filtering and adding petroleum ether. The recrystallized material exhibited dimorphism, melting at 178.3°, resolidifying and melting again at 191°.[14]

Anal. Calcd. for $C_{14}H_{10}O_{10}N_4$: C, 42.64; H, 2.54. Found: C, 42.59; H, 2.49.

1,3,6,8-Tetranitrocarbazole.—9.57 g. of 3,3',5,5'-tetranitro-2,2'-dimethoxybiphenyl was heated four hours at 135° in a sealed tube with 35 ml. of absolute alcohol saturated with ammonia. 0.22 g. of red-brown needles (44% yield) were filtered from the solution left in the tube and washed with acetone. After recrystallization from glacial acetic acid, the product was obtained as pale yellow, transparent needles melting at 295.6–296.0°.

Anal. Calcd. for $C_{12}H_5O_8N_5$: C, 41.50; H, 1.44. Found: C, 41.69; H, 1.24.

1,2,6,8-Tetranitrocarbazole.—Fifty grams of carbazole wera dissolved in 300 g. of fuming (30% SO_3) sulfuric acid, keeping the temperature at 40–50°. The mixture was then heated about two hours at 90–100°. After this heating period, there was still a large amount of solid present, but the mixture was completely water soluble. One hundred sixty grams of 93% nitric acid was then added slowly, keeping the temperature between 40–60°. The mixture was then filtered through a fritted glass funnel, and the solid was washed with water and dried. One gram of the crude product, melting at 230–234°, was dissolved in 25 ml. of boiling nitrobenzene. The solution was cooled, filtered, and 50 ml. of benzene was added. After a time, the pure 1,2,6,8-tetranitrocarbazole separated in small, glistening yellow plates, m.p. 153–154°.

Anal. Calcd. for $C_{12}H_5O_8N$: C, 41.50; H, 1.44; N, 20.17. Found: C, 41.58; H, 1.39; N, 20.06.

Infrared Absorption Spectra.—Infrared spectra were obtained using a Perkin–Elmer double-beam infrared spectrophotometer. A mineral oil mull was used between 6.0–6.6 and 7.7 and 15.0 μ. Hexachlorobutadiene was used as the mulling agent between 2.0–6.0 and 6.6–7.7 μ.

DOVER, NEW JERSEY

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[14] J. Van Alphen, *Ber.*, **64**, 1819 (1931), reports 179 and 191°.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF NOTRE DAME, AND THE RESEARCH DEPARTMENT OF THE LABORATORIES VIETA-PLASENCIA, HAVANA, CUBA]

Abnormal Chichibabin Reactions. The Condensation of Phenylacetaldehyde and Homoveratric Aldehyde with Ammonia[1]

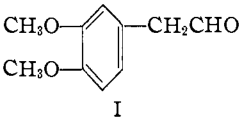
BY ERNEST L. ELIEL,[2] RICHARD T. MCBRIDE[3] AND ST. KAUFMANN

RECEIVED MARCH 14, 1953

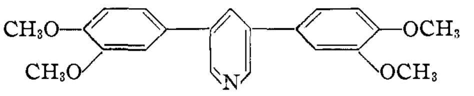
The condensation of homoveratric aldehyde (I) with ammonia in boiling ethanol solution gives rise to a base whose structure has been proved to be 3,5-diveratrylpyridine (II). When the condensation is carried out in an autoclave under pressure, the product is sometimes 3,5-diveratrylpyridine (II) and sometimes a base which appears to be 3,5-diveratryl-2-homoveratrylpyridine (III). Phenylacetaldehyde and ammonia react only in an autoclave at elevated temperatures to give 3,5-diphenylpyridine and toluene.

Several years ago,[4] in attempts to synthesize the alkaloid papaverine by novel methods, we had occasion to condense homoveratric aldehyde (3,4-dimethoxyphenylacetaldehyde, I) with ammonia. Reaction took place with surprising ease in boiling ethanol solution giving rise to a crystalline base, isolated after treatment of the reaction mixture with acid, which accounted for *ca.* 10% of the weight of the starting materials.

The base was different in properties from papaverine, and its analysis and molecular weight pointed to the formula $C_{21}H_{21}NO_4$ which contains one carbon atom more than can be accounted for by the condensation of two molecules of the aldehyde I with one molecule of ammonia. The infrared spectrum of the base indicated the absence of functional groups other than the expected methoxyl groups and suggested that the base was tertiary. These findings were corroborated by classification tests.



I



II

The new base was resistant toward hot permanganate in either acidic or basic solution. Boiling with nitric acid did not lead to oxidation, but yielded a crystalline dinitro derivative of the original compound. Treatment of the base with methyl iodide yielded a crystalline methiodide which by reaction with silver chloride slurry could be converted to a water-soluble methochloride. The same methochloride was produced when homoveratric aldehyde (I) was condensed with methylamine in boiling ethanol, and the reaction mixture treated with hydrochloric acid; it was converted to the less soluble methiodide by treatment with potassium iodide in aqueous solution.

Oxidation of the methiodide with alkaline potassium permanganate (after conversion to the methonitrate by means of silver nitrate) gave veratric acid (3,4-dimethoxybenzoic acid) in such a yield as to suggest the presence of *two* methoxyl-substituted phenyl rings in the original base. This finding, coupled with the fact that pyrolysis of the quaternary hydroxide obtained from the methiodide regenerated the original base, suggested that the base was a diveratrylpyridine, and, in view of its method of formation, probably 3,5-diveratrylpyridine (3,5-bis-(3,4-dimethoxyphenyl)-pyridine, II). Formula II was corroborated by

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[1] This paper is taken in part from the Ph.D. dissertation of Richard T. McBride.

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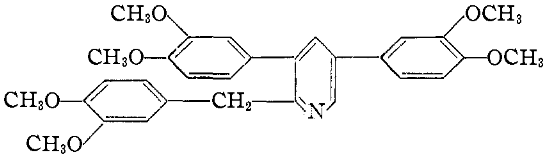
[3] Socony-Vacuum Fellow, 1951–1952; Reilly Fellow, 1952.

[4] This work was initiated in the Laboratories Vieta-Plasencia in 1945–1946. A few experiments were carried out at the University of Illinois in 1947 and the work was concluded at the University of Notre Dame, 1950–1952.

ether cleavage of the base by means of hydrobromic acid followed by permanganate oxidation which yielded pyridine-3,5-dicarboxylic acid.

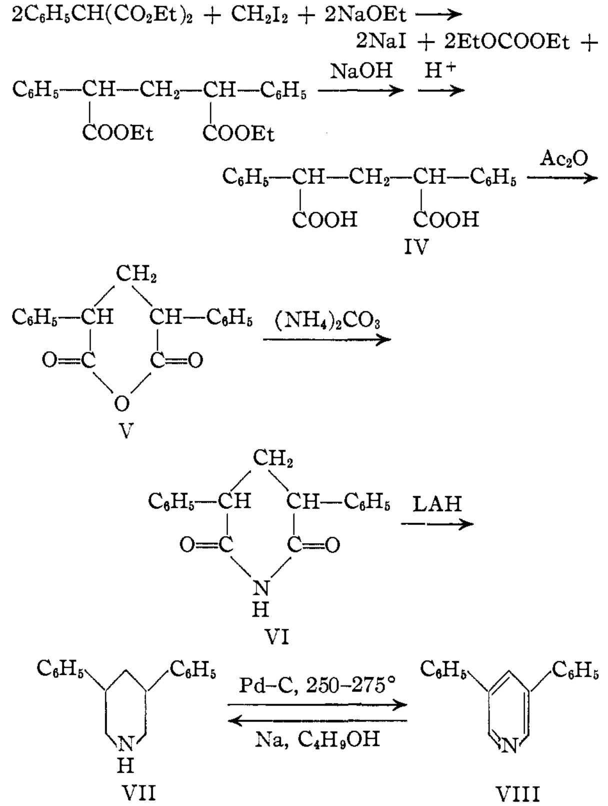
The origin of the extra carbon atom now became a matter of interest. It could not have been derived from the solvent, since the formation of II from I proceeded even in liquid ammonia in the absence of any solvent. A normal Chichibabin condensation[5] of homoveratric aldehyde (I) and ammonia should have given rise to 3,5-diveratryl-2-homoveratrylpyridine (III) and, in fact, a compound corresponding in composition to III was isolated in a few instances when the condensation of I with ammonia was carried out in an autoclave at elevated temperatures. Attempts to prove the structure of this base are outlined in the Experimental part; they were not pressed to an unequivocal conclusion because the preparation of the base could not be readily duplicated.[6]


III

Since further investigation of the condensation of homoveratric aldehyde (I) with ammonia was hampered by the difficulty of obtaining I on a large scale, the condensation of phenylacetaldehyde with ammonia was investigated next. This condensation did not proceed under the mild conditions successful in the case of II, but did occur in an autoclave in ethanol solution at *ca.* 230° giving rise to a stable crystalline base. Analysis of the base and its picrate suggested that it also was a diarylpyridine, and the 3,5-diphenylpyridine structure seemed a plausible one, in view of the analogy with compound II.

Unfortunately, 3,5-diphenylpyridine is already reported in the literature as having been prepared by a zinc dust distillation of 4-hydroxy-3,5-diphenylpyridine,[7] and its melting point and the melting point of its picrate are quite different from those of the compounds obtained in this work. It therefore became necessary to prove the structure of the diphenylpyridine obtained here.

2,4-Diphenylglutaric acid (IV) was synthesized by the published[8] method (see flow sheet) and the mixture of diastereoisomers so obtained was converted to the anhydrides (V) by treatment with acetic anhydride. Crystallization of the anhydride mixture yielded two substances, probably the diastereoisomeric anhydrides. Either of these, upon heating with ammonium carbonate yielded what appeared to be a mixture of diastereoisomeric 2,4-diphenylglutarimides (VI).


$$2C_6H_5CH(CO_2Et)_2 + CH_2I_2 + 2NaOEt \longrightarrow 2NaI + 2EtOCOOEt +$$

IV

V

VI

VII

VIII

Reduction of this mixture with lithium aluminum hydride[9] gave a stereoisomeric mixture of 3,5-diphenylpiperidines (VII) in poor yield. The infrared spectrum of this mixture was very similar to that of a mixture of diphenylpiperidines obtained by reduction of diphenylpyridine (from the Chichibabin condensation) with sodium and *n*-butyl alcohol.[10] However, definite identification of the two substances did not appear convenient, since both were diastereoisomeric mixtures. Therefore the authentic sample was converted to 3,5-diphenylpyridine (VIII) by dehydrogenation with palladium–charcoal[11]; this dehydrogenation proceeded smoothly and gave rise to a product identical with that obtained in the Chichibabin condensation. It is extremely unlikely that dehydrogenation proceeded with rearrangement, not only because of the low reaction temperature, but also because the diphenylpiperidine obtained by the above-mentioned sodium–butanol reduction of the diphenylpyridine regenerated the diphenylpyridine upon treatment with palladium–charcoal under the same conditions used for the dehydrogenation of authentic 3,5-diphenylpiperidine and in similar yield.[11a]

It appeared plausible that the synthesis of 3,5-diphenylpyridine from phenylacetaldehyde and ammonia had proceeded by the elimination of

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[5] For a review, see H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1950, pp. 455-461.

[6] The presumed compound III was first obtained in an autoclave at the University of Illinois. On one occasion it was obtained in fairly pure form, on another in admixture with II from which it could be separated by repeated recrystallization from ethanol. When the preparation of III was attemped in a stainless steel bomb at the University of Notre Dame, only II could be isolated from the products. This suggests that traces of foreign materials present in the autoclave first used catalyzed the formation of III.

[7] E. Benary and G. A. Bitter, *Ber.*, **61**, 1057 (1928).

[8] B. L. Souther, THIS JOURNAL, **46**, 1304 (1924).

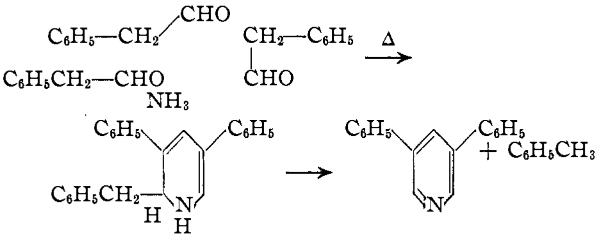
[9] A. Uffer and E. Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

[10] S. Wawzonek, M. F. Nelson and P. J. Thelen, THIS JOURNAL, **74**, 2894 (1952).

[11] N. Zelinsky and P. Borisov, *Ber.*, **57**, 150 (1924).

[11a] The slight variation in yield may have been due to different stereoisomeric composition of the products (VII), *cf.* N. J. Leonard and B. L. Ryder, *J. Org. Chem.*, **18**, 598 (1953).

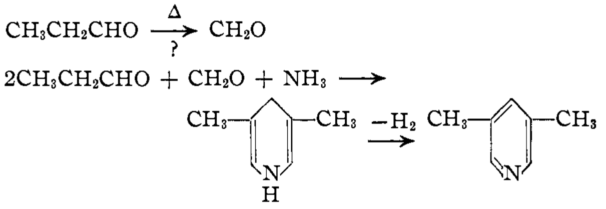
toluene from the intermediate dihydropyridine IX. That this was indeed the case was proved by the isolation of toluene from the reaction



IX

mixture, the yield (12%) of toluene being about same as that of 3,5-diphenylpyridine (13%).

The appearance of toluene demonstrates conclusively that the mechanism proposed by Chichibabin[12] for abnormal condensations in the aliphatic series does not apply to the phenylacetaldehyde case. Chichibabin studied the reaction of propionaldehyde with ammonia[13] which gives 3,5-dimethylpyridine in addition to 2-(and 4-)ethyl-3,5-dimethylpyridine as well as similar reactions with *n*-butyraldehyde and isovaleraldehyde. He postulated that the aliphatic aldehydes broke down in part to give formaldehyde, and that the abnormal products were formed by the condensation of one molecule of formaldehyde so produced with two molecules of the higher aliphatic aldehyde and one molecule of ammonia. This mechanism is open



to doubt even in the aliphatic series; it appears more likely that the 3,5-dimethylpyridine is formed by the loss of ethane from an intermediate 2-(or 4-) ethyl-3,5-dimethyldihydropyridine.

A surprising difference between the condensation of phenylacetaldehyde and that of homoveratric aldehyde (I) lies in the great ease with which the latter proceeds under mild conditions of pressure and temperature. We should like to suggest that this is due to the highly enolic nature of homoveratric aldehyde (I).[14]

The yield of 3,5-diphenylpyridine from a given quantity of phenylacetaldehyde can be increased by a factor of about three by the addition of an equimolar amount of isobutyraldehyde, basic iron acetate or methanolic formaldehyde.[15] On the other hand, addition of acetaldehyde leads to different products which are under investigation.

Experimental[16]

Methyl Eugenol Glycol.—Since the permanganate oxidation of methyl eugenol[17,18] involves the evaporation of inconveniently large volumes of water, the glycol was prepared by oxidation of the olefin with performic acid.[19,20]

To a well-stirred solution of eugenol methyl ether[21] (178 g., 0.84 mole) in 758 g. (14.1 moles) of 85% formic acid, 166 g. (1.42 mole) of 29% hydrogen peroxide was added over a 40-minute period, while the temperature was maintained at 5–10° by means of an ice-bath. The reaction mixture was held at the same temperature for an additional half-hour after which it was allowed to warm to room temperature *slowly* over a 90-minute period. Water and formic acid were then distilled at a pressure of 25 mm. until *ca.* 760 g. had been collected. The residue was made basic by the addition of 200 g. of 40% aqueous sodium hydroxide in small portions, the temperature being held at 30–40° by occasional cooling. The basic solution was again concentrated *in vacuo*, an additional 120–130 ml. of aqueous distillate being collected. The residue was taken up in 1 l. of chloroform, filtered with the aid of Supercel, and the filtrate dried over sodium sulfate and concentrated. Distillation of the residue led to the recovery of 11 g. of methyl eugenol, b.p. 80–85° (0.5 mm.) followed by 85.5 g. (43%, based on methyl eugenol consumed) of methyl eugenol glycol, b.p. 170–173° (0.25–0.35 mm., slight dec.) which solidified on standing (lit.[18] b.p. 152–162° (0.025 mm.), m.p. 67.5–69°).

3,4-Dimethoxyphenylacetaldehyde (I).—This preparation was carried out as described previously[18] by oxidation of the glycol with lead tetraacetate in chloroform solution. The product boiled at 125–128° (0.3 mm.) and gave a dinitrophenylhydrazone melting at 169–169.5°.

3,5-Diveratrylpyridine (I).—A solution of 45.5 g. of homoveratric aldehyde (I) in 250 ml. of freshly prepared[22] absolute alcohol was boiled under reflux for one hour while a current of dry ammonia gas was bubbled through it. The solvent and excess ammonia were then distilled at reduced pressure and the spongy, apparently amorphous residue was heated with 100 ml. of a normal solution of hydrogen chloride in anhydrous ethanol (or methanol). The excess ethanol and hydrogen chloride were then distilled (at atmospheric pressure or *in vacuo*) and the residue was slurried with acetone. Most of the tarry material dissolved and light-colored crystals of the hydrochloride of 3,5-diveratrylpyridine remained. They were collected, washed with acetone until nearly colorless and dissolved in 350 ml. of boiling 95% ethanol. The addition of 100 ml. of concentrated aqueous ammonia and 100 ml. of water to this solution led to the precipitation of 3,5-diveratrylpyridine (II) in the form of shiny leaflets. The suspension was chilled and the crystals (5.66 g.) collected. Recrystallization gave 4.44 g. of material

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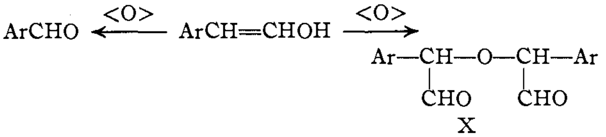
[12] A. E. Chichibabin, *J. prakt. Chem.*, [2] **107**, 122 (1924).

[13] A. E. Chichibabin and M. P. Oparina, *ibid.*, [2] **107**, 145 (1924).

[14] Although the aldehyde does not give a color with ferric chloride, it shows a marked OH-band in the infrared. Attempts to oxidize the aldehyde to the corresponding acid led to the formation of either veratraldehyde or what appears to be a product of oxidative coupling (X)



$$\mathrm{ArCHO} \xleftarrow{<O>} \mathrm{ArCH{=}CHOH} \xrightarrow{<O>} \underset{\mathrm{CHO}}{\mathrm{Ar{-}CH}}\mathrm{{-}O{-}}\underset{\mathrm{CHO}}{\mathrm{CH{-}Ar}}$$

X

Structure X was suggested by the analysis of the semicarbazone, m.p. 180–180.5°. Calcd. for $C_{22}H_{28}N_6O_7$: C, 54.10; H, 5.78; N, 17.21. Found: C, 54.63; H, 6.03; N, 17.95 (E. Eliel, Thesis, Havana University, 1946).

[15] Methyl Formcel, Celanese, 40% formaldehyde contents, containing 7% water. The increase in yield here is somewhat less than in the other two cases. We are thankful to the Chemical Division of the Celanese Corporation of America for a generous sample of Methyl Formcel.

[16] All melting and boiling points are uncorrected. Microanalyses by Micro-Tech Laboratories, Skokie, Ill.; Microanalytical Laboratory of the Chemistry Department, University of Illinois; Huffman Laboratories, Denver, Colo.; Sadtler Laboratories, Philadelphia, Pa.; and Clark Microanalytical Laboratory, Urbana, Ill.

[17] G. Wagner, *Ber.*, **24**, 3488 (1891).

[18] St. Kaufmann, E. L. Eliel and G. Rosenkranz, *Ciencia* (*Mexico*), **7**, 136 (1946).

[19] D. Swern, G. N. Billen, T. W. Findley and J. T. Scanlan, THIS JOURNAL, **67**, 1786 (1945).

[20] The oxidation of eugenol methyl ether with peracetic acid has been studied previously: Carmen Teresa Cuní, Thesis, University of Havana, 1945.

[21] Verona Chemical Co., Newark, N. J.

[22] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 358.

melting at 170–173°. The analytical sample melted at 173–174°.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.76; H, 6.03; N, 3.99; mol. wt., 351. Found: C, 71.70, 71.76, 71.82; H, 6.04, 6.00, 5.97; N, 3.90; mol. wt. 320 (ebullioscopically in benzene).

The same material was obtained in methanol or xylene solution, in liquid ammonia solution (though in low yield), with ammonium acetate by the method of Weiss,[23] as well as, in some instances, with alcoholic ammonia under pressure (see below).

3,5-Diveratrylpyridine yielded a hydrochloride melting at 216–217° (dec.). The **methiodide** was formed by boiling a solution of 0.50 g. of the base and 3 ml. of methyl iodide in 50 ml. of commercial absolute ethanol for 30 minutes. Collected after chilling of the solution and washed with ethanol and ether, it weighed 0.61 g. (87%). The melting point was 252–253° (dec.) after recrystallization from glacial acetic acid.

Anal. Calcd. for $C_{22}H_{24}NO_4I$: C, 53.74; H, 4.88. Found: C, 53.56, 53.22; H, 5.10, 4.95.

The methochloride was prepared as follows: A solution of 0.6 g. of the methiodide in 150 ml. of water was boiled for 20 minutes with a slurry of *ca.* 1 g. of freshly prepared silver chloride. The solution was then filtered, the residue washed with 75 ml. of boiling water and the combined filtrate evaporated to dryness on a steam-bath. Recrystallization of the residue from ethanol–ether with the aid of Nuchar yielded the methochloride, m.p. 247.5–248.5° (dec.), not depressed by admixture of a sample prepared from homoveratric aldehyde and methylamine (see below).

Oxidation of 3,5-Diveratrylpyridine Methiodide.—A solution of 0.4555 g. (0.9 millimole) of the above methiodide in 135 ml. of boiling water was treated with 4 ml. of a 5% aqueous silver nitrate solution and filtered to remove iodide ions in the form of silver iodide. The filtrate was heated to 85° on a steam-bath and treated with finely ground potassium permanganate until a purple color persisted for 15 minutes. A few drops of ethanol were added to destroy excess permanganate and the precipitated manganese dioxide was removed by filtration. Concentration of the filtrate followed by chilling and acidification with concentrated hydrochloric acid yielded crystals which were collected, washed and dried. The acid weighed 0.160 g., melted at 178–180° and did not depress the melting point of an authentic sample of veratric acid obtained by oxidation of veratric aldehyde. More veratric acid was obtained by concentration of the mother liquor, the total yield being 0.173 g. (0.95 millimole).

Nitration of 3,5-Diveratrylpyridine.—A suspension of 0.501 g. (1.4 millimoles) of the diveratrylpyridine in 75 ml. of water and 25 ml. of 70% nitric acid (density 1.42) was boiled for five hours. Yellow crystals appeared after three hours. The solution was chilled and the crystals collected and dried; they weighed 0.25 g. (39.5%) and melted at 210.5–211.5 after two recrystallizations from ethanol.

Anal. Calcd. (for a dinitrodiveratrylpyridine, $C_{21}H_{19}N_3O_8$): C, 57.20; H, 4.30; N, 9.52. Found: C, 57.16; H, 4.66; N, 9.33.

Attempted Exhaustive Methylation of 3,5-Diveratrylpyridine.—A solution of 1.0 g. (2 millimoles) of 3,5-diveratrylpyridine methiodide in 300 ml. of boiling water was slurried with *ca.* 2 g. of freshly prepared silver oxide and filtered after being maintained at 85° for 20 minutes. The filtrate was concentrated by evaporation on a steam-bath and transferred to a sublimation apparatus. Heating was continued in a Woods metal bath at a pressure of 0.2 mm. Decomposition set in at 250–270° and a horny material collected on the cold finger of the sublimation apparatus. Slurrying with 5% hydrochloric acid led to a crystallization of the sublimate. The crystals were collected; their melting point of 214–215° was raised to 216–217° by recrystallization from benzene and absolute ethanol. Since the material appeared to be identical with 3,5-diveratrylpyridine hydrochloride, it was converted to the free base by treatment with ammonia as described above. The base melted at 171–172° and did not depress the melting point of 3,5-diveratrylpyridine.

Oxidation of 3,5-Diveratrylpyridine to Pyridine-3,5-dicarboxylic Acid.—A suspension of 2.0 g. (5.67 millimoles) of 3,5-diveratrylpyridine in 25 ml. of glacial acetic acid was warmed until homogeneous; 5 ml. of concentrated (48%) aqueous hydrobromic acid was then added and the solution boiled under reflux for 90 minutes. It was then evaporated to dryness on a steam-bath, the residue taken up in 300 ml. of water and the resulting solution, after treatment with Nuchar, was brought to a *p*H of 8–9 by means of sodium bicarbonate solution. The precipitated phenolic material was collected and washed with water until free of bromide ions. It gave a green-blue color with ferric chloride solution.

The precipitate was suspended in 300 ml. of water and the suspension made alkaline with 5% sodium hydroxide solution. Complete solution did not take place at this point nor when the suspension was heated to 80–90°. Solid permanganate was added at this temperature with stirring until a purple color persisted for 30 minutes. A few drops of ethanol were then added, the slurry was filtered to remove manganese dioxide, and the residue was washed with 50 ml. of 5% aqueous sodium hydroxide. The combined filtrate and washings were treated with Nuchar and, after filtration, brought to a *p*H of 5 by the addition of acetic acid. Since the amino-acid did not precipitate, the solution was treated with 5% aqueous silver nitrate until precipitation was complete, and the silver salt was collected with the aid of Supercel and washed with water. The salt and filter-aid were then suspended in 100 ml. of water, and hydrogen sulfide was passed in at 70–75° for 20 minutes. The precipitated silver sulfide was filtered and the filtrate clarified with Nuchar and then evaporated to dryness. The residue weighed 0.226 g. and melted at 265–270° (dec.). Since it still reacted with hot alkaline permanganate, the oxidation and isolation through the silver salt were repeated as described above. This time the degradation product (62.0 mg., 6.6%) was obtained in crystalline form and melted at 321–321.5° (dec.). The melting point of pyridine-3,5-dicarboxylic acid is reported[24] to be 320° (dec.). The acid obtained in the degradation gave no color with ferrous sulfate[25] and its ultraviolet and infrared spectra were identical with those of an authentic specimen[26] of pyridine-3,5-dicarboxylic acid.

Dimethyl Pyridine-3,5-dicarboxylate.—A suspension of 68 mg. of the acid described above in 12 ml. of commercial absolute methanol was boiled under reflux while dry hydrogen chloride was passed through. After two hours the now homogeneous solution was cooled, the solvent distilled *in vacuo*, and the residue treated with 5% aqueous sodium bicarbonate. The alkaline solution was twice extracted with 20-ml. portions of ether which were dried over sodium sulfate and concentrated. The residual dimethyl pyridine-3,5-dicarboxylate (46.6 mg., 59%) melted at 81.5–82.5° (lit.[24] 84–85°). A sample prepared similarly from authentic[26] pyridine-3,5-dicarboxylic acid melted at 83.5–85°; there was no depression in melting point when the two samples were mixed and they had identical infrared spectra. We were unable to prepare dimethyl pyridine-3,5-dicarboxylate from the acid and diazomethane in a methanol–ether mixture.

Condensation of Homoveratric Aldehyde (I) with Methylamine.—This condensation was carried out exactly as the corresponding one with ammonia described earlier, except that methylamine gas was passed through the boiling ethanolic solution of the aldehyde which was prepared from methyl eugenol glycol. The chloride obtained in the final acetone treatment of the reaction mixture was quite water-soluble (differing, in that respect, from the hydrochloride of II) and did not deposit a base when its solution was treated with ammonia. It melted at 246–247° (dec.) and proved to be identical with 3,5-diveratrylpyridine methochloride whose melting point it did not depress on admixture.

Anal. Calcd. for $C_{22}H_{24}ClNO_4$: C, 65.73; H, 6.02; N, 3.49. Found: C, 65.19; H, 6.23; N, 3.65.

The identity of this salt as 3,5-diveratrylpyridine methochloride was further proved by conversion to the methiodide. When an ethanolic solution of the chloride was mixed with an ethanolic solution of sodium iodide, an organic iodide precipitated. It melted at 247–248° (dec.) after recrystalli-

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(23) M. Weiss, THIS JOURNAL, **74**, 200 (1952).

(24) H. Meyer and H. Tropsch, *Monatsh.*, **35**, 207 (1914).

(25) Substituted pyridines having a carboxyl group in the 2-position are reported to give a red color with ferrous sulfate: ref. 5, p. 569.

(26) We are much indebted to the Reilly Tar & Chemical Company, Indianapolis, Ind., for authentic specimens of a number of pyridinedicarboxylic acids, among them the 3,5-isomer.

zation from glacial acetic acid, and did not depress the melting point of 3,5-diveratrylpyridine methiodide prepared from the base (II) as described above; the two samples had identical infrared spectra.

Condensation of Homoveratric Aldehyde (I) with Ammonia under Pressure.—To 13.3 g. (0.074 mole) of homoveratric aldehyde, 90 ml. of a cold saturated solution of ammonia in absolute ethanol was added and the mixture sealed up in a stainless steel bomb. The bomb was heated for six hours at 180–190° with rocking and the pressure rose to about 520 p.s.i. After the bomb had cooled, the basic products were isolated from its contents in exactly the same manner as described for the condensation at atmospheric pressure. On different occasions, three different products were isolated: (a) the same base II (m.p. 171–172°, no depression on admixture of samples obtained as described above) which had resulted in the condensation carried out at atmospheric pressure; (b) a new base (III), melting at 159.5–160.5°, which depressed the melting point of II to 147–150°; (c) a mixture, melting at 146–148°, which by repeated crystallization from 95% ethanol could be separated into the new base, m.p. 159.5–160.5°, and 3,5-diveratrylpyridine (II), m.p. 168–170°.

The new base gave the correct analysis for 2-homoveratryl-3,5-diveratrylpyridine (III).

Anal. Calcd. for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.80; mol. wt., 501. Found: C, 71.94; H, 6.43; N, 3.15; mol. wt., 478 (ebullioscopically, in benzene).

The picrate melted at 174–176°.

Anal. Calcd. for $C_{36}H_{34}N_4O_{13}$: C, 59.19; H, 4.69. Found: C, 59.36; H, 4.88.

Oxidative degradation of this base was carried out as described for II. The base was first demethylated by means of hydrobromic acid in acetic acid and then oxidized by means of potassium permanganate, and the oxidation product was isolated through its silver salt. The acid so formed (59.3 mg. from 600 mg. of base) decomposed at 110–125° and gave a red color with aqueous ferrous sulfate.[25] When heated in an oven at 125–130° for 30 minutes, it evolved a gas and the melting point changed to 299–302° (dec.). Dürkopf, *et al.*,[27] report that pyridine-2,3,5-tricarboxylic acid decomposes below 150° to give the 3,5-dicarboxylic acid, m.p.[24] 322–323° (dec.).

Partial oxidation of the base was carried out as follows: A solution of 1 g. (2 millimoles) of the base in 75 ml. of acetone and 25 ml. of water was boiled under reflux on a water-bath and 10.75 g. (68 millimoles) of finely ground potassium permanganate was added gradually with stirring. When all the permanganate was decolorized, the acetone was distilled, 50 ml. of water was added, followed by dilute (1:4) sulfuric acid until the solution was acid to congo red. Sufficient sodium bisulfite was then added to dissolve the precipitated manganese dioxide and the solution was extracted twice with 50-ml. portions of chloroform. The chloroform solutions were washed with water and distilled to leave 0.65 g. of a solid which after recrystallization from ethanol melted at 182–183°. Repeated recrystallizations from the same solvent did not raise the melting point above 183–184°. The product gave the correct analysis for a 2-veratroyl-3,5-diveratrylpyridine, *i.e.*, the methylene group of III seemed to have been oxidized to a ketone group. The infrared spectrum is in agreement with this structure; it showed an absorption band at 6.05 μ, attributed to the benzophenone-type carbonyl group.

Anal. Calcd. for $C_{30}H_{29}NO_7$: C, 69.90; H, 5.67; N, 2.72. Found: C, 69.78; H, 5.80; N, 3.06.

Condensation of Phenylacetaldehyde with Ammonia. 3,5-Diphenylpyridine.—A solution of 100 g. (0.94 mole) of phenylacetaldehyde in 300 ml. of commercial absolute ethanol saturated with ammonia was placed in a one-liter stainless steel bomb. The bomb was sealed, heated to 230–235° and held at that temperature with rocking for six hours, the pressure rising to 1150 p.s.i. The bomb was then cooled and opened and the contents filtered with suction, the bomb and precipitated crystals being rinsed with ethanol. The filtrate was distilled at reduced pressure. The presence of toluene in the ethanol distillate was demonstrated by ultraviolet spectrophotometric analysis and its isolation was accomplished as follows. To 175-ml. portions of the ethanol solution there was added 400 ml. of a 20% aqueous calcium chloride solution, and the resulting emulsions were extracted twice with 150-ml. portions of pentane. After drying, the combined pentane solutions were subjected to fractional distillation which yielded 2.97 g. (11.6%) of toluene,[28] b.p. 110.5–111.5°, identified by preparation of 2,4-dinitrotoluene, melting point and mixture melting point with an authentic sample 69–70°.

The residue remaining after distillation of the alcohol was taken up in ether (200 ml.) and the ether solution extracted twice with 100-ml. portions of 10% hydrochloric acid. Treatment of the acid solution with ammonia led to the precipitation of crystalline material, which was collected and combined with the material isolated directly from the original reaction mixture. Recrystallization from alcohol (Nuchar) gave 9.34 g. (13.1%) of 3,5-diphenylpyridine which, after a second recrystallization, melted at 136–137° (lit.[7] 194°).

Anal. Calcd. for $C_{17}H_{13}N$: C, 88.23; H, 5.67; N, 6.05. Found: C, 88.52, 88.51; H, 5.63, 5.64; N, 5.74.

The picrate[29] melted at 204.5–205.5° after recrystallization from ethanol (lit.[7] 276°).

Anal. Calcd. for $C_{23}H_{16}N_4O_7$: C, 60.00; H, 3.50; N, 12.17. Found: C, 60.14; H, 3.45; N, 11.90.

The methiodide[29] crystallized from ethanol in fine white needles melting at 202–203°, but turned yellow and deteriorated rapidly on standing.

The hydrochloride, prepared from the base and ethereal hydrochloric acid, melted at 194–195° after recrystallization from acetone–petroleum ether (b.p. 30–60°).

The yield of 3,5-diphenylpyridine could be increased threefold by the addition of 75 g. (1.04 moles) of isobutyraldehyde[30] or 53.3 g. (0.28 mole) of basic iron acetate to the original charge. The addition of 66.7 ml. (0.89 mole) of 40% Methyl Formcel[15] produced a smaller increase in yield. In these three cases it was not determined whether toluene was formed in the condensation. No increase in yield resulted when the condensation was carried out in *n*-butyl alcohol at 280–285°. In the presence of acetaldehyde, different products were obtained.

Attempted Oxidative Degradation of 3,5-Diphenylpyridine.—The base was recovered from an attempted oxidation with permanganate in aqueous acetone. From an oxidation with permanganate in dilute sulfuric acid only a small amount of benzoic acid could be isolated.

Nitration of the base with mixed acids gave a mixture of nitro derivatives which were partly soluble in acetone. Reduction of the acetone-soluble fraction with stannous chloride or catalytically gave oily bases while the acetone-insoluble fraction yielded one or more crystalline bases. Oxidation of the latter with potassium permanganate in aqueous acetone yielded an acid (isolated *via* the silver salt) melting at 125° (dec.), which gave no color with ferrous sulfate solution. Reoxidation of this acid raised the melting point to 175–185° (dec.). Two further reoxidations raised the melting point to 280°, but the acid so obtained was still impure and not enough was obtained for further degradation work.

Reduction of 3,5-Diphenylpyridine: 3,5-Diphenylpiperidine.—To a well-stirred suspension of 10 g. (0.043 mole) of 3,5-diphenylpyridine in 120 ml. of commercial *n*-butyl alcohol contained in a 300-ml. flask equipped with a reflux condenser was added 16 g. (0.69 gram-atom) of sodium in small portions while the temperature was maintained at 70–80°. After all the sodium had been added, the reaction mixture jelled, so another 120 ml. of *n*-butyl alcohol was added and the temperature was raised to 145°. When all the sodium had dissolved, the reaction mixture was cooled, washed once with 100 ml. of water, treated with 50 ml. of 6 *N* hydrochloric acid and steam distilled to remove the butanol. The heterogeneous residue was made alkaline with ammonia, extracted with 200 ml. of ether and the ether solution was dried, concentrated and the residue distilled. 3,5-Diphenylpiperidine was collected at 149–150° (0.2 mm.) and weighed

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[27] E. Dürkopf, *et al.*, *Ber.*, **21**, 832, 2707 (1888); **23**, 685 (1890).

[28] No toluene was formed when phenylacetaldehyde in ethanolic solution was heated to 230–235° for six hours in an autoclave in the absence of ammonia.

[29] Prepared by standard methods. See R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

[30] This reaction also produced volatile compounds boiling over a wide range which were not investigated.

6.76 g. (66.9%). The infrared spectrum of the compound showed no aliphatic double bond, suggesting the absence of tetrahydropyridines.[10]

The *p*-toluenesulfonamide[29] was separated into two isomers by repeated crystallization from ethanol. Isomer 1 melted at 243–244°, isomer 2 at 198–199°.

Anal. Calcd. for $C_{24}H_{25}NO_2S$: C, 73.62; H, 6.44. Found: isomer 1: C, 73.60; H, 6.81; isomer 2: C, 73.60; H, 6.47.

A mixture of the two isomers melted at 200–210°, thus it is not certain whether these are two pure diastereoisomers or one pure isomer and a eutectic mixture of the two. Neither isomer decolorized bromine in carbon tetrachloride solution.

2,4-Diphenylglutaric Anhydride.—2,4-Diphenylglutaric acid was prepared by the method of Souther,[8] but separation of the diastereoisomers was not attempted. The crude acid (10.8 g., 0.038 mole, m.p. *ca.* 156°) was dissolved in 100 ml. of acetic anhydride and boiled for one hour. The excess acetic anhydride was removed *in vacuo* and the residue boiled with 100 ml. of dry benzene and filtered, the residue being 1.34 g. (12.4%) of unchanged acid. The filtrate was treated with Nuchar, refiltered, and petroleum ether (b.p. 30–60°) was added to it to promote crystallization. The first crop of crystals (4.83 g., 47.8%) melted at 136–137°, the second and fourth crops (combined weight 2.23 g., 22.1%) melted at 84–86° and 95–96°, respectively, the remaining material was oily. Three recrystallizations from benzene–petroleum ether raised the melting point of isomer 1 to 142.5–143.5° and that of isomer 2 to 95.5–96.5°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: isomer 1: C, 76.81; H, 5.38; isomer 2: C, 76.68; H, 5.37.

2,4-Diphenylglutarimide.—A mixture of 4.3 g. (0.016 mole) of either isomer of the anhydride and 4.3 g. (0.045 mole) of ground ammonium carbonate was heated to 160–165° for 30 minutes in a 50-ml. flask equipped with an air condenser. The reaction mixture was a clear liquid which turned to a glass upon cooling. Treatment of the glass with warm 50% aqueous ethanol converted it to a slurry of crystals which were collected, washed and dried, melted at 153–156° and weighed 3.05 g. (71%). Three recrystallizations from ethanol raised the melting point to 166–168° and although this material had the composition of the imide, its melting range indicates that it might be a mixture of stereoisomers.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70. Found: C, 76.71; H, 5.92.

3,5-Diphenylpiperidine from 3,5-Diphenylglutarimide.—A solution of 3.75 g. (0.014 mole) of 3,5-diphenylglutarimide in 55 ml. of dry tetrahydrofuran was added slowly, over a period of 50 minutes, to a well-stirred, boiling solution of 2.67 g. (0.07 mole) of lithium aluminum hydride in 75 ml. of dry tetrahydrofuran. Boiling was continued with stirring for six hours and without stirring for 14 hours. The light green solution was then treated with 10 g. of ethyl acetate to destroy excess lithium aluminum hydride, followed by 30 ml. of 20% sodium hydroxide solution. Ether was added and the homogeneous solution was decanted from the precipitated aluminum salts. Distillation of the solvents left a residue which was taken up in 75 ml. of ether and extracted with two 60-ml. portions of 5% hydrochloric acid and a 50-ml. portion of 20% hydrochloric acid. The combined acid extracts were made alkaline with 20% aqueous sodium hydroxide, and the oil which separated was extracted with 150 ml. of ether. Drying and concentration of the ether solution left a residue which could be distilled in part; it boiled at 140–142° (0.1 mm.) and weighed 0.59 g. (17.6%). About half the basic material was left in the distilling flask as a dark residue.

The infrared spectrum of the distillate was identical with that of the diphenylpiperidine from the sodium–butanol reduction of diphenylpyridine except for the relative intensity of some of the bands, which suggested that the stereoisomeric composition of the two liquids might not have been the same. The *p*-toluenesulfonamide of the authentic specimen melted at 206–210°; because of the small amount of material available, separation of the diastereoisomers was not attempted.

Dehydrogenation of 3,5-Diphenylpiperidine.—The authentic 3,5-diphenylpiperidine from the lithium aluminum hydride reduction of 2,4-diphenylglutarimide (0.59 g.) was heated with 0.1 g. of 10% palladium–charcoal. Gas evolution commenced at 250° and was nearly complete after 30 minutes at 250–260°; the temperature was then raised to 275° for 15 minutes. The reaction mixture was cooled and extracted repeatedly with small portions of hot ethanol, which, upon cooling, deposited a total of 0.22 g. (38%) of 3,5-diphenylpyridine, m.p. 136–137°, not depressed upon admixture of a sample obtained from phenylacetaldehyde and ammonia. The picrate melted at 203.5–204° and likewise did not depress the melting point of the picrate obtained from the diphenylpyridine obtained by condensation.

The diphenylpiperidine obtained by the reduction of diphenylpyridine (from phenylacetaldehyde and ammonia) with sodium and butanol, when treated with palladium–charcoal as described above, gave off hydrogen at 240–250° and regenerated the diphenylpyridine in 52% yield.

Acknowledgment.—We wish to express our appreciation to Dr. José R. Vega and Dr. Mario González for technical assistance in the early experiments. One of us (R.T.M.) is grateful to the Socony–Vacuum Oil Company and to the University of Notre Dame (Peter C. Reilly Fund) for fellowships granted during the course of this work.

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