[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE STEREOISOMERS OF *vic*-DIALKYLPIPERIDINES. THE 2-*n*-BUTYL-3-METHYLPIPERIDINES[1]

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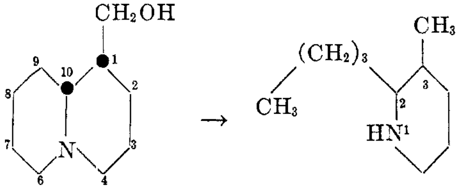
Certain alkaloids can be related structurally to *vicinal*-dialkylpiperidines by convergence of degradative and synthetic procedures, and assignment of stereochemical configuration in such an alkaloid becomes possible when the stereochemistry of the corresponding dialkylpiperidine has been determined. A notable example is the establishment of the stereochemistry of the *Cinchona* alkaloids through the aid of their correlation with the *cis* form of 3,4-diethylpiperidine (1, 2). The method, in its possible future applications, is necessarily limited by the paucity of information relating the properties and stereochemical configuration of *vic*-dialkylpiperidines. We have sought to remedy this situation in one instance, that of the geometrical isomers of 2-*n*-butyl-3-methylpiperidine, and to indicate a method which we hope can be further developed for distinguishing between *cis*- and *trans*-forms of *vic*-dialkylpiperidines. 2-*n*-Butyl-3-methylpiperidine was selected for study because of the relation of this compound to the lupin alkaloids.

Lupinine (I) was degraded to a 2-*n*-butyl-3-methylpiperidine (II) by Winterfeld and Holschneider in 1931 (3) and assignment of the relative configurations at C_1 and C_{10} in lupinine might have been possible at that time if the steps involved in the conversion of I to II were assuredly stereochemically unique and if the stereochemistry of the 2-*n*-butyl-3-methylpiperidines had been determined. Actually, our knowledge of the stereochemistry of lupinine has been improved only recently, by the synthesis (4) of the racemic form corresponding to *dl*-lupinine. Since the synthetic route of Boekelheide and Lodge utilized hydrogenation over platinum in neutral medium to establish the asymmetric centers at C_1 and C_{10}, and since a homogeneous product consisting of only one of the diastereoisomeric racemates was obtained, the structure of (*l*-)lupinine was very reasonably assigned as one of the enantiomorphs with the hydrogens on C_1



I II

(a, $COOCH_3$ in place of CH_2OH at C_1).

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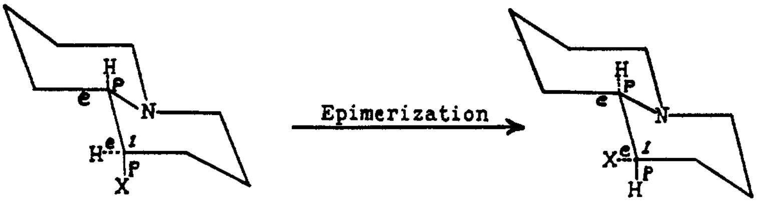
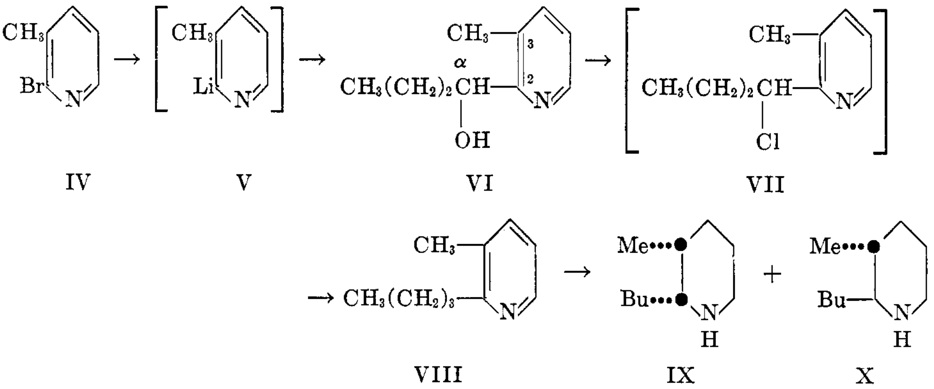
[2] Eli Lilly and Company Fellow, 1950–1952.

and C_{10} in the *cis* relation (I). This assignment is in accord with the observed epimerization of methyl *l*-lupininate (Ia) by sodium methoxide (5) and of *l*-lupinine (I) by sodium (3, 6–9), which would correspond to a shift from 1,10-polar, equatorial bonding to the preferred 1,10-diequatorial bonding (10). By the same reasoning, it has been somewhat puzzling to note the widespread occurrence of *l*-lupinine in nature (11) in contrast to the absence of the more stable epimer (III). The query has now been partially resolved by White's discovery (9) of *d*-isolupinine (III) in *Lupinus pilosus L.*, and it is reasonable to assume that this *trans*-isomer will be found in other lupins (11).



I or Ia III or IIIa

The pure *cis*- and *trans*-forms of 2-*n*-butyl-3-methylpiperidine (II) have not been prepared previously. The degradation product, 2-*n*-butyl-3-methylpiperidine, obtained by Winterfeld and Holschneider (3) from *l*-lupinine, was of unstated optical rotation and, as indicated by their dehydrogenation and subsequent oxidation experiments, was possibly contaminated with the 2,6-position isomer (12). In the present work, in order to be certain of the purity of the 2-*n*-butyl-3-methylpiperidines, it was first necessary to obtain the precursor, 2-*n*-butyl-3-methylpyridine (VIII), free from isomeric contaminant. The most satisfactory method was found to be the conversion of 2-bromo-3-methylpyridine (IV) through the lithium derivative (V) to 3-methyl-α-propyl-2-pyridinemethanol (VI), and thence to the corresponding chloro compound (VII) followed by reduction to VIII. The 2-bromo-3-methylpyridine (IV) was prepared by the method of Mariella and Kvinge (13) from 2-amino-3-methylpyridine (m.p.



33.3°), which was readily available in pure form because of the wide difference in melting point from that of the 2,5-isomer. The condensation of *n*-butyraldehyde with the lithium derivative (V) of IV insured the location of the four-carbon side chain at C_2. Subsequent treatment with thionyl chloride and reduction with zinc and acetic acid likewise offered no possibility of rearrangement. The 2-*n*-butyl-3-methylpyridine (VIII) thus obtained had characteristic infrared absorption maxima at 1576 and 1588 cm.$^{-1}$, whereas the isomeric 2-*n*-butyl-5-methylpyridine, prepared in pure form by a similar reaction scheme starting with 2-amino-5-methylpyridine, exhibited maxima at 1568 and 1602 cm.$^{-1}$.

Two alternative methods for preparing 2-*n*-butyl-3-methylpyridine (VIII) were found to be equivocal. Thus, the product resulting from the treatment of β-picoline with butyllithium predominated in the 2,3-isomer (VIII), but contained some of the 2,5-isomer, as evidenced by the infrared absorption spectrum. The reaction between 2-bromo-3-methylpyridine and butylmagnesium bromide (13) also failed to produce pure VIII.

The methods selected for the reduction of 2-*n*-butyl-3-methylpyridine resulted in mixtures of the two racemates of 2-*n*-butyl-3-methylpiperidine; nevertheless, the use of sodium and ethanol produced a mixture predominant in one isomer (A), while hydrogenation in the presence of Raney nickel at 150–190° and 225–250 atmospheres gave a mixture predominant in another isomer (B). It was possible to obtain both isomers in the pure form by means of careful fractional distillation and/or purification through the picrolonic acid salt. The isomers are characterized as follows: A—b.p. 61° (4.4 mm.); n_D^{20} 1.4541; d_4^{20} 0.8474; *hydrochloride*, m.p. 140.5–141°; *hydrobromide*, m.p. 157.5–158.5°; *picrolonate*, m.p. 222–223°; B—b.p. 59.5° (3.1 mm.); n_D^{20} 1.4575; d_4^{20} 0.8506; *hydrochloride*, m.p. 154–155°; *hydrobromide*, m.p. 179–180°; picrolonate, m.p. 204–206°. The infrared absorption spectra of the pure liquids (Figure 1) and their liquid N-acetyl derivatives (Figure 2) provide further means of identification and differentiation of the two isomers.

The decision as to which is the *cis*-form (IX, only one enantiomorph is shown) and which the *trans*- (X) was reached by dehydrogenation studies. Ehrenstein and Bunge (14) found that *cis*-decahydroquinoline is more readily dehydrogenated than *trans*-decahydroquinoline. Similarly, Witkop (15) found that *cis*-decahydroisoquinoline is more readily dehydrogenated with palladium than *trans*-decahydroisoquinoline, and concluded that the difference may be due to the relatively easier approach of the *cis* compound to the catalyst surface for removal of pairs of adjacent hydrogen atoms. Dehydrogenation of isomer A and of isomer B of 2-*n*-butyl-3-methylpiperidine was effected at 305–310° over palladized asbestos that was brought into equilibrium with hydrogen before introduction of the piperidine compound into the closed system. Conditions for the dehydrogenation of the two isomers were exactly the same for isomers A and B in three parallel runs. The increase in volume of the system (hydrogen) was measured, and corrected to standard conditions, to determine the extent of dehydrogenation under the applied conditions. For the triplicate runs, it was found that isomer A evolved, on the average, 51% of the hydrogen theoretically

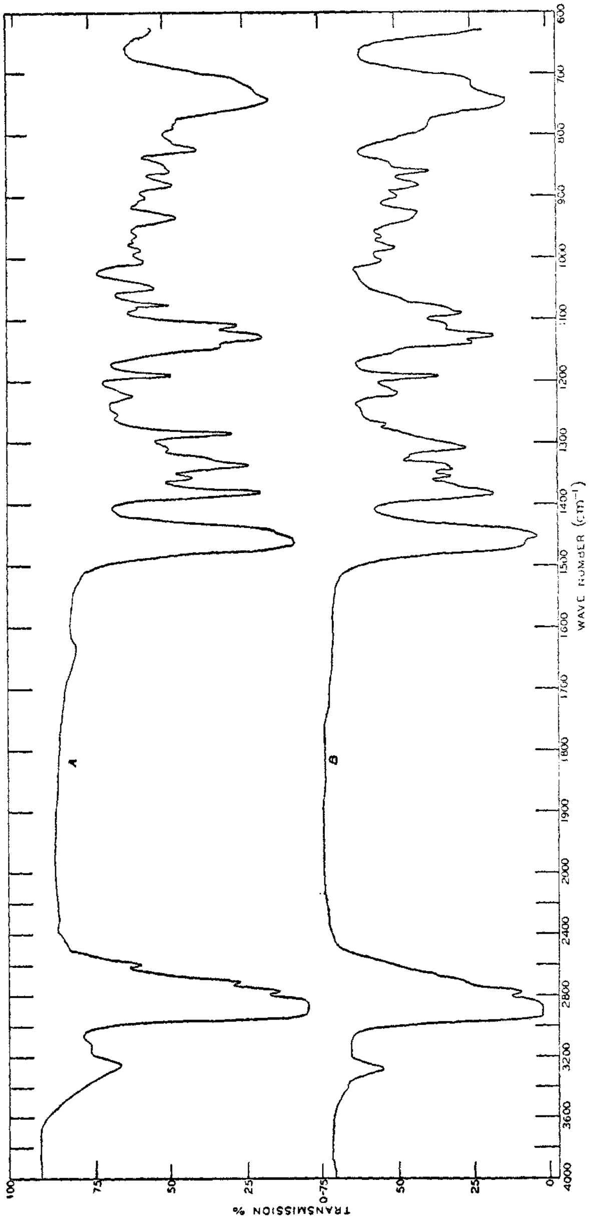


FIG. 1. INFRARED ABSORPTION SPECTRA. *trans*- (A) AND *cis*- (B) 2-*n*-BUTYL-3-METHYLPIPERIDINES.

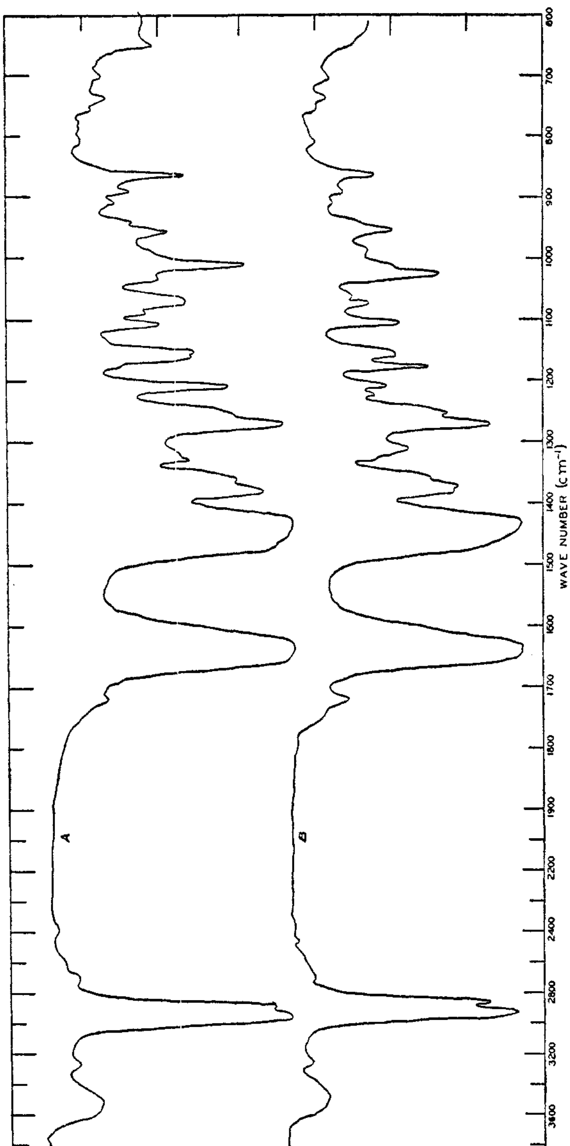


FIG. 2. INFRARED ABSORPTION SPECTRA. *trans*- (A) AND *cis*- (B) 1-ACETYL-2-*n*-BUTYL-3-METHYLPIPERIDINES.

necessary for complete dehydrogenation to 2-*n*-butyl-3-methylpyridine, whereas isomer B evolved 85%. Expressed on a relative basis, the volume of hydrogen liberated by A was 60% of that liberated by B. Assuming that only *cis* adjacent hydrogens can be withdrawn to form a double bond and assuming that the configuration of the nitrogen does not limit the dehydrogenation process (*i.e.*, that the configuration of the $>$N—H is not fixed), the volume of hydrogen evolved from the *cis*-2-*n*-butyl-3-methylpiperidine (IX) should exceed that evolved from the *trans*-isomer (X). Upon the basis of the less complete (or less easy) dehydrogenation of isomer A of 2-*n*-butyl-3-methylpiperidine, this isomer is assigned the *trans*-configuration, and isomer B, the *cis*-configuration about positions 2 and 3. The presence of 2-*n*-butyl-3-methylpyridine (VIII) was established in the product of each dehydrogenation experiment. The fact that the *trans*-2-*n*-butyl-3-methylpipieridine was less completely dehydrogenated than the *cis* was further established by determining the extent of hydrogen uptake by the crude products. Under catalytic hydrogenation conditions (hydrogen over platinum in glacial acetic acid) which were shown to be effectual for 100% reduction of the fully aromatic 2-*n*-butyl-3-methylpyridine, the *trans* dehydrogenation product absorbed 52.5% of the hydrogen theoretically necessary for pyridine → piperidine reduction, whereas the *cis* dehydrogenation product absorbed 89.4%. These figures serve as a check for the values obtained in the dehydrogenation experiments (average of runs 2 and 3 and 5 and 6).

EXPERIMENTAL[3]

2-Bromo-3-methylpyridine. This compound was prepared from 2-amino-3-methylpyridine, m.p. 33.3° (16) (Reilly Tar and Chemical Corporation), by the procedure of Mariella and Kvinge (13) and was fractionally distilled through a twelve-inch Fenske column, b.p. 97.5–98.5° (16 mm.); n_D^{20} 1.5664; d_4^{20} 1.536; MR_D 36.57. The physical properties are here recorded since they are in slight variance with those previously reported (13, 17, 18). The following derivatives have not been reported earlier: *picrate,* prepared in and recrystallized from ethanol, yellow plates, m.p. 119–121°; *chloroplatinate,* prepared in and recrystallized from ethanol, orange microcrystals, m.p. 201–202° with decomposition.

Synthesis of 2-n-butyl-3-methylpyridine from 2-bromo-3-methylpyridine.[4] *3-Methyl-α-propyl-2-pyridinemethanol.* In an adaptation of the method used for the preparation of (3-methyl-2-pyridyl)phenylcarbinol (19) a solution of 380 g. (2.2 moles) of 2-bromo-3-methylpyridine in 500 ml. of absolute ether was added dropwise with stirring during 15 minutes to 2.3 moles of *n*-butyllithium in 2 l. of absolute ether under an atmosphere of nitrogen at −40°. The stirring was continued for 15 minutes. Then 216 g. (3 moles) of freshly distilled *n*-butyraldehyde was added dropwise to the stirred mixture at −30°, and stirring

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[3] All melting points are corrected. The microanalyses were performed by Mrs. Jean Fortney, Mrs. Katherine Pih, Mrs. Esther Fett, Mr. Joseph Nemeth, and Miss Emily Davis. The infrared absorption spectra were determined by Miss Helen Miklas. The infrared curves recorded in Figures 1 and 2 were obtained using cell thicknesses of 0.02 mm. for each of the pure liquids except *trans*-1-acetyl-2-*n*-butyl-3-methylpiperidine, for which the cell thickness was approximately 0.025 mm.

[4] This is the preferred method for obtaining isomerically pure 2-*n*-butyl-3-methylpyridine.

was continued 1 hour after the addition was complete. The mixture was poured over 1 l. of 6 *N* hydrochloric acid and 3 kg. of ice, and the layers were separated. The acid layer was made alkaline with gaseous ammonia and extracted three times with ether. The combined organic solutions were dried and the solvent was removed. The residual oil was distilled with fractionation, b.p. 93.5° (2.4 mm.); m.p. 46.5–47.5°; yield 311 g. (86)%.

Anal. Calc'd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48.

Found: C, 72.62; H, 9.27; N, 8.31.

The *picrate*, prepared in and recrystallized from absolute ethanol, was collected as yellow prisms, m.p. 146.5–148.5°.

The *picrolonate*, prepared in and recrystallized from absolute ethanol, separated as clumps of yellow-brown prisms, m.p. 149–150° with decomposition.

2-n-Butyl-3-methylpyridine. In an adaptation of the method used for the preparation of 2-benzyl-3-methylpyridine (19) 196 g. (1.65 moles) of thionyl chloride (Eastman Kodak Company, white label) was added to a stirred, cooled solution of 248 g. (1.5 moles) of 3-methyl-α-propyl-2-pyridinemethanol in 2.5 l. of anhydrous benzene at a rate slow enough to keep the reaction temperature below 25°. Stirring was continued an additional hour after the addition was complete. The mixture was kept below 30° while being made alkaline with 25% aqueous sodium hydroxide. The organic layer which separated was washed with cold water and subsequently dried. The solvent was removed by distillation *in vacuo*, leaving a red oil, which was dissolved directly in 1.9 l. of glacial acetic acid. To the stirred solution was added in small portions 240 g. (3.68 moles) of zinc dust (Mallinckrodt). The resulting mixture was stirred 12 hours on the steam-bath and then extracted with ether. The combined extracts were dried, the solvent was removed, and the residual oil was fractionally distilled, b.p. 67° (3.5 mm.); n_D^{20} 1.4966; d_4^{20} 0.9134; MR_D 47.78; yield 175 g. (78%) [reported (13) b.p. 205–207° (756 mm.), n_D^{20} 1.4950].

Anal. Calc'd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39.

Found: C, 80.40; H, 10.21; N, 9.45.

The infrared spectrum of the pure liquid exhibited characteristic absorption bands at 1576 and 1588 cm.$^{-1}$.

The *picrate*, prepared in and recrystallized from absolute ethanol, separated as yellow needles, m.p. 76–77° after slight preliminary softening at 66° [reported (13) m.p. 64–65°].

Anal. Calc'd for $C_{16}H_{18}N_4O_7$: C, 50.79; H, 4.80; N, 14.82.

Found: C, 50.88; H, 5.02; N, 14.76.

The *chloroplatinate*, prepared in and recrystallized from ethanol, separated as orange microcrystals, m.p. 186.5–187.5° with decomposition (temperature rise = 2° per min.) [reported m.p. 183–185° (13), m.p. 190–191° (3)].

The *picrolonate* crystallized from absolute ethanol as clumps of yellow needles, m.p. 163°.

Reaction of β-picoline and butyllithium. The procedure for 2-phenylpyridine (20) was followed for the reaction between pure β-picoline (21, 22) and standardized butyllithium (23, 24). The product was obtained in 69% yield, b.p. 101° (18 mm.); n_D^{20} 1.4950, and the picrate, picrolonate, and chloroplatinate derivatives had properties correct for those of 2-*n*-butyl-3-methylpyridine (see above). Mixture of the picrates from the two sources did not depress their melting points. The fact that the product was not isomerically pure, however, was indicated since the distilled liquid, even after careful fractionation, showed infrared absorption peaks at 1568 and 1602 cm.$^{-1}$ as well as at 1576 and 1588 cm.$^{-1}$. The former two peaks have been shown in the present work (see below) to be representative of 2-*n*-butyl-5-methylpyridine.

In our hands, the interaction of 2-bromo-3-methylpyridine with butylmagnesium bromide (13) failed to produce pure 2-*n*-butyl-3-methylpyridine in a reasonable yield.

2-Bromo-5-methylpyridine. The procedure employed was similar to that used for the preparation of 2-bromo-3-methylpyridine (see above). From 2-amino-5-methylpyridine, m.p. 76.5–79.5° (16) (Reilly Tar and Chemical Corporation), the 2-bromo-5-methylpyridine, b.p. 95.5–96° (12.5 mm.), m.p. 47.5–48.5°, was obtained in 75% yield [reported (18) b.p. 80° (7 mm.), m.p. 49–50°]. The following derivatives have not been reported previously: *picrate*, yellow prisms from ethanol, m.p. 126–129°; *chloroplatinate*, reddish orange prisms from ethanol, m.p. 245–246° with decomposition.

Synthesis of 2-n-butyl-5-methylpyridine from 2-bromo-5-methylpyridine. 5-Methyl-α-propyl-2-pyridinemethanol. The method followed was that used for the isomeric 3-methyl-α-propyl-2-pyridinemethanol. The product boiled at 93–94° (1.7 mm.) and solidified on standing. Recrystallized from hexane, the colorless prisms melted at 49.5–50°; yield 73%.

Anal. Calc'd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48.

Found: C, 72.98; H, 9.22; N, 8.45.

Picrate, *chloroplatinate*, and *hydrobromide* derivatives could not be isolated in the crystalline state.

2-n-Butyl-5-methylpyridine. This compound was obtained from the carbinol as in the case of the isomeric 2-*n*-butyl-3-methylpyridine. Careful fractionation gave a colorless liquid, b.p. 92.5–93° (12 mm.); n_D^{20} 1.4912; d_4^{20} 0.9044; MR_D 47.82; yield 64%.

Anal. Calc'd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39.

Found: C, 80.53; H, 10.24; N, 9.19.

The infrared spectrum of the pure liquid exhibited characteristic absorption bands at 1568 and 1602 cm.$^{-1}$.

The *picrate*, prepared in absolute ethanol and recrystallized from 50% aqueous ethanol, separated as yellow prisms, m.p. 91.5°.

The *picrolonate*, prepared in and recrystallized from absolute ethanol, formed yellow-brown prisms, m.p. 151.5–153°.

STEREOISOMERS OF 2-*n*-BUTYL-3-METHYLPIPERIDINE

Reduction of 2-n-butyl-3-methylpyridine with sodium and ethanol. In an adaptation of the procedure used for the reduction of 2,3-dimethylquinoline (25) a solution of 40 g. (0.27 mole) of 2-*n*-butyl-3-methylpyridine in 842 ml. of absolute ethanol at the reflux temperature was treated with 120 g. (5.2 gram-atoms) of sodium, added in small pieces. After completion of the addition, the reaction mixture was heated under gentle reflux for 3 hours. The excess sodium was then decomposed by the addition of absolute ethanol. The mixture was diluted with an equal volume of water and was steam-distilled until no further basic material was collected. The distillate was acidified by the addition of dilute hydrochloric acid and was concentrated to remove the ethanol. The residue was then made strongly basic with 20% aqueous sodium hydroxide. The alkaline mixture was extracted with ether, the combined ether extracts were dried, and the ether was removed. The residual oil was distilled through an eight-inch Fenske column and redistilled through a Podbielniak column rated at 100 plates, at a reflux ratio of 100:1. Sixteen fractions were collected over a boiling range of 54–73° (3.5–5.0 mm.). Fractions 2–7, b.p. 55.0–60.5° (3.6–4.0 mm.), were identical in refractive index, n_D^{20} 1.4541, and in the melting point, 221–223°, of the picrolonate as obtained directly from each fraction, without recourse to recrystallization. These fractions were therefore considered to constitute one of the racemates of 2-*n*-butyl-3-methylpiperidine, referred to as isomer A. Succeeding fractions of distillate had successively higher refractive indices and lower picrolonate melting points. Based upon an estimate of the %A in each fraction, calculated from the refractive index, the total weight of isomer A obtained was 20.3 g. or 49% of the theoretical yield of reduction product. At least 3.3 g. (8%) of isomer B was present. Fraction 4, representative of pure A, was unchanged in physical properties upon redistillation with fractionation, b.p. 61° (4.4 mm.), n_D^{20} 1.4541; d_4^{20} 0.8474. The infrared absorption spectrum for the pure liquid is recorded in Figure 1.

Anal. Calc'd for $C_{10}H_{21}N$: C, 77.35; H, 13.63; N, 9.02; MR_D 49.79.

Found: C, 77.32; H, 13.50; N, 9.17; MR_D 49.62.

The *hydrochloride* was prepared by passing hydrogen chloride into a solution of 2-*n*-butyl-3-methylpiperidine, isomer A, in anhydrous ether containing a trace of ethanol. Recrystallization from acetone gave fine, colorless needles, m.p. 140.5–141°.

The *hydrobromide*, prepared in a similar manner, crystallized from acetone as fine, colorless needles, m.p. 157.5–158.5°.

The *picrolonate*, prepared in and recrystallized from absolute ethanol, separated as yellow needles, m.p. 222–223° with slight decomposition.

The *N-acetyl* derivative was prepared similarly to 1-acetyl-2-benzylpiperidine (26). A solution of 1.6 g. (0.01 mole) of isomer A in 2.0 g. (0.02 mole) of acetic anhydride was heated at 90° for 1 hour. The reaction mixture was stirred into 5 ml. of ice-water, acidified with 1 *N* hydrochloric acid, and the acid solution was extracted three times with ether. The combined extracts were washed first with 0.1% aqueous sodium bicarbonate, then with water. The ethereal solution was dried, the ether was removed, and the residual colorless oil was distilled, b.p. 111.5–112° (2.6 mm.); n_D^{20} 1.4752; d_4^{20} 0.9437. The infrared absorption spectrum is recorded in Figure 2.

Anal. Calc'd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; MR_D 59.26.

Found: C, 72.95; H, 11.91; N, 7.32; MR_D 58.89.

Catalytic reduction of 2-n-butyl-3-methylpyridine. A solution of 50 g. (0.34 mole) of 2-*n*-butyl-3-methylpyridine in absolute ethanol was hydrogenated in the presence of 7 g. of Raney nickel catalyst at 150–190° and 225–250 atm. The catalyst was removed by filtration. The filtrate was acidified with dilute hydrochloric acid and heated on the steam-bath to remove the ethanol. The residue was made strongly basic with 25% aqueous sodium hydroxide and the basic mixture was steam-distilled. The steam-distillate was rendered basic and extracted with ether. The combined ethereal extracts were dried; the ether was removed. The residual oil was distilled through a 100-plate Podbielniak column at a reflux ratio of 100:1. Seventeen fractions were collected, and the content of each in isomer A and B was estimated by the refractive index and indicated somewhat by the melting point of the picrolonate as formed directly from each fraction. The first five fractions, b.p. 81–85° (11.9 mm.), were richer in isomer A than in B, the second five fractions, b.p. 85–86.3° (11.9–12.6 mm.), were progressively richer in isomer B, and fractions 10–15 were nearly pure B. The total amount of isomer B in the distilled material was estimated as 30.6 g. (59% of the theoretical yield of reduction product). At least 10.3 g. (20%) of isomer A was present. Fraction 11, b.p. 86.3° (12.6 mm.), representative of pure B, was converted to the picrolonate, m.p. 203.5–206°, unaltered in melting point upon recrystallization. The picrolonate was decomposed and the liberated base was distilled, b.p. 59.5° (3.1 mm.); n_D^{20} 1.4575 (unchanged); d_4^{20} 0.8506. The infrared absorption spectrum for pure isomer B is recorded in Figure 1.

Anal. Calc'd for $C_{10}H_{21}N$: C, 77.35; H, 13.63; N, 9.02; MR_D 49.79.

Found: C, 77.47; H, 13.62; N, 9.20; MR_D 49.84.

The following derivatives were prepared by the same procedures as those from racemate A: *hydrochloride*, colorless needles from acetone, m.p. 154–155°; *hydrobromide*, colorless needles from acetone, m.p. 179–180°; *N-acetyl* derivative, b.p. 113.5° (2.6 mm.); n_D^{20} 1.4750; d_4^{20} 0.9444; infrared absorption spectrum, see Figure 2.

Anal. Calc'd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; MR_D 59.26.

Found: C, 72.85; H, 11.58; N, 7.28; MR_D 58.81.

Dehydrogenation of the isomers of 2-n-butyl-3-methylpiperidine. The procedure and apparatus adapted from those described by Ehrenstein and Bunge (14) for the dehydrogenation of decahydroquinoline were used for the 2-*n*-butyl-3-methylpiperidines A and B. The dehydrogenation tube was charged with 1.0 g. of palladized asbestos. All parts of the apparatus except the eudiometer tube were flushed with dry nitrogen for 15 minutes. The apparatus was then flushed with dry hydrogen for 15 minutes, during which time the temperature of the tube was brought to 305–310°. The eudiometer tube was then connected and a small initial volume of hydrogen was introduced in order to permit operation of the apparatus at a slightly reduced pressure. Fifteen minutes was allowed for the apparatus to come to equilibrium before a reading of the initial volume of hydrogen was made. An accurately-weighed sample of approximately 1 g. (6 millimoles) of the isomer was introduced into the small separatory-funnel, from which the compound was permitted to enter the dehydrogenation tube at the rate of one drop every five minutes. After all the compound had been added, the apparatus was allowed to stand thermostatted for three hours before a reading of the final volume of hydrogen in the eudiometer tube was made. The results of dehydrogenation studies are given in Table I.

From samples of each of the liquid distillates picrates were prepared and were recrystalized from absolute ethanol: all yellow needles, m.p. 78–79.5°, undepressed in melting point on admixture with authentic 2-*n*-butyl-3-methylpyridine picrate. While the preponderance of 2-*n*-butyl-3-methylpyridine in the distillates was thus indicated, the yellowing of the originally colorless distillates indicated the presence of incompletely dehydrogenated products, especially from isomer A. If the per cent yield of hydrogen from isomer B for each run is considered as 100%, the values for the relative per cent yield of hydrogen from isomer A are as follows:

Runs no. 1,4 (Catalyst—36.8% Pd)—61.9%
2,5 (Catalyst—38.4% Pd)—58.8% } ave. 59.6%
3,6 (Catalyst—38.4% Pd)—58.1%

Rehydrogenation of the dehydrogenation products. As a check on the per cent dehydrogenation of the two piperidine isomers, the liquid dehydrogenation products (aliquots) were subjected to quantitative catalytic hydrogenation. The conditions selected were those which were shown to effect 100% hydrogenation of 2-*n*-butyl-3-methylpyridine and which would certainly reduce partially dehydrogenated pyridines: platinum in glacial acetic acid at 28–30° and 1 atm. Corrections in the observed hydrogen uptake were made for the vapor pressure of acetic acid, absorption of hydrogen by catalyst and solvent, and conversion to S.T.P. The theoretical uptake of hydrogen was calculated on the basis that the dehydrogenation product was the fully aromatic pyridine compound. The liquid dehydrogenation product from the A or *trans*-isomer absorbed 1.575 moles of hydrogen per mole of sample (52.5%); that from the B or *cis*-isomer absorbed 2.679 moles of hydrogen per mole of sample (89.4%). (Compare the average of dehydrogenation runs 2 and 3 with that of runs 5 and 6, Table I.)

TABLE I

DEHYDROGENATION OF ISOMERS A AND B OF 2-*n*-BUTYL-3-METHYLPIPERIDINE

RUN NO. →	1	2	3	4	5	6
ISOMER	A	A	A	B	B	B
Conc'n of Pd in catalyst, %	36.8	38.4	38.4	36.8	38.4	38.4
Wt. sample—grams	0.9236	0.9827	0.8543	0.9267	0.9216	0.8830
millimoles	5.948	6.329	5.502	5.968	5.935	5.686
Ml. of H_2-calc'd	399.7	425.3	369.7	401.1	398.8	382.1
Increase in vol. of system (S.T.P.)	190.5	224.6	192.7	309.2	358.1	342.6
Hydrogen, % of theoretical	47.7	52.8	52.1	77.1	89.8	89.7
Liquid distillate—wt., g.	0.7878	0.8785	0.7563	0.5545	0.8141	0.7879
n_D^{20}	1.4753	1.4750	1.4761	1.4952	1.4933	1.4900

SUMMARY

2-*n*-Butyl-3-methylpyridine and 2-*n*-butyl-5-methylpyridine have been prepared by methods which preclude the presence of isomeric contaminants in these products. The two racemates of 2-*n*-butyl-3-methylpiperidine were obtained by reduction of 2-*n*-butyl-3-methylpyridine. One isomer was predominant in the sodium and ethanol reduction, the other, in the hydrogenation over nickel. Careful fractionation of the reduction products and further purification through

derivatives served to establish the distinctness of the two isomers. Dehydrogenation of each isomer was effected over palladized asbestos at 305–310°, and it was found, in triplicate runs, that the volume of hydrogen liberated by one isomer (A) was 60% of that liberated by the second isomer (B). Upon the basis of the less complete dehydrogenation of isomer A of 2-*n*-butyl-3-methylpiperidine (n_D^{20} 1.4541; d_4^{20} 0.8474; picrolonate, m.p. 222–223°), as consistently observed in these experiments, this isomer is indicated to have the *trans*-configuration, and isomer B (n_D^{20} 1.4575; d_4^{20} 0.8506; picrolonate, m.p. 204–206°), the *cis*-configuration about positions 2 and 3.

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