[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

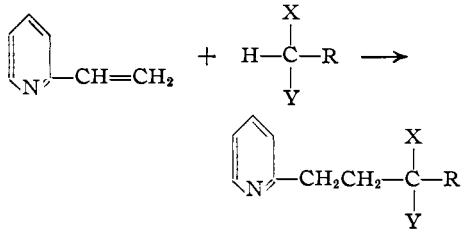
Curariform Activity and Chemical Structure. V.[1] Syntheses in the Quinolizidine Series[2]

BY V. BOEKELHEIDE AND SEYMOUR ROTHCHILD[3]

An examination of the compounds possessing curariform activity reveals that a fused bicyclic ring system with nitrogen common to both rings is a structural feature present in many of the highly active compounds.[4] For example, such a ring system is present, or thought to be present, in members of the erythrina, calabash curare, and canadine alkaloids as well as in certain active synthetic compounds.[5] In view of this coincidence between curariform activity and the presence of a bicyclic, fused, nitrogen-containing ring system, model compounds based on the quinolizidine[6] nucleus have been prepared and tested to determine whether this structural unit, by itself, is sufficient for curariform activity. The results of testing the various derivatives, which are described in this paper, indicate that simple quinolizidines, either as tertiary or quaternary amine salts, do not possess appreciable curariform activity.

Although the simple quinolizidines did not have the desired physiological activity, the chemistry of their preparation proved to be quite interesting. Despite the number of syntheses of quinolizidine derivatives which have been reported,[7] particularly in investigations of the lupinane alkaloids, it seemed desirable to find a method which would be simpler and of more general applicability than those available. The development of such a method was facilitated by the discovery that 2-vinylpyridine can be employed effectively in the Michael reaction.[8a,b] It has now been found that the addition products of 2-vinylpyridine with active methylene compounds are particularly well suited for conversion to quinolizidines by reductive cyclization. Thus, the combination of Michael addition followed by reduction represents a two-step synthesis for a variety of quinolizidine derivatives.

In the present study the Michael additions of diethyl malonate, diethyl ethylmalonate, ethyl acetoacetate and acetylacetone to 2-vinylpyridine have been utilized to obtain I, II, III and IV, respectively. With the exception of acetylacetone, the additions proceeded readily and gave good yields of product.



I, X = $-CO_2Et$, Y = $-CO_2Et$, R = $-H$
II, X = $-CO_2Et$, Y = $-CO_2Et$, R = $-Et$
III, X = $-CO_2Et$, Y = $-COCH_3$, R = $-H$
IV, X = $-COCH_3$, Y = $-COCH_3$, R = $-H$
V, X = $-CO_2Et$, Y = $-H$, R = $-Et$
VI, X = $-COCH_3$, Y = $-H$, R = $-H$

The addition reactions of 2-vinylpyridine have been pictured by Doering and Weil[8a] as an attack by nucleophilic reagents on the electrophilic 2-vinylpyridine. In agreement with this picture it was found that the additions of the active methylene compounds, mentioned above, were most effectively catalyzed by bases, such as sodium or sodium ethoxide, which act by producing the nucleophilic anion of the active methylene compound. However, with ethyl acetoacetate, the addition could also be accomplished in good yield by the use of an acidic catalyst, dry hydrogen chloride. In this case the reaction probably involves an attack by the electrophilic 2-vinylpyridinium ion on the neutral ethyl acetoacetate molecule.

When basic catalysts were employed, it was necessary to control the reaction conditions carefully to avoid the side reactions typical of Michael additions. For example, the addition of diethyl ethylmalonate in the absence of solvent gave the expected adduct, II, but, when alcohol was employed as solvent, the main product was V. Apparently II is dissociated by base in the presence

(1) For paper IV in this series, see Craig and Tarbell, THIS JOURNAL, **71**, 465 (1949).

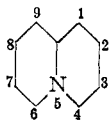
(2) Aided by a Grant from the National Foundation for Infantile Paralysis.

(3) Present address: Tracerlab, Inc., Boston, Massachusetts.

(4) For a summary on curariform activity and chemical structure, see Craig, *Chem. Rev.*, **42**, 285 (1948).

(5) Craig and Tarbell, THIS JOURNAL, **70**, 2783 (1948).

(6) The name quinolizidine is employed in this paper to designate the saturated compound shown at the right. This compound has been referred to in the literature by various names including octahydroquinolizine, quinolizidine, octahydropyridoccoline, norlupinane, and 1-azabicyclo-(0,4,4)decane. *Chemical Abstracts* lists both octahydroquinolizine and norlupinane. The name quinolizidine seems superior and has been chosen for the following reasons: (1) The corresponding unsaturated compound is generally called quinolizine, and so quinolizidine has a structural basis which norlupinane does not have. (2) Although octahydroquinolizine is indicative of structure, it is too unwieldy for referring to large numbers of compounds. (3) The use of quinolizidine is consistent with the use of pyrrolizidine, which is commonly accepted for 1-azabicyclo(0,3,3)octane. The system of numbering used for quinolizidine is that employed by *Chemical Abstracts*.



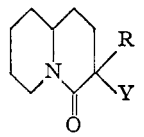
(7) See, for example, Clemo, Ramage and Raper, *J. Chem. Soc.*, 2959 (1932); Clemo, Morgan and Raper, *ibid.*, 965 (1937); Diels and Alder, *Ann.*, **498**, 16 (1932); Winterfeld and Holschneider, *ibid.*, **499**, 109 (1932); and Prelog and Bozicevic, *Ber.*, **72**, 1103 (1939).

(8) (a) Doering and Weil, THIS JOURNAL, **69**, 2461 (1947); (b) Boekelheide and Rothchild, *ibid.*, **69**, 3149 (1947).

of alcohol to give diethyl carbonate and V.[9] Likewise, the addition of acetylacetone gave both IV and VI, although under the proper conditions IV was the primary product. The formation of adducts, corresponding to two molecules of 2-vinylpyridine to one of active methylene compound, occurred to an appreciable extent only in the case when 2-vinylpyridine and diethyl malonate were employed in a 1:1 molar ratio.

The reductive cyclization of the addition products of 2-vinylpyridine to give quinolizidine derivatives was investigated under various conditions using as catalysts, Raney nickel, platinum oxide, and copper chromite, respectively. A few experiments were also carried out using lithium aluminum hydride. Inasmuch as the nature of the products differed under different catalytic conditions, the reductive cyclizations are discussed according to the catalyst employed.

Raney Nickel Reductions.—When substituted γ-(2′-pyridyl)-butyric esters were treated with Raney nickel catalyst at 125–150° under hydrogen pressures of one hundred atmospheres or more, it was found that reduction and cyclization occurred simultaneously to give the corresponding 4-ketoquinolizidines in high yields. By this method I, II, III, and V were converted to VII, VIII, IX and X, respectively, in yields ranging from 75 to 97%.



VII, R = —H, Y = —CO_2Et
VIII, R = —Et, Y = —CO_2Et
IX, R = —H, Y = —$CHOHCH_3$
X, R = —Et, Y = —H
XI, R = —H, Y = —H

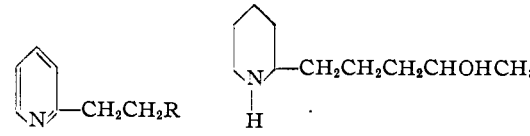
The structure of VII was established by its conversion on hydrolysis and decarboxylation to 4-ketoquinolizidine, XI, which was identified by the preparation of the hydrochloride[10] and also by its reduction with copper chromite to quinolizidine, XV. The structures of VIII, IX and X were assumed on the basis of analogy and because their subsequent reactions were consistent with these structures.

The reduction with Raney nickel of 1-(2′-pyridyl)-4-pentanone, VI, which was obtained from III by hydrolysis and decarboxylation, followed a different course at low temperatures than at high. At 120°, VI gave primarily XIV, whereas at 200° the product was almost entirely XVI. Since the reductive cyclization of 1-(2′-piperidyl)-4-pentanone would be expected to occur very readily, it can be concluded that the carbonyl group was reduced prior to the pyridine ring. The reaction must proceed by reduction of the intermediate 1-(2′-pyridyl)-4-pentanol, XII, to XIV, which at low temperatures is stable but which at higher temperatures undergoes cyclodehydration to give XVI.

(9) Similar reverse Claisen condensations have been frequently observed; see Cope and McElvain, THIS JOURNAL, **54**, 4319 (1932); and Connor, *ibid.*, **55**, 4597 (1933).

(10) For previous identifications of 4-ketoquinolizidine, see Ochiai, Tsuda and Yokoyama, *Ber.*, **68**, 2291 (1935), and ref. 8.

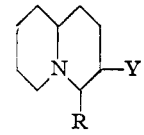
In support of this it was found that treatment of XIV with Raney nickel at 200° gave XVI. This is in agreement with the results previously found for the reductive cyclization of 2-(γ-hydroxypropyl)-pyridine.[11]

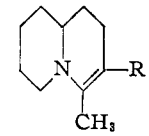


XII, R = —$CH_2CHOHCH_3$
XIII, R = —$CH(CH_2OH)_2$

XIV

Further evidence that the carbonyl group was reduced prior to the pyridine ring was obtained from a study of the reduction of III. If the pyridine ring were reduced first, it would be expected that cyclization would occur with the carbonyl group rather than the ester, and the product would be XVII. However, at 115°, III gave a 75% yield of IX and only 14% of XVII. The formation of XVII occurred in better yield at higher temperatures, though. At 200° there was obtained a 35% yield of XVII, a 15% yield of IX, and a small amount of XVI.





XV, R = —H, Y = —H
XVI, R = —CH_3, Y = —H
XVII, R = —CH_3, Y = —CO_2Et
XVIII, R = —H, Y = —Et
XIX, R = —CH_3, Y = —$CHOHCH_3$
XX, R = —CH_3, Y = —CO_2H
XXI, R = —CH_3, Y = —CH_2OH

XXII, R = —CO_2Et
XXIII, R = —$CHOHCH_3$

Platinum Oxide Reductions.—Since the pyridine ring is readily reduced in acid with platinum oxide at room temperature under an atmospheric pressure of hydrogen, this method was applied to several pyridyl ketones in an attempt to obtain cyclization of the pyridine ring with the carbonyl group. When III was reduced in this way, there was obtained a 42% yield of XVII plus a 38% yield of XXII.

The relationship of XXII to XVII was clearly established by the fact that XXII, on reduction in alcohol with platinum oxide catalyst, gave XVII in excellent yield. The presence of unsaturation in XXII was also shown by a test with permanganate solution. Since XXII is much less basic than XVII, the double bond must be adjacent to the nitrogen.

Although the structure of XVII was not rigorously established, there can be little doubt as to its correctness. XVII underwent the reactions to be expected of it and was readily shown to possess a carbethoxyl group. On hydrolysis, it gave the corresponding acid, XX, and by reduction with lithium aluminum hydride it was converted to the corresponding alcohol, XXI.

(11) Boekelheide and Rothchild, THIS JOURNAL, **70**, 864 (1948).

The formation of incompletely reduced products, such as XXII, during reductive cyclization with platinum oxide in acid is apparently a common behavior. When IV was reduced in acid solution, there was obtained in excellent yield an unsaturated compound, to which structure XXIII is assigned. In support of this structure, it was found that the compound reduced permanganate solution, did not react with carbonyl reagents, did not form a picrate, and decomposed on standing. Furthermore XXIII was readily reduced in neutral solution with platinum oxide to give the corresponding saturated derivative, XIX. As would be expected, XIX was a stable, colorless oil, which readily formed a picrate.

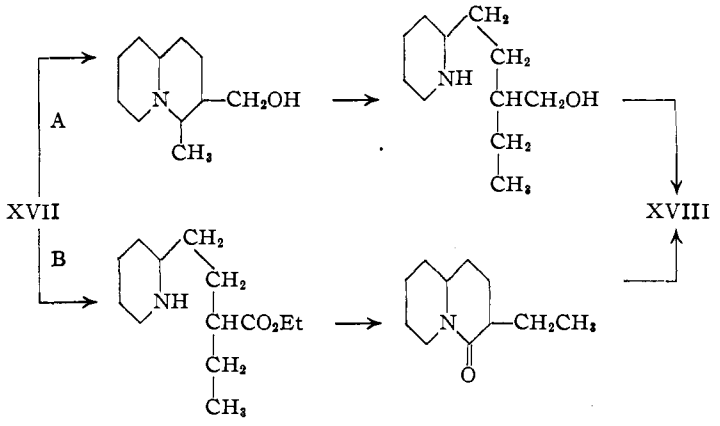
In agreement with the work of Galinovsky and Stern,[12] it was found that, with platinum oxide in acid, 4-ketoquinolizidines were reduced to the corresponding saturated derivatives. In this manner 3-ethyl-4-ketoquinolizidine, X, was reduced to 3-ethylquinolizidine, XVIII.

Copper Chromite Reductions.—The use of copper chromite at 250° was first attempted in order to convert the 4-ketoquinolizidines, obtained by Raney nickel reduction, to the corresponding saturated derivatives. In this way XI was readily reduced to quinolizidine, XV, in 75% yield. Also it was found that the reduction of V gave XVIII in good yield, illustrating that γ-pyridylbutyric esters can be converted in one step by copper chromite reduction to the corresponding saturated, cyclic derivatives. However, when the reduction of VII was attempted in the hope of preparing 3-hydroxymethylquinolizidine, an isomer of lupinine, there was obtained mainly quinolizidine plus a small amount of XI.

The loss of the carbethoxyl group in the reduction of VII is not surprising, though, in view of the well-known cleavages of substituted malonic esters by copper chromite.[13] Actually the copper chromite cleavage may be utilized for the preparation of quinolizidine on a practical scale.[8b] The direct copper chromite reduction of I gave a 65% yield of quinolizidine.

When reduction with copper chromite was tried with III, it was again found that cleavage occurred and from the reaction there was isolated quinolizidine and 3-ethylquinolizidine. However, the reaction product represented a complex mixture of which at least one of the components was not identified. In an attempt to simplify the number of reaction products, copper chromite reductions of IX and XVII, the intermediate cyclization products of III, were investigated. It was found that IX gave mainly 3-ethylquinolizidine plus some quinolizidine and a small amount of material which was not identified. On the other hand XVII was reduced with copper chromite to give a fair yield of 3-ethylquinolizidine.

Although the formation of 3-ethylquinolizidine would be expected from IX, its formation from XVII can only be accomplished by rearrangement. Two plausible routes for such a rearrangement are as follows:



The cleavage of a carbon to nitrogen bond during reduction of a β-amino ester, which is the essential step in route B, seems quite likely since Folkers and Adkins have found that this type of cleavage occurs during the reduction of ethyl N-ethyl nipecotate.[14] However, the reductive cleavage of a β-amino alcohol, which is the essential step in route A, has also been reported.[15] At present it is not possible to decide between the two routes.

Lithium Aluminum Hydride.—Lithium aluminum hydride was found to be of value chiefly for the reduction of esters to the corresponding carbinols. Thus, I with an excess of lithium aluminum hydride gave only the corresponding glycol, 2-hydroxymethyl-4-(2′-pyridyl)-1-butanol (XIII). Reduction of the pyridine ring did not occur. Similarly, XVII on reduction with lithium aluminum hydride gave XXI in good yield.

When VII was treated with an excess of lithium aluminum hydride, the reaction took an unusual course and the only product to be isolated was XI. Apparently, lithium aluminum hydride can cause cleavages similar to those which occur during copper chromite reductions.

The compounds in this series were tested by intraperitoneal injection into mice. Compounds VII, VIII, IX and XXI were tested as aqueous emulsions, whereas the hydrochloride salts of XV, XVII, XIX, XXI, 5-methylquinolizidinium iodide and 5-benzyl-3-hydroxymethyl-4-methylquinolizidinium bromide were tested as aqueous solutions. None of these compounds exhibited curariform activity.

(12) Galinovsky and Stern, *Ber.*, **76**, 1034 (1943).

(13) Connor and Adkins, THIS JOURNAL, **54**, 4678 (1932); and Mozingo and Folkers, *ibid.*, **70**, 227 (1948).

(14) Folkers and Adkins, *ibid.*, **54**, 1145 (1932).

(15) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 88–89.

Acknowledgment.—We are indebted to F. M. Berger, M.D., of the Department of Pediatrics, University of Rochester School of Medicine and Dentistry, for the pharmacological tests which have been reported.

Experimental[16]

Michael Additions to 2-Vinylpyridine

Diethyl β-(2-Pyridyl)-ethylmalonate, I.—Diethyl malonate (375 g., 2.35 moles) was added to a solution of sodium ethoxide (23 g. of sodium in 225 ml. of absolute alcohol) in a 1-liter flask equipped with condenser, drying tube, and a dropping funnel. To the boiling mixture, freshly distilled 2-vinylpyridine (106 g., 1.0 mole) in 175 ml. of absolute alcohol was added slowly. After the mixture had boiled under reflux for two hours, the alcohol was removed by distillation and the residue was acidified with dilute hydrochloric acid. The unreacted malonic ester was extracted with ether, the aqueous phase was made basic with dilute sodium hydroxide, and the basic organic layer was extracted with ether. After the ethereal solution had been dried over Drierite, the ether and recovered 2-vinylpyridine (b. p. 58° at 16 mm.) were removed *in vacuo*. The residue on distillation yielded 140 g. (53%) of a clear yellow oil; b. p. 135–140° at 0.02 mm.; $n^{25}D$ 1.4845.

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.35; H, 7.26; N, 5.27.

The **picrate** of I formed slowly in ethanol over a period of several days and was obtained after recrystallization from ethanol as yellow needles, m. p. 85.0–85.5.

Anal. Calcd. for $C_{20}H_{22}O_{11}N_4$: C, 48.73; H, 4.24. Found: C, 48.58; H, 4.48.

Diethyl Di-(β-(2-pyridyl)-ethyl)-malonate.—When the preparation of I was carried out as above with equimolar quantities of 2-vinylpyridine and diethyl malonate, the maximum yield of I was only 15%. The major product was a dark viscous oil which was obtained by molecular distillation at above 190° at 1 mm. The dark oil formed a picrate in ethanol and, after crystallization from ethanol, the picrate was obtained as yellow crystals, m. p. 171–172°. The composition of the picrate, as revealed by analysis, agrees with that for the dipicrate of diethyl di-(β-(2-pyridyl)-ethyl)-malonate.

Anal. Calcd. for $C_{33}H_{32}N_8O_{18}$: C, 47.77; H, 3.89. Found: C, 47.95; H, 3.77.

Diethyl Ethyl-β-(2-pyridyl)-ethylmalonate, II.—A mixture of 2-vinylpyridine (31.5 g., 0.3 mole), diethyl ethylmalonate (84.7 g., 0.45 mole) and 2.3 g. of sodium was boiled under reflux for two hours. After the mixture had cooled, there was added 75 ml. of dilute hydrochloric acid. The product was then isolated according to the procedure given for the isolation of I, yielding 34.0 g. (39%) of a yellow oil; b. p., 138–150° at 0.2 mm.; $n^{20}D$ 1.4894.

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.91. Found: C, 65.11; H, 7.97.

The **picrate** of II formed in ethanol over a period of several days and was obtained by recrystallization from ethanol as yellow crystals, m. p. 88.5–89.5°.

Anal. Calcd. for $C_{22}H_{26}N_4O_{11}$: C, 50.57; H, 5.02. Found: C, 50.58; H, 4.84.

When a small amount of II was boiled with concentrated hydrochloric acid, both hydrolysis and decarboxylation occurred. By careful neutralization of the acidic solution there was obtained a white granular solid. After crystallization from dilute ethanol, the white solid, α-ethyl-γ-(2-pyridyl)-butyric acid, was found to melt at 126.5–128°. A sample of the acid, when mixed with a sample of the acid obtained from V (see below), melted at 127–128°.

(16) Analyses by Mrs. G. L. Sauvage and the Micro-Tech Laboratories: all melting points are corrected.

Ethyl α-Ethyl-γ-(2-pyridyl)-butyrate, V.—When the addition of diethyl ethylmalonate to 2-vinylpyridine was carried out according to the procedure given for the preparation of I, there were obtained two fractions on distillation of the product. The higher boiling fraction, obtained in 28% yield, was shown to be II by preparation of the picrate. The lower boiling fraction, V, was obtained in 47% yield as a yellow oil; b. p. 115–122° at 0.5 mm.; $n^{22}D$ 1.4851.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 69.85; H, 8.59.

α-Ethyl-γ-(2-pyridyl)-butyric Acid.—A solution of V (5.9 g.) in 10 ml. of concentrated hydrochloric was boiled under reflux for three hours. The reaction mixture was evaporated to dryness, the residue was taken up in dilute sodium hydroxide solution, and the basic solution was extracted with ether. When the aqueous phase was acidified with acetic acid, a white granular solid (2.6 g.) separated from the solution. After several recrystallizations from dilute ethanol, the acid was obtained as white crystals, m. p. 129–129.5°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.38; H, 7.83. Found: C, 67.88; H, 7.90.

Ethyl β-(2-Pyridyl)-ethylacetoacetate, III.—Dry hydrogen chloride was bubbled rapidly into a mixture of 2-vinylpyridine (26.0 g.) and ethyl acetoacetate (65.0 g.) for ten minutes. The mixture was then boiled under reflux for three hours. After the mixture had cooled, there was added 100 ml. of 3 *N* hydrochloric acid. The product was then isolated according to the procedure given for the isolation of I, yielding 29.0 g. (50%) of III; b. p. 138–150° at 1.0 mm.; $n^{22}D$ 1.500.

III was also prepared by the method of Doering and Weil.[8a] The yields by their procedure varied from 57 to 62%.

In the preparation of III by the method of Doering and Weil, there was also obtained a small yield of a white, needle-like solid, m. p. 172–173°. It is presumed that this is the same compound as that obtained by Collie and Chrystall[17] by heating ethyl acetoacetate with sodium ethoxide.

3-Acetyl-1-(2′-pyridyl)-4-pentanone, IV.—The addition of acetylacetone to 2-vinylpyridine was carried out according to the procedure described for the preparation of I using 31.5 g. of 2-vinylpyridine, 60.0 g. of acetylacetone, 2.3 g. of sodium and 50 ml. of absolute ethanol. Two fractions were obtained on distillation of the product. The lower boiling fraction consisted of 3.7 g. (7%) of a light yellow oil; b. p. 89–116° at 0.05 mm.; $n^{22}D$ 1.5062. This was shown to be 1-(2′-pyridyl)-4-pentanone, VI, by preparation of the picrate, m. p. 111–112°. A mixture of the picrate with the picrate of an authentic sample of VI showed no depression of melting point.

The higher boiling fraction, IV, consisted of 10.8 g. (16%) of a light yellow oil; b. p. 116–122° at 0.05 mm.; $n^{22}D$ 1.5228.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.20; H, 7.37. Found: C, 70.07; H, 7.42.

The **picrate** of IV formed readily in ethanol and was obtained by recrystallization from ethanol as yellow clusters, m. p. 117–118°.

Anal. Calcd. for $C_{18}H_{18}N_4O_9$: C, 49.77, H, 4.18. Found: C, 49.53; H, 4.18.

When the preparation of IV was attempted according to the method of Doering and Weil for the preparation of III, the only product was a small yield of VI. Also, when the preparation of IV as given above was altered by employing larger amounts of sodium and ethanol, the yield of IV was markedly decreased and the yield of VI was increased.

1-(2′-Pyridyl)-4-pentanone, VI.—This was prepared by the hydrolysis and decarboxylation of III according to the procedure of Doering and Weil.[8a] VI was obtained in yields of 87 to 90%.

(17) Collie and Chrystall, *J. Chem. Soc.*, **91**, 1802 (1907).

Reductions with Raney Nickel

3-Carbethoxy-4-ketoquinolizidine, VII.—A mixture of 27.2 g. of I, 15 ml. of ethanol, and 5 g. of Raney nickel was heated at 145° for one hour under a hydrogen pressure of 200 atmospheres. After separation of the catalyst by filtration, the solvent was removed *in vacuo* and the residue was distilled. There was obtained 22.2 g. (97%) of a pale yellow oil; b. p. 145–155° at 0.5 mm.; $n^{22}D$ 1.5022.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.92; H, 8.47; N, 5.97.

4-Ketoquinolizidine, XI.—A solution of 13.4 g. of VII in 50 ml. of concentrated hydrochloric acid was boiled under reflux for three hours. The solution was evaporated to dryness, and the residue was treated according to the procedure which Ochiai, Tsuda and Yokoyama[10] employed for the conversion of γ-(2-pyridyl)-butyric acid hydrochloride to 4-ketoquinolizidine. On distillation there was obtained 5.2 g. (57%) of a colorless oil; b. p. 97° at 1.5 mm.

The identity of the 4-ketoquinolizidine was established by the preparation of the hydrochloride which melted at 143–145° (lit.,[10] m. p. 146–147°). Also the 4-ketoquinolizidine was reduced by copper chromite to quinolizidine (*vide infra*).

3-Ethyl-3-carbethoxy-4-ketoquinolizidine, VIII.—Following the procedure given above for the preparation of VII, the reductive cyclization of II was readily accomplished. Reduction was complete in three hours, and on working up the product there was obtained an 84% yield of a colorless oil; b. p. 140–145° at 0.8 mm.; $n^{22}D$ 1.4891.

Anal. Calcd. for $C_{14}H_{23}O_3N$: C, 66.38; H, 9.15. Found: C, 66.49; H, 9.06.

3-Ethyl-4-ketoquinolizidine, X.—The reductive cyclization of V was carried out according to the procedure given above for the preparation of VII. From 4.9 g. of V there was obtained 3.1 g. (78%) of a colorless oil; b. p. 125–128° at 0.5 mm.; $n^{23}D$ 1.4957.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.87; H, 10.56. Found: C, 72.69; H, 10.54.

Reduction of Ethyl β-(2-Pyridyl)-ethylacetoacetate.—The reduction of ethyl β-(2-pyridyl)-ethylacetoacetate, III, was carried out according to the procedure previously given for the preparation of VII. On distillation there were obtained two products: 3-(α-hydroxyethyl)-4-ketoquinolizidine, IX, and 3-carbethoxy-4-methylquinolizidine, XVII. The reduction was repeated several times to find the effect of temperature on the relative yields of IX and XVII. The results are shown in Table I.

TABLE I

Temperature, °C.	% of IX	% of XVII	Total yield, %
115	75	14	89
140	73	20	93
200	15	36	56[a,b]

[a] This includes a 5% yield of 4-methylquinolizidine, XVI, which was identified by its picrate, m. p. 191–194°. A mixed melting point determination with the picrate of an authentic sample of XVI showed no depression. [b] Total yield is low because of mechanical loss.

IX and XVII were characterized as follows:

3-Carbethoxy-4-methylquinolizidine, XVII, was obtained as a colorless oil; b. p. 105–120° at 1.5 mm.; $n^{22}D$ 1.4820.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.30; H, 10.29. Found: C, 69.41; H, 10.45.

The picrate of XVII formed readily in ethanol and was obtained by recrystallization from ethanol as a yellow granular solid, m. p. 127.5–128.5°.

Anal. Calcd. for $C_{19}H_{26}N_4O_9$: C, 50.22; H, 5.77. Found: C, 50.65; H, 5.69.

3-Carboxy-4-methylquinolizidine, XX, was readily obtained by hydrolysis of a small amount of XVII with dilute hydrochloric acid. An attempt to isolate the acid as the hydrochloride was unsucessful, but the picrate was readily prepared. After crystallization from ethanol, the picrate of XX was obtained as a yellow amorphous solid, m. p. 203–205°.

Anal. Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.88; H, 5.20. Found: C, 48.08; H, 5.32.

3-(α-Hydroxyethyl)-4-ketoquinolizidine, IX, was obtained as a viscous, slightly yellow oil; b. p. 145–155° at 1.5 mm.; $n^{20}D$ 1.5090.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.66. Found: C, 66.69; H, 9.26.

Reduction of 1-(2′-Pyridyl)-4-pentanone.—The reduction of 1-(2′-pyridyl)-4-pentanone, VI, was carried out according to the procedure previously given for the preparation of VII. On distillation there were obtained two products: 4-methylquinolizidine, XVI, and 1-(2′-piperidyl)-4-pentanol, XIV. The effect of temperature on the relative yields of XIV and XVI is shown in Table II.

TABLE II

Temperature, °C.	% of XIV	% of XVI	Total yield, %
125	67	9	76
150	55	26	81
200	15	69	84

XIV and XVI were characterized as follows:

1-(2′-Piperidyl)-4-pentanol, XIV, distilled as a colorless oil (b. p. 118° at 1.5 mm.) which crystallized in the receiver. After recrystallization from petroleum ether (60–70°), it was obtained as a hygroscopic, white solid, m. p. 64.5°.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.11; H, 12.36. Found: C, 69.90; H, 12.31.

The hydrochloride of XIV was prepared in ether using dry hydrogen chloride. After recrystallization from a mixture of acetone and ethyl acetate, it was obtained as a white, crystalline solid, m. p. 107–108°.

Anal. Calcd. for $C_{10}H_{22}ClNO$: C, 57.81; H, 10.68. Found: C, 57.63; H, 10.74.

4-Methylquinolizidine, XVI, was obtained as a colorless oil; b. p. 79° at 13 mm.; $n^{19}D$ 1.4813.

Anal. Calcd. for $C_{10}H_{13}N$: C, 78.36; H, 12.50. Found: C, 78.21; H, 12.47.

The picrate of XVI formed readily in ethanol and was obtained by recrystallization from ethanol as yellow needles, m. p. 191–195°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80. Found: C, 50.29; H, 5.60.

Although there should be two diastereoisomeric forms of XVI, no other picrate was isolated. Similar results have been noted previously for compounds of this type.[18,19]

The cyclization of XIV to yield XVI was accomplished by heating 0.6 g. of XIV in 3 ml. of absolute alcohol in a bomb at 200° for one hour in an atmosphere of hydrogen and in the presence of Raney nickel catalyst. After removal of the catalyst, the product was isolated through the formation of the picrate. The picrate, which was isolated in good yield, was shown to be identical with the picrate of XVI by a mixed melting point determination.

Reductions with Platinum Oxide

Reduction of Ethyl β-(2-Pyridyl)-ethylacetoacetate.—A mixture of 47.1 g. of ethyl β-(2-pyridyl)-ethylaceto-

(18) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1743 (1935).

(19) While correcting proof of this manuscript, the article by Lukes and Sorm, *Coll. Czechoslov. Chem. Commun.*, **12**, 356 (1947); *Chem. Abst.*, **42**, 7780 (1948), in which they describe two picrates of the possible diastereoisomeric racemates of 4-methylquinolizidine (allolupinane), became available to us. Our picrate appears to correspond to the picrate which they describe as melting at 195°. In view of their results and the fact that the crude preparation of our picrate melted at 188–192°, it would seem that essentially only one racemate was produced by the reductive cyclization.

acetate, III, 200 ml. of dilute hydrochloric acid and 0.89 g. of platinum oxide was reduced under a hydrogen pressure of 3 atm. at room temperature for one hour. The catalyst was removed by filtration, the solution was made basic, and the organic layer was extracted with ether. After the ethereal solution had been dried over anhydrous sodium carbonate, the ether was removed *in vacuo* and the residue was distilled. By careful distillation through a column packed with glass helices, there were obtained two fractions. The lower boiling fraction consisted of 19.0 g. (42%) of an oil which by its physical properties (b. p. 116–122° at 1.3 mm.; $n^{22}D$ 1.4820) and by formation of the picrate (m. p. 127–128°, mixed melting point determination with the picrate of an authentic sample of XVII showed no depression) was shown to be XVII.

The higher boiling fraction, **3-carbethoxy-3-ene-4-methylquinolizidine** (XXII), consisted of 17.2 g. (38%) of a semi-viscous, colorless oil; b. p. 129–132° at 0.8 mm.; $n^{20}D$ 1.5426.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48. Found: C, 69.72; H, 9.72.

XXII readily decolorized a solution of potassium permanganate in acetone. Although no hydrogen absorption was observed when 5.6 g. of XXII in 20 ml. of ethanol was shaken under a pressure of 3 atm. of hydrogen at 50° in the presence of Raney nickel catalyst, reduction occurred rapidly when 0.10 g. of platinum oxide was added. The product was isolated in the usual manner and on distillation there was obtained 4.6 g. (82%) of a colorless oil. In the same manner as given above, this oil was shown to be XVII.

3-(α-Hydroxyethyl)-3-ene-4-methylquinolizidine, XXIII.—The reduction of IV with platinum oxide as catalyst was carried out according to the procedure given above for the reduction of III. From 6.2 g. of IV there was obtained on distillation of the residual oil 4.9 g. (85%) of a colorless oil; b. p. 92–100° at 0.5 mm.; $n^{21}D$ 1.4931.

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.79; H, 10.84. Found: C, 73.55, 73.70; H, 10.92, 11.04.

XXIII decolorized a solution of potassium permanganate, and it did not form a semi-carbazone, a 2,4-dinitrophenylhydrazone, or a picrate.

3-(α-Hydroxyethyl)-4-methylquinolizidine, XIX.—The reduction of 1.40 g. of XXIII in 10 cc. of ethanol in the presence of 0.093 g. of platinum oxide took place under an atmospheric pressure of hydrogen at room temperature. The uptake of hydrogen was complete in twelve hours. A colorless oil, about 1 g., was isolated by distillation; bath temp. 110–120° at 1.5 mm.; $n^{23}D$ 1.4920.

Anal. Calcd. for $C_{12}H_{23}ON$: C, 73.05; H, 11.75. Found: C, 73.27; H, 11.65.

The **picrate** of XIX was obtained, after recrystallization from ethanol, as yellow crystals, m. p. 198–201°.

Anal. Calcd. for $C_{18}H_{26}O_8N_4$: C, 50.70; H, 6.15. Found: C, 50.78; H, 5.80.

3-Ethylquinolizidine, XVIII.—The reduction of X was carried out according to the procedure given by Galinovsky and Stern for the reduction of 4-ketoquinolizidine.[12] A mixture of 1.81 g. of X and 0.70 g. of platinum oxide in 50 ml. of a 1.5% solution of hydrochloric acid was shaken in an atmosphere of hydrogen at room temperature. After the mixture had been shaken for seventy-six hours, 88% of the calculated volume of hydrogen had been absorbed. The catalyst was removed and the solution was extracted with ether. The aqueous layer was then made basic and extracted again with ether. After the ethereal solution had been dried and the ether removed *in vacuo*, the residual oil was divided into two parts and converted directly to the corresponding picrate and hydrochloride. The picrate, after crystallization from ethanol, melted at 152–156°, and the hydrochloride, after crystallization from ethyl acetate, melted at 198–199°. The picrate and hydrochloride of 3-ethylquinolizidine were shown by the method of mixed melting points to be identical with the samples of these derivatives prepared previously (see the section on the copper chromite reduction of ethyl α-ethyl-γ-(2-pyridyl)-butyrate).

Reductions with Copper Chromite

Quinolizidine, XV, from 4-Ketoquinolizidine, XI.—A mixture of 5.6 g. of XI and 1.5 g. of copper chromite in 20 cc. of ethanol was heated at 260° for five hours under a hydrogen pressure of 250 atm. After separation of the catalyst by filtration and removal of the ethanol *in vacuo*, the residual oil was distilled yielding 3.8 g. (75%) of a colorless oil; b. p. 79° at 18 mm.; $n^{20}D$ 1.4796. The oil was shown to be quinolizidine by the preparation of the picrate, which melted at 198–199° (lit.,[7,12] m. p. 194°, 196°; 199–200°), and the chloroaurate, which melted at 168–169° (lit.,[7] m. p. 171°).

The **methiodide** of XV formed readily and was obtained as white crystals, dec. 309–311° (lit.,[7,12] dec. 335°; 333°).

Anal. Calcd. for $C_{10}H_{20}IN$: C, 42.71; H, 7.17. Found: C, 42.50; H, 7.09.

The **hydrochloride** of XV formed readily in ether but it did not give a definite melting point.

Anal. Calcd. for $C_9H_{18}ClN$: C, 61.53; H, 10.32. Found: C, 61.20; H, 10.01.

Quinolizidine, XV, from 3-Carbethoxy-4-ketoquinolizidine, VII.—When the reduction of VII was carried out as given above for the reduction of XI, there was obtained on distillation a 76% yield of XV. The identity of XV was established through the preparation of the picrate, m. p. 198–199°, and the methiodide, dec. 309–311°. Mixtures of these derivatives with the corresponding derivatives of quinolizidine prepared previously (see above) showed no depression of melting point.

Quinolizidine, XV, from Diethyl β-(2-Pyridyl)-ethylmalonate, I.—The reduction of I was carried out on a 0.05 molar scale according to the procedure used for the reduction of XI. When the reduction was allowed to proceed overnight, there was obtained, on working up the product and distilling, a 65% yield of quinolizidine and a 13% yield of 4-ketoquinolizidine. The quinolizidine was identified in the same manner as described previously. The 4-ketoquinolizidine was identified by preparing the hydrochloride, m. p. 139–142°; no depression of melting point occurred when the hydrochloride was mixed with the hydrochloride of an authentic sample of 4-ketoquinolizidine. A sample of the 4-ketoquinolizidine was also converted by hydrolysis in dilute hydrochloric acid to the hydrochloride of γ-(2-piperidyl)-butyric acid, m. p. 191–192° (lit.,[10] m. p. 188–189°).

When the time of reduction was shortened to one-half hour, the yield of quinolizidine was only 42% but the yield of 4-ketoquinolizidine increased to 25%. In addition a small amount of a crystalline solid, m. p. 90–93°, separated during the distillation. The amount of solid was insufficient for further characterization.

3-Ethylquinolizidine, XVIII, from Ethyl α-Ethyl-γ-(2-pyridyl)-butyrate, V.—A mixture of 9.7 g. of V and 2.0 g. of copper chromite was heated at 250° for one hour under a hydrogen pressure of about 150 atm. After removal of the catalyst, the residual oil was fractionally distilled and there was obtained two fractions. The higher boiling fraction consisted of 2.8 g. (35%) of a colorless oil, which on the basis of its physical properties (b. p. 112–115° at 0.2 mm.; $n^{21}D$ 1.4933) must be 3-ethyl-4-ketoquinolizidine, a product which was obtained previously from the Raney nickel reduction of V.

The lower boiling fraction, XVIII, consisted of 3.1 g. (43%) of a colorless oil; b. p. 104–108° at 20 mm.; $n^{21}D$ 1.4735.

Anal. Calcd. for $C_{11}H_{21}N$: C, 78.97; H, 12.65. Found: C, 78.70; H, 12.65.

The **picrate** of XVIII was prepared in ethanol and, after several recrystallizations from ethanol, was obtained as yellow crystals, m. p. 156–157°.

Anal. Calcd. for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10. Found: C, 51.62; H, 6.08.

The **hydrochloride** of XVIII was prepared in ether with

dry hydrogen chloride and, after several recrystallizations from ethyl acetate, was obtained as white crystals, m. p. 198–199°.

Anal. Calcd. for $C_{11}H_{22}ClN$: C, 64.84; H, 10.88. Found: C, 64.53; H, 10.72.

The picrate and hydrochloride of XVIII were shown by the method of mixed melting points to be identical with the corresponding derivatives of the oil obtained by the platinum oxide reduction of X. Since any sort of rearrangement during platinum oxide reduction at room temperature would be extremely unlikely, there can be little doubt that XVIII is 3-ethylquinolizidine. Even though isomerism due to the nitrogen atom is neglected, there should be two diastereoisomeric forms of XVIII. The presence of two such forms was indicated by the fact that the crude derivatives of XVIII melted over a wide range. However, no pure derivative corresponding to a second diastereoisomer was isolated, even though several attempts to do so were made.

Reduction of Ethyl β-(2-Pyridyl)-ethylacetoacetate, III.—A mixture of 21.2 g. of III and 5.0 g. of copper chromite in 26 ml. of ethanol was shaken at 250° under a pressure of 150 atm. of hydrogen for three hours. After removal of the catalyst and solvent, the residual oil was fractionally distilled and there was obtained three fractions.

The first fraction consisted of 3.4 g. (27%) of a colorless oil, b. p. 66–70° at 10 mm., which was shown to be quinolizidine by a comparison of the picrate and methiodide with the corresponding derivatives of an authentic sample of quinolizidine.

The second fraction consisted of 4.6 g. (31%) of a colorless oil, b. p. 80–87° at 10 mm., which was shown to be 3-ethylquinolizidine by the preparation of the picrate, m. p. 155–157°. A mixture of this picrate with the picrate of an authentic sample of 3-ethyl-quinolizidine (see above) showed no depression of melting point. Since mixtures of picrates of related compounds in this series were found to give marked depressions of melting point, the method of mixed melting points is assumed to be a valid test for identity.

The third fraction consisted of 6.3 g. of a colorless oil; b. p. 113–116° at 1.5 mm.; $n^{21}D$ 1.4956. The composition of the oil, as indicated by analysis, does not agree with any logical formula. A portion of the oil was converted to the picrate, m. p. 204–206°, but no further identification was carried out.

Reduction of 3-(α-Hydroxyethyl)-4-ketoquinolizidine, IX.—When the reduction of 5.0 g. of IX was carried out according to the procedure given previously for the reduction of III, there was obtained, on distillation, three fractions. The first two fractions, which weighed 0.6 g. and 1.2 g. respectively, were shown to be quinolizidine and 3-ethylquinolizidine in the same manner as described above. The third fraction consisted of 1.1 g. of a colorless oil; b. p. 102–108° at 1.5 mm.; $n^{20}D$ 1.4963. A portion of the oil from the third fraction was converted to the picrate, m. p. 158–160°, but further identification was not carried out. A mixture of the picrate of the oil from the third fraction with the picrate of 3-ethylquinolizidine showed a marked depression in melting point. The composition of the oil, as indicated by analysis, does not agree with any logical formula.

Reduction of 3-Carbethoxy-4-methylquinolizidine, XVII.—A mixture of 6.7 g. of XVII, 1.5 g. of copper chromite and 8 ml. of absolute alcohol was heated at 250° for two hours under a pressure of 200 atm. of hydrogen. When the reaction mixture was worked up in the usual fashion, there was obtained two fractions on distillation.

The lower boiling fraction consisted of 2.1 g. (42%) of a colorless oil, b. p. 83–90° at 8 mm., which was shown by the preparation of the corresponding picrate, m. p. 155–157°, and hydrochloride, m. p. 197–199, to be 3-ethylquinolizidine, XVIII. Neither the picrate nor the hydrochloride, when mixed with authentic samples of these derivatives previously prepared from 3-ethylquinolizidine, showed any depression of melting point. In one attempt to prepare the hydrochloride of the lower boiling fraction, there was obtained a sample of white crystals, m. p. 179–180°, whose melting point was not raised by further recrystallization from ethyl acetate. The composition of this hydrochloride (*Anal.* Calcd. for $C_{11}H_{22}ClN$: C, 64.84; H, 10.88. Found: C, 64.60; H, 11.07.) agrees with that for 3-ethylquinolizidine, and it was thought, at first, that this hydrochloride represented a diastereoisomer of the hydrochloride previously isolated. However, when a supersaturated solution of the hydrochloride melting at 179–180° was seeded with crystals from the hydrochloride melting at 198–199°, the crystals, which separated, melted at 183–187°, indicating that the two hydrochlorides are probably different polymorphic forms of the same diastereoisomer.

The higher boiling fraction consisted of 2.2 g. of a colorless oil, b. p. 105–110° at 1 mm. The composition of the oil, as indicated by analysis, did not agree with any logical formula, and the oil was not further identified.

Reductions with Lithium Aluminum Hydride

2-Hydroxymethyl-4-(2'-pyridyl)-1-butanol, XIII.—A solution of 13.3 g. of I in 30 ml. of dry ether was added dropwise with stirring to 100 ml. of a 0.6 molar solution of lithium aluminum hydride in ether. The reaction mixture was decomposed with water and then hydrolyzed with dilute sulfuric acid. The ether layer was separated, and the aqueous layer was made strongly basic with sodium hydroxide solution. The organic layer was extracted from the basic solution with *s*-amyl alcohol, the amyl alcohol was removed from the extract *in vacuo*, and the residual oil was distilled. There was obtained 2.2 g. (24%) of a slightly green oil; b. p. 165–170° at 0.4 mm. When the oil was triturated with acetone, it crystallized to give a white solid, m. p. 57–59°.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.28; H, 8.35. Found: C, 66.66; H, 8.20.

3-Hydroxymethyl-4-methylquinolizidine, XXI.—The reduction of 4.7 g. of XVII was carried out according to the procedure given above for the reduction of I. In this case the basic oil was extracted with ether instead of amyl alcohol. On distillation of the residual oil there was obtained 1.9 g. (50%) of a viscous, colorless oil; b.p. 98–110° at 0.8 mm.; $n^{19}D$ 1.5072.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.12; H, 11.52. Found: C, 72.24; H, 11.40.

The benzyl bromide salt of XXI was readily formed by heating a sample of XXI with benzyl bromide. After recrystallization from an ethanol–acetone mixture, the benzyl bromide salt was obtained as white crystals, m. p. 179.5–180.5°.

Anal. Calcd. for $C_{18}H_{28}BrNO$: C, 61.02; H, 7.97. Found: C, 60.75; H, 7.95.

Reduction of 3-Carbethoxy-4-ketoquinolizidine, VII.—The reduction of 2.1 g. of VII was carried out according to the procedure given above for the reduction of I. Extraction of the basic aqueous solution was done with ether instead of amyl alcohol. On distillation of the residual oil there was obtained 0.3 g. of 4-ketoquinolizidine, b. p. 100–105° at 1 mm.; $n^{22}D$ 1.5131. The identity of the 4-ketoquinolizidine was established by the preparation of the hydrochloride, m. p. 143–145°. When a sample of this hydrochloride was mixed with an authentic sample of the hydrochloride of 4-ketoquinolizidine, there was no depression of melting point.

Summary

The Michael addition of active methylene compounds to 2-vinylpyridine followed by reductive cyclization has been found to be an easy and practical method of synthesis for a variety of quinolizidine derivatives. Several methods of reductive cyclization have been employed, and, depending on the method of reduction used, either substituted quinolizidines or 4-ketoquinoli-

zidines may be obtained. When copper chromite was employed as catalyst for reductive cyclizations, examples of both skeletal cleavage and rearrangement were found.

Compounds[3], having the simple quinolizidine nucleus, were found not to possess appreciable curariform activity.

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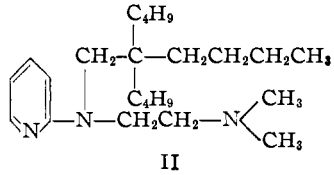
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Quaternary Carbon Compounds. II. N,N-Dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine and the Diethyl Homolog

BY NATHAN SPERBER AND DOMENICK PAPA

In a publication[1] describing the synthesis of N′-benzyl-N′-(2-pyridyl)-N,N-dimethylethylenediamine (I) and related compounds, several substances in which the benzyl group of I was replaced by lower alkyl radicals such as ethyl, isopropyl and propyl are reported. The latter substances showed a low order of antihistaminic activity in experimental animals as compared with the benzyl compound.

In the course of studies on trialkyl-substituted compounds of pharmacological importance,[2] we have prepared a highly branched compound related to I, namely, N,N-dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine (II), in order to establish whether this type of substitution would show appreciably greater antihistaminic activity than the lower alkyl derivatives. In animal experiments, II has shown approximately $^1/_{250}$ the antihistaminic activity of I. The diethyl homolog (III) of II was also prepared and was $^1/_5$–$^1/_{10}$ as active as II.



II

The synthesis of II and the diethyl homolog was carried out in two steps. The condensation of 2-bromopyridine, (2,2-dibutylhexyl)-amine and anhydrous sodium carbonate in xylene or cymene yielded, after prolonged refluxing, N-(2,2-dibutylhexyl)-2-aminopyridine. The latter on alkylation with dimethylaminoethyl chloride or diethylaminoethyl chloride gave good yields of II and III, respectively.[3] Attempts to condense N,N-diethyl-N′-(2,2-dibutylhexyl)-ethylenediamine and 2-bromopyridine with sodamide were unsuccessful.

(1) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(2) (a) Junkmann and Allardt, U. S. 2,186,976, Jan. 16, 1940; (b) Allardt and Junkmann, U. S. 2,361,524, Oct. 31, 1944; (c) Sperber, Papa and Schwenk, Quaternary Carbon Compounds. I, THIS JOURNAL, **70**, 3091 (1948).

(3) These experiments were completed prior to the publication of Huttrer, *et al.*, and were based on the directions of Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

Experimental

(2,2-Dibutylhexyl)-amine.—Capronitrile was dialkylated with butyl bromide and sodium amide according to the directions of Ziegler and Ohlinger.[4] The resulting 2,2-dibutylcapronitrile was reduced to (2,2-dibutylhexyl)-amine[2b]; yield 90%; b. p. 123–124° (4 mm.); hydrochloride m. p. 135°.

N-(2,2-Dibutylhexyl)-2-aminopyridine.[5]—A mixture of 32 g. of 2-bromopyridine, 50 g. of (2,2-dibutylhexyl)-amine and 21 g. of anhydrous sodium carbonate in 100 cc. of *p*-cymene was refluxed and stirred for sixty-seven hours. The mixture was poured into water, the cymene layer separated and, after drying, concentrated *in vacuo*. The residue was fractionated. After a forerun of 12.6 g., b. p. 95–163° (1 mm.), the substituted aminopyridine was obtained as a yellow viscous oil; yield 45 g., b. p. 172–174° (2 mm.); $n^{28}D$ 1.5045. Calcd. for $C_{19}H_{34}N_2$: N, 9.65. Found: N, 9.28.

N,N-Dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine.—To a sodium amide suspension[6] (2.5 g. of sodium) in 75 cc. of dry toluene, was added 29 g. (0.1 mole) of N-(2,2-dibutylhexyl)-2-aminopyridine.[7] The mixture was heated with stirring for two hours on the steam-bath. A solution of 12 g. of dimethylaminoethyl chloride in 20 cc. of dry toluene was added dropwise to the stirred suspension and the reaction heated with stirring for twenty hours on the steam-bath. The reaction mixture was cooled and then decomposed with water. The organic layer was separated, dried and the solvent removed *in vacuo*. The residue distilled as a yellow viscous oil; yield 28.5 g., b. p. 175–177° (2 mm.), $n^{23}D$ 1.5002. Calcd. for $C_{23}H_{43}N_3$: C, 76.36; H, 11.99; N, 11.62. Found: C, 76.60; H, 11.99; N, 11.61.

The dihydrochloride was prepared as follows: A solution of 6 g. of the free base in 75 cc. of dry ethyl acetate was saturated with anhydrous hydrogen chloride. Upon cooling and scratching, a crystalline solid was obtained. Dry ether was added, the solid collected and washed with ether: recrystallized twice from alcohol–ether; yield 5.8 g.; m. p. 184.5–185.5°. Calcd. for $C_{23}H_{45}N_3Cl_2$: N, 9.67; Cl, 16.33. Found: N, 9.45; Cl, 16.00.

N,N-Diethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine.—N-(2,2-Dibutylhexyl)-2-aminopyridine was alkylated with diethylaminoethyl chloride and sodium amide as described for the corresponding dimethyl compound; yield 70%; yellow viscous oil; b. p. 190–195° (2 mm.); $n^{21}D$ 1.5005. The free base was converted to

(4) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

(5) The reaction of 16 g. of 2-bromopyridine, 39 g. of (2,2-dibutylhexyl)-amine and 50 cc. of pyridine for ten hours at 155–160° essentially as described by Whitmore[3] did not yield any of the substituted aminopyridine.

(6) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 99.

(7) Although King, King and Muir (*J. Chem. Soc.*, 5 (1946)) alkylated diphenylamine with diethylaminoethyl chloride by means of the Grignard reagent, N-(2,2-dibutylhexyl)-2-aminopyridine with methylmagnesium iodide and dimethylaminoethyl chloride yielded none of the expected tertiary amine.