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The Reaction of Aldehydes with Aldimines[1]

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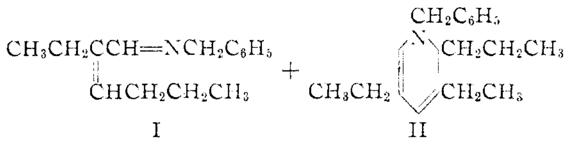
When an aldimine is treated with an aliphatic aldehyde, a mixture of a 1,2,3,5-tetralkyldihydropyridine and an N-alkenylidenealkylamine is obtained, often in good yield. The method offers a convenient route to many pyridine and piperidine derivatives not readily obtained by the conventional reaction of an aldehyde with an amine.

For many years it has been known that aldehydes would react with ammonia to give pyridine derivatives[2-4] but such reactions are frequently characterized by the fact that a variety of difficultly-separable products is obtained and none in very good yield. This work was undertaken with the thought that certain substituted pyridines and piperidines might better be prepared with greater selectivity by the reaction of aldehydes with aldimines. This reaction appears to have received very little attention in the past.

It has now been shown that a principal product of the condensation of an aliphatic aldehyde with an aliphatic aldimine is a 1,2,3,5-tetralkyldihydropyridine. Much of the balance of the reaction mixture consists of an N-alkenylidenealkylamine.

$CH_3CH_2CH_2CHO + CH_3CH_2CH_2CH{=}NCH_2C_6H_5 \longrightarrow$



$CH_3CH_2C(=CHCH_2CH_2CH_3)CH{=}NCH_2C_6H_5$

I II

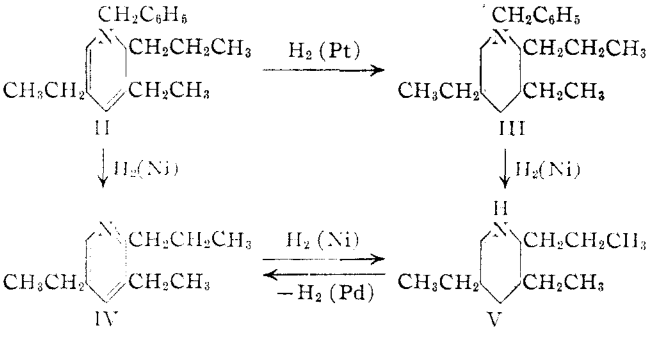
In order to prove the structure of the substituted dihydropyridines, N-butylidenebenzylamine was selected as one reactant, and in order to eliminate the possibility of complications by possible aldehyde interchange with the Schiff base, butyraldehyde was chosen as the other.

An excess of butyraldehyde was brought into contact with N-butylidenebenzylamine at ice-bath temperature and the mixture was then brought to reflux. Water was removed azeotropically from the reaction mixture with a small amount of benzene. Alternatively, the reaction was carried out in boiling ethanol. Two amines, $C_{15}H_{21}N$ (I) and $C_{19}H_{27}N$ (II), were formed in 40 and 37% yield, respectively. I was shown to be N-(2-ethyl-2-hexenylidene)-benzylamine by acid hydrolysis to 2-ethyl-2-hexenal and benzylamine. II absorbed two moles of hydrogen in the presence of platinum to give 93% $C_{19}H_{31}N$ (III), indicating the presence of two double bonds which would require the presence of a second ring. Upon treatment with hydrogen at 1800 lb. and 150-200° in the presence of nickel, II was hydrogenolyzed to 84% of toluene and 61% of $C_{12}H_{19}N$ (IV). IV had been fractionated through a metal-packed column and, in order to exclude the possibility of dehydrogenation of $C_{12}H_{25}N$ (V), the expected product, during fractionation, the experiment was repeated using an all-glass apparatus for fractionation. Again IV was the product obtained.

IV evidently was a trialkylpyridine, and this was confirmed in part by permanganate oxidation to an acid which gave a blood-red color with ferrous sulfate solution, a test characteristic of an α-pyridinecarboxylic acid. The acid decomposed at about 160° and finally melted with decomposition at 321°. The only carboxylic acid in the pyridine series which melts over 300°, is dinicotinic (3,5-) m.p. 323°.[5] There are only two tricarboxylic acids which can be decarboxylated to dinicotinic acid. These are the 3,4,5- and the 2,3,5-. The former is excluded since it fails to give the ferrous sulfate test.

There is only one way in which three four-carbon straight chains can be combined to give a 2,3,5-trialkylpyridine if the possibility of rearrangement involving scission of a carbon-carbon bond is excluded. This requires that a propyl group be in position 2 and that ethyl groups be in positions 3 and 5. It is clear that IV must be 3,5-diethyl-2-propylpyridine, and further substantiation was given by comparing the melting points of its picrate and chloroplatinate with the melting points of these derivatives of Chichibabin's 3,5-diethyl-2-propylpyridine.[3]

The ring of IV could not be saturated with low pressure hydrogen at room temperature over platinum, but in the presence of nickel at 4000 lb. and 225°, 90% of V was obtained. V exhibited a rather wide boiling range and it is believed that this may be due to the presence of two or more *cis–trans* isomers in the product, although no attempt has been made by way of confirmation.



Surprisingly, the infrared spectrum of V failed to show the presence of an absorption band in the region expected for the piperidine N–H group. In order to eliminate the possibility of migration of

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[1] Presented before the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951.

(2) M. M. Sprung, *Chem. Revs.*, **26**, 301 (1940).

(3) A. E. Chichibabin, *J. Russ. Phys.-Chem. Soc.*, **37**, 1229 (1905); *Chem. Zentr.*, **77**, I, 1438 (1906).

(4) L. Haskelberg, *Chemistry & Industry*, **54**, 261 (1935).

(5) I. M. Heilbron, "Dictionary of Organic Compounds," Vol. I, 2nd Ed., Oxford University Press, New York, N. Y., 1943, p. 970.

an alkyl group from carbon to nitrogen during hydrogenation, V was dehydrogenated over palladium to 62% of IV. V also was prepared in 35% yield by hydrogenolysis of III in the presence of nickel at 2200 lb. and 175°.

At this time no attempt has been made to fix the position of the heterocyclic double bonds in II, and the structure of II was written in arbitrary fashion, as being the most logical. Craig, Schaefgen and Tyler,[6] who have prepared 3,5-diethyl-1-phenyl-2-propyldihydropyridine from the reaction of butyraldehyde and aniline have pointed out the possibility of three structures. These authors favor the 1,4-dihydro structure over either of the conjugated double bond possibilities, their premise being based largely on differences in behavior of their compound as compared to Karrer's 1-phenyl-1,2-dihydropyridine.[7]

1-Butyl-3,5-diethyl-2-propyldihydropyridine and 3,5-diethyl-1,2-dipropyldihydropyridine were prepared from N-butylidenebutylamine and N-butylidenepropylamine, respectively, in somewhat better yields than the benzyl derivative. An attempt was made to prepare 1-ethyl-2-methyldihydropyridine by the reaction of acetaldehyde with N-ethylidene-ethylamine, but the reaction was difficult to control and much tar resulted.

A preliminary attempt to condense crotonaldehyde with N-butylidenebenzylamine to give 1-benzyl-2-propyldihydropyridine was unsuccessful. The product was desired as a precursor of the alkaloid coniine.

Experimental

Preparation of Aldimines.—The procedure was essentially that of Campbell, Sommers and Campbell.[8] In the case of N-ethylidene-ethylamine, a 33% aqueous solution of ethylamine was used quite as satisfactorily as the anhydrous higher homologs. Yields were consistently 80–85%.

1-Benzyl-3,5-diethyl-2-propyldihydropyridine and N-(2-Ethyl-2-hexenylidene)-benzylamine.—Twenty-five milliliters of benzene was placed in a 500-ml., three-necked flask fitted with a stirrer, a thermometer and two dropping funnels. The benzene was cooled to 5–10° by an ice-bath and 80.5 g. (0.5 mole) of N-butylidenebenzylamine and 108 g. (1.5 moles) of butyraldehyde were added simultaneously over a 10-minute period with stirring. The ice-bath was removed and the dropping funnels were replaced by a reflux condenser. The temperature rose to a maximum of 43° during 45 minutes. The mixture was then boiled under reflux for one hour. A Dean and Stark trap, previously filled with benzene, was then interposed in the system, and refluxing was continued for two hours longer. During this period 14.5 ml. (0.8 mole) of water had collected. The mixture was distilled, and in addition to lower-boiling materials, 109.1 g. of deep yellow liquid, b.p. 83–142° (1.3 mm.), was collected. The residue weighed 11.0 g. The distillate was fractionated through a 2-ft. Vigreux column to give 45.0 g. (42% yield) of N-(2-ethyl-2-hexenylidene)-benzylamine, the major portion of which boiled at 115° (1.5 mm.) –118° (2 mm.), $n^{25}\mathrm{D}$ 1.5276, d^{25}_{25} 0.922.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.68; H, 9.83; N, 6.51. Found: C, 83.94; H, 9.64; N, 6.45.

There was also obtained 43.6 g. (32% yield) of 1-benzyl-3,5-diethyl-2-propyldihydropyridine, the major portion of which boiled at 118° (1.2 mm.) –122° (1.4 mm.), $n^{25}\mathrm{D}$ 1.5338, d^{25}_{25} 0.941.

Anal. Calcd. for $C_{19}H_{27}N$: C, 84.67; H, 10.10; N, 5.20. Found: C, 84.57; H, 9.78; N, 5.37.

In a similar experiment the aldimine was added to the benzene solution of the aldehyde without cooling. The yield of I was 40% and of II was 30%.

Slightly better results were obtained by carrying out the reaction in ethanol. To a stirred solution of 97.5 g. (0.606 mole) of the aldimine in 350 ml. of absolute ethanol, there was added during 90 minutes 131 g. (1.82 moles) of butyraldehyde. The temperature rose from 24 to 41° during this time. The solution was then boiled under reflux for two hours before distillation. There were obtained a 40% yield of I and a 37% yield of II.

Structure Proof of N-(2-Ethyl-2-hexenylidene)-benzylamine.—A solution of 21.5 g. (0.1 mole) of N-(2-ethyl-2-hexenylidene)-benzylamine in 250 ml. of 5% hydrochloric acid was steam distilled until about 250 ml. of distillate was collected. The yellow oil was separated from the distillate and the aqueous portion was extracted twice with benzene. The combined extracts and oil were dried over anhydrous sodium sulfate, and then distilled to give 7.8 g. (62%) of 2-ethyl-2-hexenal, b.p. 68–72° (20 mm.) (68° (19 mm.)),[9] $n^{25}\mathrm{D}$ 1.4528. Its 2,4-dinitrophenylhydrazone melted at 122–123°[10] (122°).[9]

The residue from the steam distillation was made basic with aqueous sodium hydroxide and steam distillation was continued until an additional 300 ml. was collected. The cloudy distillate was extracted three times with benzene, and the combined extracts were dried over anhydrous potassium carbonate. Distillation gave 4.5 g. (42%) of benzylamine, b.p. 67–70° (10 mm.) (182° (749 mm.)),[11] $n^{25}\mathrm{D}$ 1.5393 ($n^{20}\mathrm{D}$ 1.54015).[11] Its acetamide melted at 58–61° (60–61°).[12]

1-Benzyl-3,5-diethyl-2-propylpiperidine.—To a solution of 19.9 g. (0.0739 mole) of 1-benzyl-3,5-diethyl-2-propyldihydropyridine in 150 ml. of absolute ethanol there was added 0.20 g. of platinum oxide. The mixture was hydrogenated at room temperature in a Parr hydrogenation assembly at an initial pressure of 25 lb. Hydrogenation was complete in less than 2.5 hours. A pressure drop of 11.4 lb. corresponded to 0.143 mole of hydrogen absorbed, or 1.94 moles of hydrogen per mole of amine. The reaction mixture was filtered and distilled to give 18.7 g. (93% yield) of crude product, which was redistilled to give 11.7 g. (58%) of 1-benzyl-3,5-diethyl-2-propylpiperidine, b.p. 119–121° (0.5 mm.), $n^{25}\mathrm{D}$ 1.5069, d^{25}_{25} 0.929.

Anal. Calcd. for $C_{19}H_{31}N$: C, 83.42; H, 11.43. Found: C, 83.47; H, 11.47.

3,5-Diethyl-2-propylpyridine.—Five grams of Raney nickel and 97.8 g. (0.364 mole) of 1-benzyl-3,5-diethyl-2-propyldihydropyridine were placed in a stainless steel rocking autoclave and hydrogenated at 1800 lb. pressure for one hour at 150° and then for two hours at 200°. Distillation gave 28.2 g. (84%) of toluene, b.p. 53–55° (100 mm.) and 50.7 g. (79%) of crude 3,5-diethyl-2-propylpyridine, b.p. 97° (10 mm.) –117° (11 mm.), $n^{25}\mathrm{D}$ 1.4869.

The toluene was redistilled (b.p. 109°, $n^{25}\mathrm{D}$ 1.4934) and a small sample was oxidized with alkaline potassium permanganate to give benzoic acid, m.p. 122–123°.

The amine was fractionated through a 30-in. Lecky column to give 39.4 g. (61%) of 3,5-diethyl-2-propylpyridine, b.p. 110.5° (11 mm.) to 113° (11.5 mm.), $n^{25}\mathrm{D}$ 1.4877–1.4925. An analytical sample boiled at 112.5° (11.5 mm.), (125° (18 mm.)),[4] $n^{25}\mathrm{D}$ 1.4920, d^{25}_{25} 0.898 (d^{20} 0.9042)).[3]

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.27; H, 10.80; N, 7.93. Found: C, 81.15; H, 11.03; N, 8.09.

The picrate of the amine melted at 122° (123.5°)[3] after recrystallization from ethanol.

The chloroplatinate of the amine melted at 166–167° (167°)[3] after three recrystallizations from aqueous ethanol.

Another similar hydrogenation was carried out on a smaller scale at 185° and 3600 lb. pressure for three hours. In order to preclude the possibility of dehydrogenation during fractionation, the product was distilled through a 2-ft. all-glass Vigreux column to give 45% of crude 3,5-diethyl-2-propylpyridine, b.p. 107–111.5° (11 mm.), $n^{25}\mathrm{D}$ 1.4782–1.4915.

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[6] D. Craig, L. Schaefgen and W. P. Tyler, THIS JOURNAL, **70**, 1624 (1948).

[7] P. Karrer, G. Schwarzenbach and G. E. Utzinger, *Helv. Chim. Acta*, **20**, 72 (1937).

[8] K. N. Campbell, A. H. Sommers and B. K. Campbell, THIS JOURNAL, **66**, 82 (1944).

[9] M. Backès, *Compt. rend.*, **196**, 278 (1933).

[10] All melting points are corrected.

[11] M. Konowalow, *Ber.*, **28**, 1861 (1895).

[12] H. Amsel and A. W. Hofmann, *ibid.*, **19**, 1286 (1886).

Permanganate Oxidation of 3,5-Diethyl-2-propylpyridine.—A mixture of 5.0 g. of 3,5-diethyl-2-propylpyridine, 10 g. of potassium permanganate and 150 ml. of water containing 1 ml. of 20% sodium hydroxide was boiled under reflux for an hour. The permanganate was completely reduced. The manganese dioxide was removed by filtration. The filtrate contained a few drops of insoluble oil. Five grams of permanganate was added to the filtrate and refluxing was continued for an hour. Again the permanganate was completely consumed, but oil droplets remained in the filtrate. The procedure was repeated until a total of 30 g. of permanganate had been used, and oxidation appeared complete. Enough ethanol (1–2 ml.) was added to reduce the excess permanganate, and the final filtrate was clear and nearly colorless. It was acidified to *p*H 4 with dilute nitric acid. An excess of aqueous silver nitrate was added, and the precipitated white silver salt was washed three times with water. It was suspended in 50 ml. of hot water and hydrogen sulfide was added until the silver was completely converted to the sulfide. The latter was removed by filtration and four crops of crystals were obtained by successive partial evaporation, chilling and filtration. The first three crops all melted below 173° and failed to give a red color with ferrous sulfate solution. The fourth crop gave a blood-red color with ferrous sulfate, and after some decomposition at about 160°, melted with further decomposition at 321°. This was the expected behavior for 2,3,5-pyridinetricarboxylic acid.

3,5-Diethyl-2-propylpiperidine: By Hydrogenation of 3,5-Diethyl-2-propylpyridine.—A mixture of 34.0 g. (0.192 mole) of 3,5-diethyl-2-propylpyridine, 150 ml. of absolute ethanol and 0.40 g. of platinum oxide was subjected to 33 lb. hydrogen pressure in a Parr hydrogenation assembly for one hour at room temperature. Only a 0.5-lb. pressure drop was noted. The platinum catalyst was removed by filtration, and 5 g. of Raney nickel was added to the filtrate. Another 50 ml. of ethanol was added in rinsing. This mixture was treated with hydrogen at 4000 lb. and 225° for five hours in a stainless steel rocking autoclave.

The reaction mixture was fractionated through a 30-in. Lecky column into seven cuts totalling 31.6 g. (90% yield), over-all b.p. 101.2–113° (10.5 mm.), $n^{25}\text{D}$ 1.4533–1.4610. Fraction II, 4.3 g., had b.p. 104–106° (10.5 mm.), $n^{25}\text{D}$ 1.4578, d^{25}_{25} 0.853. Fraction VII, 16.2 g., had b.p. 111–113° (10.5 mm.), $n^{25}\text{D}$ 1.4592, d^{25}_{25} 0.850.

Anal. Calcd. for $C_{12}H_{25}N$: C, 78.61; H, 13.75; N, 7.64. Found for II: C, 78.47; H, 13.47; N, 7.55. Found for VII: C, 79.23; H, 13.55; N, 7.22.

By Hydrogenolysis of 1-Benzyl-3,5-diethyl-2-propylpiperidine.—A mixture of 10.6 g. (0.039 mole) of 1-benzyl-3,5-diethyl-2-propylpiperidine, 25 ml. of absolute ethanol and 1 g. of Raney nickel was treated with hydrogen at 2200 lb. pressure for two hours at 175°. Distillation of the filtered reaction mixture gave 2.5 g. (35% yield) of 3,5-diethyl-2-propylpiperidine, b.p. 102–107° (10 mm.), $n^{25}\text{D}$ 1.4600, d^{25}_{25} 0.860.

Anal. Calcd. for $C_{12}H_{25}N$: C, 78.61; H, 13.75; N, 7.64. Found: C, 78.17; H, 13.50; N, 7.64.

Dehydrogenation of 3,5-Diethyl-2-propylpiperidine.—Three grams (0.0164 mole) of 3,5-diethyl-2-propylpiperidine (Fraction VII, above) was slowly heated with 1.0 g. of 5% palladium on activated carbon over a period of 90 minutes to a maximum of 236°. Evolution of gas, which was collected over water, had ceased in this time. It measured 675 ml. (0.030 mole), or about 61% of the theoretical for complete dehydrogenation. The residue was filtered, using benzene for rinsing, and distilled. The distillate was a colorless liquid, 1.8 g. (62% yield), b.p. 106–113° (10 mm.), $n^{25}\text{D}$ 1.4930. Its picrate formed readily in good yield as yellow, well-defined crystals from ethanol. Upon recrystallization from ethanol, it melted at 122–123°. The m.p. of a mixture with the picrate of 3,5-diethyl-2-propylpyridine was unchanged.

1-Butyl-3,5-diethyl-2-propyldihydropyridine.—In an experiment similar to the foregoing, a mixture of 108 g. (1.5 moles) of butyraldehyde and 63.5 g. (0.5 mole) of N-butylidenebutylamine was brought to reflux whereupon water soon began to separate. A Dean and Stark trap was interposed in the system and 50 ml. of benzene was added. The mixture was then boiled under reflux until the formation of water (20.5 ml., 1.14 moles) was complete. Fractionation through a 2-ft. Vigreux column gave 81.9 g. (70%) of crude 1-butyl-3,5-diethyl-2-propyldihydropyridine, b.p. 127–134° (12 mm.), $n^{25}\text{D}$ 1.4843–1.4846. Of this material, 61.6 g. (52% yield) boiled at 132.5–133° (12 mm.), $n^{25}\text{D}$ 1.4843, d^{25}_{25} 0.859.

Anal. Calcd. for $C_{16}H_{29}N$: C, 81.58; H, 12.42; N, 5.95. Found: C, 81.59; H, 12.26; N, 6.18.

Attempts to prepare a crystalline picrate of this amine were unsuccessful.

3,5-Diethyl-1,2-dipropyldihydropyridine.—3,5-Diethyl-1,2-dipropyldihydropyridine was prepared from butyraldehyde and N-butylidenepropylamine. The procedure was identical to that used for 1-butyl-3,5-diethyl-2-propyldihydropyridine. The yield of pure product, b.p. 120–121° (12 mm.), $n^{25}\text{D}$ 1.4860, d^{25}_{25} 0.854, was 66%.

Anal. Calcd. for $C_{15}H_{27}N$: C, 81.40; H, 12.30; N, 6.33. Found: C, 80.79; H, 12.02; N, 6.56.

A crystalline picrate could not be prepared from this product.

Ten-gram samples of the amine were boiled under reflux with 50 ml. of 5% potassium hydroxide in 80% ethanol for six hours, and with 50 ml. of 3 *N* hydrochloric acid for 90 minutes, respectively. The amine was obtained unchanged by distillation in 77% recovery from the attempted alkaline hydrolysis, and in 50% recovery from the attempted acid hydrolysis.

Attempted Preparation of 1-Ethyl-2-methyldihydropyridine.—When acetaldehyde was mixed with N-ethylidene-ethylamine at room temperature, a violent reaction occurred with the production of much heat. In other experiments acetaldehyde was added gradually to N-ethylidene-ethylamine at 0°, and N-ethylidene-ethylamine was added to acetaldehyde at 0°. In each case benzene was added and water was removed azeotropically as before. However, nearly all of the reaction product appeared as an intractable, acid-soluble tar. Only traces of distillable material were obtained in the range expected for 1-ethyl-2-methyldihydropyridine.

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