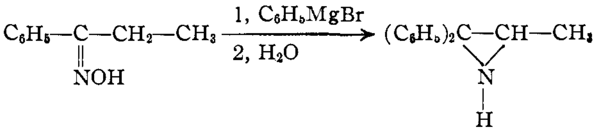
The major requirement of the mechanism of the Neber rearrangement is the sterically indiscriminate character of the reaction. An attractive formulation which satisfies all of the facts known about the first step of the reaction is set forth below. The mechanism might be further complicated with other intermediates, but none other are demanded by the evidence available. The hydrolytic stage of the Neber rearrangement probably occurs by much the same mechanism as that involved in the hydrolysis of ketals. The reduction of the ethoxyethylenimines with lithium aluminum hydride possibly goes as shown in the formulation. The preferential cleavage of the O–C bond is analogous to the well known reduction of amides to amines, and the recently reported reduction of oxazolidines to N-substituted α-amino alcohols.[10]







The new synthesis of ethylenimines which has been developed in the present investigation is at least formally related to the reaction of ketoximes with Grignard reagents.[11] As an example of the latter reaction, when propiophenone oxime was treated with phenylmagnesium bromide under forcing conditions and the resulting complex was decomposed, an ethylenimine was produced.[11] The question of whether mechanistic similarities exist in the reactions of these two types of synthesis has yet to be settled.



Experimental Part

Desoxybenzoinoxime Tosylate.—The following procedure was substituted for that of Neber and Huh[3d] (58% yield). A solution of 84.0 g. of desoxybenzoinoxime (0.40 mole) in a mixture of 1300 ml. of acetone and 780 ml. of 1.37 *N* aqueous potassium hydroxide at 5° was stirred vigorously while 72.2 g. (0.0396 mole) of pure *p*-toluenesulfonyl chloride (powdered) was added in portions during a period of ten minutes. The temperature was held at between 0–7° during the addition and for a period of 25 minutes longer (mixture was still stirred). The resulting mixture was stirred into 5 l. of ice-water. The solid that separated was dissolved in 2 l. of a one-to-one mixture of benzene and ether. This solution was washed with water, dried and mixed with 15 ml. of methanol, 300 ml. of ligroin and 1500 ml. of pentane. When cooled at −25° the resulting solution deposited pure product; yield 73%, m.p. 81.5–83.5 (dec., bath was preheated).

Preparation of 2,3-Diphenylethylenimine from Desoxybenzoinoxime Tosylate.—Pulverized oxime ester (10.8 g. or 0.0296 mole) was suspended in 40 ml. of commercial absolute ethanol (0°), and a solution of potassium ethylate (1.25 g. of potassium plus 15 ml. of commercial absolute ethanol) was added to the mixture during a period of two minutes. The cold mixture was vigorously beaten for five hours (ice-bath cooled), and the potassium *p*-toluenesulfonate was collected and washed with absolute ethanol. Ice-

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[10] E. D. Bergmann, D. Lavie and S. Pinchas, THIS JOURNAL, **73**, 5662 (1951).

[11] K. N. Campbell, B. K. Campbell and E. P. Chaput, *J. Org. Chem.*, **8**, 99 (1943); K. N. Campbell, B. K. Campbell, J. F. McKenna and E. P. Chaput, *ibid.*, **8**, 103 (1943).

water added to the filtrate caused the separation of a white solid which after standing at 0° for 15 minutes was collected and dissolved in ether. The resulting solution was chilled to −78°, decanted from the ice that separated, dried at 0° for ten minutes and added to a well-stirred slurry of 4.0 g. (0.10 mole) of lithium aluminum hydride and 1200 ml. of dry ether. A vigorous evolution of hydrogen occurred.

After the mixture had been stirred for 15 minutes at room temperature, water was cautiously added, the ether layer was separated and the aqueous layer was extracted with ether. The organic solutions were combined, dried and concentrated under vacuum to an oil. This oil crystallized upon addition of hexane. The solid that separated (4.2 g.) was boiled with 10 ml. of hexane, and the resulting solution was filtered from a small amount of white solid.

Upon cooling, the filtrate deposited 2.3 g. of fine white needles m.p. 77–82° (first crop), and 0.1 g. of material, m.p. 75–100° (second crop). Recrystallization from hexane of the combined crops gave 2.01 g. (35% yield) of *cis*-2,3-diphenylethylenimine, m.p. 80.5–82.5°. An analytical sample was prepared, by several recrystallizations of crude material from methanol and water, m.p. 82–83°, undepressed by admixture with an authentic sample. The authentic sample was prepared according to the directions of Weissberger and Bach[12] and Darapsky and Spannagel.[5] The ultraviolet and infrared spectra (Figs. 1 and 2, respectively) of the two samples are identical.

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.17; H, 6.71. Found: C, 85.88; H, 6.37.

Preparation and Characterization of 2,3-Diphenyl-2-ethoxyethylenimine.—Pulverized, pure desoxybenzoinoxime tosylate (6.1 g. or 0.017 mole) was suspended in 30 ml. of commercial absolute ethanol (0°), and a solution of potassium ethylate (0.90 g. of potassium plus 15 ml. of absolute ethanol) was added over a period of two minutes and with vigorous stirring (*ca.* 1200 r.p.m., Hershberg stirrer). The resulting mixture was stirred at 0° for three hours under a nitrogen atmosphere. Cold water (60 ml.) was then added, the mixture was stirred for five more minutes, and the soft white solid that separated was collected in an atmosphere of nitrogen and immediately stirred with 70 ml. of a one-to-one mixture of pure ether and pentane at 0°. The water was frozen out at −78°, the solution was allowed to warm to −40° and poured onto a 1.5 × 25 cm. column of Harshaw activated alumina (not preheated) which was cooled to −25° by means of a jacket through which was circulated a Dry Ice-cooled methanol–water mixture. The bottom of the column led directly into a flask, and the delivery tube to this flask was fitted with a side arm by means of which cold, pure pentane could be introduced to wash the delivery tube. The column was developed with pentane, and the column eluates were kept cold by direct evaporation under a high capacity vacuum line. After a fraction had been evaporated the residue was immediately stored at −78°. The first fraction (140 ml.) gave *ca.* 95 mg. of a colorless oil, the second (70 ml.) gave *ca.* 0.5 g. of a white solid, the third (70 ml.) gave *ca.* 0.5 of a white solid and the fourth (70 ml.) gave 75 mg. of colorless oil. Fraction three was rechromatographed as before on a 1.5 × 35 cm. column to give only colorless oils in the first 500 ml. of eluate, 0.15 g. of chunky soft crystals in the next 35 ml. of eluate and colorless oils in the next 150 ml. of eluate. When the column was stripped with 150 ml. of pure ether, 0.15 g. of a soft, yellow-tinged solid was obtained. The crystals were rapidly washed with two portions (5 ml.) of pure pentane, dried under high vacuum at −25° and analyzed immediately.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.03; H, 7.16; mol. wt., 239. Found: C, 80.04; H, 7.24; mol. wt., 219.[13]

Another method of purifying 2,3-diphenyl-2-ethoxyethylenimine was developed involving fractional crystallization at from 0 to −78° from ether–pentane mixtures. This method did not produce quite as pure material as that obtained by the chromatographic method.

The melting point of the pure material varied greatly with rate and time of heating: heated from room temperature at 14° per minute, m.p. 81.5–83.5°; placed in a preheated bath (75°) and heated at 7° per minute, m.p. 83–85°. Ethoxy determinations[14] were run on slightly impure material (m.p. 78–80°, bath preheated to 75°), and values of 16.8, 21.7 and 23.2% were obtained (theoretical is 18.8%). The ultraviolet and infrared spectra of the compound are recorded in Figs. 1 and 2, respectively. The compound showed evidence of partial decomposition (softening and turning yellow) within 30 minutes at room temperature, but could be stored at −78° in the dark for several weeks without visible evidence of deterioration.

Hydrolysis of 2,3-Diphenyl-2-ethoxyethylenimine.—A solution of 0.131 g. of 2,3-diphenyl-2-ethoxyethylenimine (m.p. 75.5–78.5 in a preheated bath) in 10 ml. of ethyl ether was shaken with two 5-ml. portions of 2 *N* hydrochloric acid solution. The combined aqueous layers were evaporated at room temperature under good vacuum to 3 ml. The solid that separated was collected, washed with a very small amount of ethanol and dried, wt. 0.084 g., m.p. 232–235° (dec. and effervescence). A second crop was also isolated of like melting point, wt. 0.038 g. (total yield, 90%). These materials showed no depression in melting point when mixed with an authentic sample of desylamine hydrochloride.[3d]

Reduction of 2,3-Diphenyl-2-ethoxyethylenimine.—A solution of 0.129 g. of 2,3-diphenyl-2-ethoxyethylenimine (m.p. 75.5–78.5°, preheated bath) in 25 ml. of dry ether was added *immediately* to a stirred slurry of 0.10 g. of lithium aluminum hydride and 50 ml. of ether. The mixture was stirred for ten minutes and 2 ml. of water was cautiously added. The mixture was well stirred, the organic layer was decanted and the aqueous layer was twice washed with ether. The combined ether extracts were washed with water, dried and evaporated under reduced pressure to about 0.5 ml. When *ca.* 1 ml. of warm pentane was added and the resulting mixture was cooled, white needles separated, wt. 0.050 g., m.p. 81–82.5° (undepressed by admixture with an authentic sample of *cis*-2,3-diphenylethylenimine). Another 0.014 g. of product was isolated from the mother liquors, m.p. 80.5–82° (total yield 61%).

Preparation of *p,p′*-Dichlorodesoxybenzoinoxime Tosylate.—The compound, *p,p′*-dichlorodesoxybenzoin, was prepared (32% yield, m.p. 112–113°) by the method of Jenkins and Richardson[8] except that *p*-chorobenzyl chloride was substituted for the previously used *p*-chlorobenzyl bromide. The oxime was prepared in 71% yield (m.p. 124–125.5° from benzene and hexane) by the usual method.[8] The corresponding oximetosylate was prepared in 72% yield (m.p. 94–96.5°) by the method employed for the preparation of desoxybenzoinoxime tosylate. An analytical sample (recrystallized from a benzene–hexane mixture) melted at 95–97° preheated bath).

Anal. Calcd. for $C_{21}H_{17}NSO_3Cl_2$: C, 58.07; H, 3.95. Found: C, 57.85; H, 3.89.

The Neber Rearrangement with *p,p′*-Dichlorodesoxybenzoinoxime Tosylate.—The reaction was performed in the usual manner[3] to give a 56% yield (m.p. 256.5–258°, bath preheated to 254°) of *p,p′*-dichlorodesylamine hydrochloride. An analytical sample was prepared by recrystallization of the material from methanol, m.p. 254.5–255.5° (bath preheated to 251°).

Anal. Calcd. for $C_{14}H_{12}OCl_3$: C, 53.11; H, 3.82. Found: C, 53.20; H, 3.91.

Preparation of *p,p′*-Dichlorodiphenylethylenimine from *p,p′*-Dichlorodesoxybenzoinoxime Tosylate by Lithium Aluminum Hydride Reduction of the Neber Reaction Intermediate.—The procedure for this reaction was analogous to that employed for the preparation of 2,3-diphenylethylenimine from desoxybenzoinoxime tosylate, except no solid was obtained on adding water to the filtered reaction mixture. Therefore the water–ethanol mixture (cold) was extracted with ether, the ether layer was well washed with water (0°) and cooled to −78°. This ether solution was then reduced with lithium aluminum hydride in the usual

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[12] A. Weissberger and H. Bach, *Ber.*, **64B**, 1095 (1931).

[13] The method of H. N. Wilson and A. E. Heron, *J. Chem. Ind.*, **60**, 167 (1941), was modified and standardized to make it similar to that of E. P. Clark, "Semimicro Quantitative Organic Analysis," Academic Press, Inc., New York, N. Y., 1943, pp. 82–93. In order to keep the temperature of the determination as low as practical, cyclohexanol was used which contained *ca.* 2.5 moles of water (m.p. 15.7°). Only very slight decomposition occurred while the molecular weight was being determined.

[14] S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 27–30.

manner, and the product was isolated. From 7.25 g. of starting ester was obtained 2.53 g. of white opaque prisms (hexane) of *p,p'* dichlorodiphenylethylenimine, m.p. 103–104°. Another 0.14 g. of product, m.p. 101–102.5°, was obtained by chromatography of the mother liquors; total yield 60%. Two recrystallizations of a portion of the product from ethanol (80%) gave an analytical sample, m.p. 104–105°.

Anal. Calcd. for $C_{14}H_{11}NCl_2$: C, 63.65; H, 4.20; mol. wt., 264. Found: C, 63.68; H, 4.45; mol. wt., 288 (Rast).

Reduction of *p,p'*-Dichlorodesylamine Hydrochloride with Lithium Aluminum Hydride to α-Amino-β-hydroxy-*p,p'*-dichlorodibenzyl.—Amine hydrochloride (3.00 g. or 0.0095 mole) was added in small portions to a slurry of 1.00 g. (0.028 mole) of lithium aluminum hydride. Hydrogen was evolved. After the mixture had been stirred (reflux) for 12 hours, water was added. The ether layer was separated, the aqueous layer was extracted with 100 ml. of ether, and the ether solutions were combined. After drying the solution, the solvent was evaporated under aspirator pressure to give pure white crystalline product, 1.94 g. (73% yield), m.p. 162.5–164°. Recrystallization of a sample of material (twice) from hot ethanol gave product of m.p. 163.5–164°.

Anal. Calcd. for $C_{14}H_{13}NOCl_2$: C, 59.59; H, 4.64. Found: C, 59.46; H, 4.61.

The hydrochloride of this aminoalcohol was prepared as follows. The aminoalcohol (1.50 g. or 0.0047 mole) was dissolved in 40 ml. of hot absolute ethanol and dry hydrogen chloride gas was bubbled through the solution for five minutes. The ethanol solution was then concentrated under vacuum. The white solid that formed was filtered and ether washed, wt. 1.45 g. Concentration of the filtrates produced another 0.12 g. of hydrochloride, total yield 94%, m.p. 236.5–237.5° (dec., heated at a rate of 7° per minute).

Preparation of *p,p'*-Dichlorodiphenylethylenimine from α-Amino-β-hydroxy-*p,p'*-dichlorodibenzyl Hydrochloride.—The hydrochloride (1.00 g.) was suspended in 35 ml. of ethanol-free chloroform, and 1.0 g. of phosphorus pentachloride was added at room temperature in six portions over a period of 30 minutes. The reaction vessel was shaken occasionally and allowed to stand for an hour. The mixture was concentrated to approximately 20 ml. under vacuum, and 100 ml. of dry ether was added. The white solid that separated was collected; wt. 0.78 g., m.p. 239.5–242.5° (dec.).

This salt (0.50 g.) was dissolved in 30 ml. of commercial absolute ethanol, and 0.30 ml. of 85% hydrazine was added. After standing for two hours the mixture was extracted with a three-to-one mixture of pure pentane and ether. When evaporated this extract left a small amount of oil which was dissolved in 4 ml. of pure benzene. The resulting solution was chromatographed through a 1.5 × 5 cm. column of alumina with a two-to-three mixture of benzene and pentane as eluant. The fraction of the column filtrates (*ca.* 135 ml.) collected after *ca.* 80 ml. of eluate had appeared provided (upon concentration under vacuum) 75 mg. of a solid. This solid largely dissolved in petroleum ether containing a small amount of benzene. The solution was decanted from the remaining material and was again submitted to chromatography on alumina as before. From the column eluates was isolated by evaporation of the solvent a solid which upon recrystallization (twice) from ether and pentane gave 6 mg. of white opaque needles, m.p. 104–105°. This melting point was undepressed by admixture of this material with the sample of *p,p'*-dichlorodiphenylethylenimine prepared by reduction of the intermediate obtained in the Neber arrangement. The two samples of ethylenimine had identical ultraviolet absorption spectra (see Fig. 1).

Preparation of 1,1-Bis-(*p*-chlorophenyl)-2-methylglycol.—Dry *p*-chlorobromobenzene (530 g. or 2.8 moles) in 800 ml. of dry ether was added to magnesium turnings (67.5 g. or 2.8 moles) under a nitrogen atmosphere. After the Grignard reagent was formed, a solution of 106 g. (0.90 mole) of ethyl lactate dissolved in 400 ml. of ether was added slowly. The mixture was stirred at reflux temperature for an hour, allowed to stand for 40 hours, and was decomposed by addition of 550 ml. of a 40% aqueous acetic acid solution. The ether layer was separated, filtered, washed with water, dried and the ether was evaporated. The oily residue largely solidified on standing, wt. 264 g. Recrystallization of the product from hot ligroin gave pure white clumps, m.p. 95.5–96°.

Anal. Calcd. for $C_{15}H_{14}Cl_2O_2$: C, 60.59; H, 4.75. Found: C, 60.54; H, 4.99.

Dehydration of 1,1-Bis-(*p*-chlorophenyl)-2-methylglycol and Oximation of the Ketonic Product.—The glycol (11.5 g. or 0.0387 mole) was dissolved in 140 ml. of concentrated sulfuric acid at 0°. The glycol became a gum which went into solution slowly. After standing at 0° for one hour and at room temperature for two hours, the mixture was poured onto *ca.* 600 ml. of cracked ice. The resulting aqueous mixture was extracted with ether, the extracts were washed with water, dried and the solvent was evaporated. The residual oil did not crystallize and was therefore converted directly to the oxime as follows. The oil was boiled for 15 minutes with a threefold molar quantity of hydroxylamine hydrochloride and a twofold molar quantity of sodium acetate in 70% ethanol. The mixture was allowed to stand overnight, and the crystals that separated were collected (fine white needles), wt. 7.4 g., m.p. 167–170°. From the filtrate was obtained a second crop, wt. 2.4 g., m.p. 165–167° (over-all yield 86%). A portion of the material after recrystallization from ethanol and water gave pure 1,1-bis-(*p*-chlorophenyl)-2-propanoneoxime, m.p. 173°.

Anal. Calcd. for $C_{15}H_{13}Cl_2NO$: C, 61.34; H, 4.58. Found: C, 61.30; H, 4.58.

Hydrolysis of a small amount of oxime with 2 *N* hydrochloric acid at reflux temperature gave oily ketone which was converted to the semicarbazone in the usual manner, m.p. 182–183°. The melting points of both the oxime and semicarbazones correspond well with those reported for the substances prepared by an entirely different method.[15]

Preparation of 1,1-Bis-(*p*-chlorophenyl)-2-propanoneoxime Tosylate.—Recrystallized oxime (8.82 g. or 0.030 mole, m.p. 172–173°) dissolved in 105 ml. of chloroform and 350 ml. of pure ether was mixed with 4.73 g. (0.030 mole) of pure *p*-toluenesulfonyl chloride, and the mixture was cooled to 0°. An aqueous solution of potassium hydroxide (33 g. in 150 ml. of water) was added, and the resulting mixture was shaken violently for three hours at room temperature. The organic layer was separated, additional ether was added (100 ml.), and the solution was washed three times with 200-ml. portions of water. The solution was then dried with anhydrous potassium carbonate, and the solvent was evaporated under vacuum to a sticky white solid. This material was crystallized from a mixture of chloroform, ether and hexane to give 9.2 g. (60% yield) of ester, m.p. 82–83.5° (dec., heated from room temperature at 1° per minute). Two recrystallizations of the material gave white plates, m.p. 92–94° (dec., heated from room temperature at 1° per minute). This compound was very unstable and had to be analyzed immediately.

Anal. Calcd. for $C_{22}H_{19}Cl_2NSO_3$: C, 58.93; H, 4.27. Found: C, 59.16; H, 4.56.

Reaction of 1,1-Bis-(*p*-chlorophenyl)-2-propanoneoxime Tosylate with Potassium Ethylate.—Oxime tosylate (2.75 g., m.p. 84–85° dec.) was powdered and suspended in 24 ml. of commercial absolute ethanol, and the solution was cooled to at least −10°. A solution of potassium ethylate (0.24 g. of potassium plus 8.0 ml. of commercial absolute ethanol) was added in three portions. The mixture was shaken for one hour at room temperature and the precipitated potassium ethylate was collected and washed with ether (wt. 1.16 g.). The filtrate was evaporated under reduced pressure (below 30°) to give a viscous translucent residue which was dissolved in 20 ml. of ether. The ether solution was filtered from a small amount of potassium tosylate and one-tenth of the filtrate was removed. Hydrogen chloride gas (dry) when bubbled through this aliquot produced only a slight cloudiness. The remainder of the solution was concentrated as before, and the sirup produced (1.5 g.) was allowed to stand at 0°. After ten days the material largely crystallized, and recrystallization of part of the material from hexane gave a soft white powder, m.p. 62–63° (1°/min.). This material is possibly the O-ethyl ether of the oxime and not the N-ethyl derivative, since the latter class of compounds are basic enough to form salts with dry hydrogen chloride in dry ether.

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(15) H. Erlenmeyer, P. Bitterle and E. Sorkin, *Helv. Chim. Acta*, **31**, 466 (1948).

Anal. Calcd. for $C_{17}H_{17}Cl_2NO$: C, 63.36; H, 5.32. Found: C, 62.94; H, 5.32.

Pyrolysis of 1,1-Bis-(*p*-chlorophenyl)-2-propanoneoxime Tosylate.—Oxime tosylate (2.8 g., m.p. 86–87°, 1 deg. per min.) was heated in a short-path still equipped with a Dry Ice cooled receiver. The temperature of the heating-bath was 100° at the start and was allowed to rise over a 20-minute period to 160°. A colorless distillate (0.20 g.) which was miscible with water was obtained. This was demonstrated to be acetonitrile from its boiling and melting points and through its conversion to acetophenone. The latter compound was converted to a 2,4-dinitrophenylhydrazone which was compared to an authentic sample, m.p. 240–241° (dec.), m.m.p., 240–241° (dec.).

Preparation and Rearrangement of 1,1-Diphenylacetoneoxime Tosylate.—The oxime of 1,1-diphenylacetone (4.5 g., m.p. 164–165°)[16] was converted to the tosylate ester by a procedure analogous to that employed for the preparation of *p,p'*-dichlorodesoxybenzoinoxime tosylate from the corresponding oxime; yield 72%, m.p. 72–73° (dec., bath preheated to 70°).

Anal. Calcd. for $C_{23}H_{21}NSO_3$: C, 69.62; H, 5.58. Found: C, 69.74; H, 5.60.

This oxime ester (0.95 g.) in 10 ml. of pyridine was heated at reflux for 15 minutes. The mixture was then poured into 300 ml. of water. The precipitate that separated was recrystallized from benzene to give 0.30 g. of white needles, m.p. 133–136°. Two more recrystallizations of the substance gave m.p. 147°, which corresponds to the melting point of N-acetylbenzhydrylamine.[17] This compound when warmed with concentrated hydrochloric acid and a little ethanol gave a pronounced odor of ethyl acetate.

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[16] R. Stoermer, *Ber.*, **39**, 2302 (1906).

[17] M. Busch and L. Leefhelm, *J. prakt. Chem.*, **72**, 14 (1908).

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

Alkaloids from *Tripterygium wilfordii* Hook. The Structure of Wilforine, Wilfordine, Wilforgine and Wilfortrine

BY MORTON BEROZA

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All the fragments resulting from the degradation of the ester alkaloids wilforine, wilfordine, wilforgine and wilfortrine have been isolated, and the formula for the sum of the components of each alkaloid is in agreement with the molecular formula calculated from the elementary analyses of each alkaloid. It has been shown by elementary analysis, paper chromatography and X-ray diffraction patterns that the four alkaloids possess the same polyhydroxy nucleus, $C_{15}H_{26}O_{10}$. This nucleus contains ten hydroxyl groups, but only eight of them are esterified in the intact alkaloid—five with acetic acid, one with either benzoic or 3-furoic acid, and two with a nitrogen-containing dicarboxylic acid. Wilforine and wilforgine possess the same dicarboxylic acid and wilfordine and wilfortrine possess the same dicarboxylic acid, but the latter acid is the hydroxy congener of the former. Permanganate oxidation of both dicarboxylic acids gives acetic, oxalic and quinolinic acids. The dicarboxylic acids are 2-substituted nicotinic acid derivatives, and the probable formulas of these acids are given.

Wilfordine, the insecticidal alkaloid isolated from the roots of *Tripterygium wilfordii* Hook,[1] has been shown by countercurrent distribution to be a mixture.[2] From this mixture four ester alkaloids, designated wilforine, wilfordine, wilforgine and wilfortrine[3,4] have been isolated by partition chromatography employing ultraviolet absorbancy ratios.[2] Countercurrent distribution patterns of the alkaloids indicate that they were pure. Upon saponification wilforine and wilfordine yielded 1 mole of benzoic acid, 5 moles of acetic acid and 2 moles of steam non-volatile acid per mole of alkaloid, whereas wilforgine and wilfortrine yielded 1 mole of 3-furoic acid, 5 moles of acetic acid and 2 moles of steam non-volatile acid per mole of alkaloid.

In addition to acetic and benzoic acids, the saponification of wilforine yielded a steam non-volatile nitrogeneous dibasic acid of molecular formula $C_{11}H_{13}O_4N$, m.p. 195–196°. From wilforgine an identical acid was obtained.

A steam non-volatile nitrogeneous dibasic acid was also obtained from wilfordine and wilfortrine. These acids, which were found to be identical, had a molecular formula of $C_{11}H_{13}O_5N$, m.p. 178–179°.

The solutions remaining after the removal of the acids were neutralized and evaporated to dryness, and the residue was extracted with hot methanol. Evaporation of these extracts yielded in each case the same polyhydroxy nucleus, whose molecular formula is $C_{15}H_{26}O_{10}$. The compound does not have a definite melting point, but darkens as the temperature is slowly raised above 240°. It shows no absorption in the ultraviolet.

The sums of the component parts of wilforine, wilfordine, wilforgine and wilfortrine are in agreement with the respective formulas calculated from the elementary analyses on the intact alkaloids.

Experimental[5]

The operations in the structure studies are summarized in the diagram.

Isolation of Acids from Saponified Alkaloid.—The alkaloids were saponified as already described.[3,4] The neutralized saponification mixture was made alkaline to phenolphthalein with a few drops of 0.1 *N* sodium hydroxide and then continuously extracted with ether in an all-glass apparatus for 24 hours to remove the diethylene glycol. The ether extract was discarded. The extracted water solution was carefully acidified with dilute sulfuric acid to *p*H 2.8 and continuously extracted with ether for at least 24 hours. A soda lime tube was used to exclude atmospheric carbon dioxide. If the *p*H of the water solution after the ether extraction differed much from 2.8, it was readjusted to this *p*H and again extracted for 24 hours. Extraction was complete when the ultraviolet absorbancy of the water solution was low: ml. × absorbancy at 272 mμ ÷ 26 = mg. dibasic acid (approximate). The water solution contained the polyhydroxy nucleus of the alkaloid and was held aside to be worked up as described below. The ether extract, which

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(1) F. Acree and H. L. Haller, THIS JOURNAL, **72**, 1608 (1950).

(2) M. Beroza, *Anal. Chem.*, **22**, 1507 (1950).

(3) M. Beroza, THIS JOURNAL, **73**, 3656 (1951).

(4) M. Beroza, *ibid.*, **74**, 1585 (1952).

(5) All m.p.'s are corrected. Determinations of carbon, hydrogen and nitrogen were made by Oakwold Laboratory, Alexandria, Virginia.