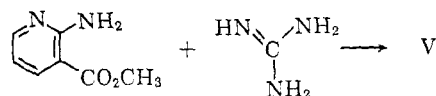


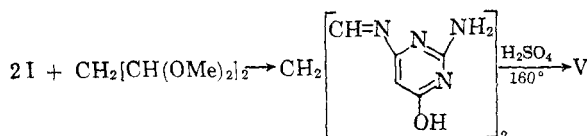
far milder conditions than those reported earlier for other 1,3-dicarbonyl compounds.<sup>8,9</sup>

The structure of V was confirmed by its synthesis from guanidine and methyl 2-aminonicotinate



The formation of V from both a pyridine and a pyrimidine can leave little doubt as to the structure assigned to V.

V was also synthesized from I and malonaldehyde (X = H, as its tetramethyl acetal). In this case, the primary product appeared to be the di-anil,<sup>10</sup> which was converted to V by hot concentrated sulfuric acid.



Incidentally, the stability of V in concentrated sulfuric acid is quite remarkable; 50% of it is recovered unchanged after 20 minutes at 260°.

This indicates a considerably greater stability than for the pteridine ring system.<sup>11</sup>

While the 6-amino group of III was successfully diazotized and replaced by hydrogen or iodine, numerous efforts to obtain the 6-cyano compound were unsuccessful. Either the compound was not formed or was so intractable as to defy our efforts to isolate and characterize it.

Our efforts to introduce a carbon function at the 6-position which might be used for the synthesis of the folic acid analog then turned to the malonaldehyde with X = CO<sub>2</sub>Et. Condensation with I appeared to proceed normally to give products with ultraviolet spectra in accord with the assignment of a pyrido[2,3-d]pyrimidine structure (see Table I). All of our efforts to convert either the 6-carbomethoxy (VII) or 6-carboxy (VIII) compounds to amide or hydroxymethyl analogs failed.

(8) S. Checchi and M. Ridi, *Ann. chim.*, **45**, 439 (1955); **46**, 428 (1956); **47**, 728 (1957).

(9) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **80**, 3449 (1958).

(10) Robins and Hitchings<sup>9</sup> have proposed on good grounds that the first condensation of dicarbonyl compounds occurs at the 5-position rather than the amino group. Since acetals condense particularly readily with amines to form anils, we suggest the alternate course here.

(11) "Chemistry and Biology of Pteridines," G. E. W. Wolstenholme and M. P. Cameron, Little, Brown & Co., Boston, 1954, p. 26.

## Photochemical Preparation, Rearrangement, and Dehydration of Symmetrical Methyl and Phenyl Pyridyl Glycols

W. L. BENCZE, C. A. BURCKHARDT, AND W. L. YOST

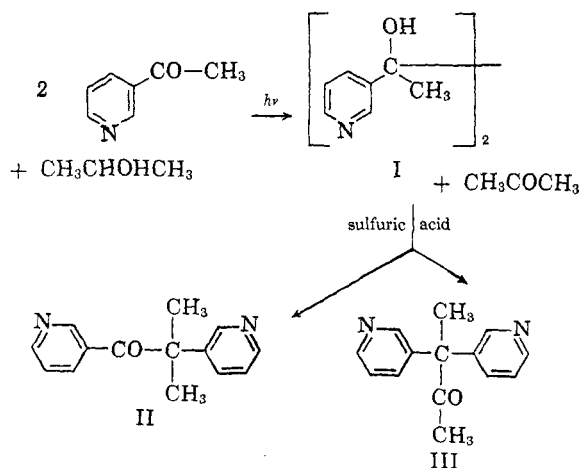
Research Department, CIBA Pharmaceutical Co., Summit, N. J.

Received March 19, 1962

The effect of the 2-, 3-, and 4-pyridyl residues upon light-induced bimolecular reduction of the three isomeric pairs of methyl and phenyl pyridyl ketones and on the rearrangement and dehydration of the resulting pyridyl glycols has been discussed. Several compounds in this series possessed a valuable and specific adrenal cortical inhibitory activity.

Pinacol-pinacolone type rearrangement of the symmetrical ditertiary glycol (I), which in turn was obtained by a bimolecular reduction of methyl 3-pyridyl ketone, yielded two isomeric ketones (II and III).<sup>1</sup> One of the two ketones, 2-methyl-1,2-di-3-pyridyl-1-propanone (II), Mepyrapone,<sup>2</sup> was found to act as a specific 11-β-hydroxylase inhibitor in the biosynthesis of corticoid hormones in animals<sup>3</sup> as well as in man.<sup>4</sup> It has been advocated that this compound may serve as a valuable tool in the diagnosis of certain pathological derangements of the pituitary adrenal system.<sup>5</sup>

The present report deals with the photochemical



(1) W. L. Bencze and M. J. Allen, *J. Am. Chem. Soc.*, **81**, 4015 (1959).

(2) Trade name Metopirone<sup>TM</sup> formerly designated as Su-4885.

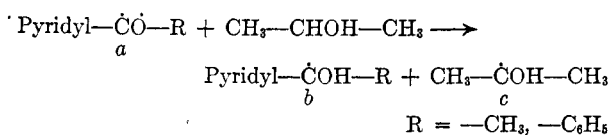
(3) J. J. Chart, H. Sheppard, M. J. Allen, W. L. Bencze, and R. Gaunt, *Experientia*, **14**, 151 (1958).

(4) J. S. Jenkins, L. Polthier, W. J. Reddy, D. Nelson, and G. W. Thorn, *Brit. Med. J.*, **1959**, I (398) [*Chem. Abstr.*, **53**, 15334 (1959)].

(5) G. W. Liddle, H. L. Estep, J. W. Kendall, Jr., W. Carter Williams, Jr., and A. W. Townes, *J. Clin. Endocrinol. and Metab.*, **19**, 875 (1959) [*Chem. Abstr.*, **53**, 22444 (1959)].

reduction of three isomeric pairs of methyl and phenyl pyridyl ketones, and the dehydration, cyclodehydration, and rearrangement of the resultant pinacol type glycols.

Benzophenone,<sup>6</sup> acetophenone,<sup>7</sup> and 3-benzoylpyridine<sup>8</sup> are known to undergo bimolecular reduction in isopropyl alcohol on irradiation with ultraviolet light. On this basis, it was expected that the acetylpyridines would also be prone to the light induced one electron reduction by isopropyl alcohol. Moreover, a broader influence of structural effects could be expected in the case of the isomeric pyridyl ketones.



The formation, the life time, and the redox potential of the ketonic biradical *a* is assumed to be influenced differently by the 2-, 3-, and 4-pyridyl residues. One can also assume that in the case of pyridyl ketones the reaction scheme of the photochemical pinacol reduction would not differ substantially from that which seems to be established for benzophenone and acetophenone.<sup>9</sup>

The prerequisite of this reduction consists of the formation of the triplet state, *i.e.*, the highly reactive biradical *a*, resulting from the uncoupling of the spins of one electron pair of the carbonyl bond.<sup>10</sup> Such photoreactions are believed to occur exclusively between this metastable state of the ketone and a hydrogen donor, *e.g.*, isopropyl alcohol. The one electron reduction of the ketonic biradical *a* by the hydrogen donor is the essential step in the light-induced pinacol reduction and leads to the formation of the two monoradicals *b* and *c*.<sup>9</sup> Combination of two *b* radicals then affords the end product of the photochemical pinacol reduction.

Evidence for the formation of radical *c* was established by the isolation of terebic acid upon concomitant irradiation of benzophenone, isopropyl alcohol, and maleic acid.<sup>11</sup> Radical *c* being of a strongly reducing nature,<sup>12</sup> is able to reduce a new molecule of ketone by a one electron process yielding another radical *b*, and acetone by oxidation of *c*. This reaction serves as an explanation of the fact that the quantum yield of the photo-reduction of benzophenone to benzopinacol was

found to be close to unity, although two radicals are needed to form one molecule of the pinacol.<sup>9</sup>

A further complicating aspect of the fate of radical *b* has been cleared recently by Franzen<sup>13</sup> who proved that a redox exchange reaction takes place between benzophenone and the diphenylhydroxymethyl radical. On the other hand disproportionation of radical *c* was thought to be improbable.<sup>9</sup>

Among the six simple methyl and phenyl pyridyl ketones only 2- and 4-benzoylpyridine did not undergo bimolecular photochemical reduction in isopropyl alcohol. Phenyl 4-pyridyl ketone was reported to give 4-pyridylphenylcarbinol<sup>8</sup> indicative of a two electron reduction process. In this instance the intermediary 4-pyridylphenylhydroxymethyl radical possesses a relatively high symmetry leading to a greater resonance stabilization. Hence, the possibility that this radical would undergo a redox disproportionation to 4-benzoylpyridine and 4-pyridylphenylcarbinol is not to be discounted. On the same basis, the difference in redox potential between this radical and *c* is also expected to be greater than that between 3-pyridylphenylcarbinol and *c*. Therefore, it seems probable that radical *c* is responsible for the reduction of the 4-pyridylphenylhydroxymethyl radical rather than a molecule of 4-benzoylpyridine. With such a course of reduction a quantum yield close to two should be found.

It was thought that the utilization of a hydrogen donor derived from a primary alcohol would possess a lower reduction potential than *c* and would not initiate a two electron reduction process. However, irradiation of 4-benzoylpyridine in ethanol afforded merely 4-pyridylphenylcarbinol and no pinacol was formed. Moreover, complete exclusion of any difference of redox potentials between radicals *b* and *c* is feasible by irradiating a 1:1 molar mixture of 4-pyridyl phenyl ketone and 4-pyridylphenylcarbinol in benzene. However, when this reaction was carried out, the reactants did not respond to irradiation. The distilled reaction mixture contained the recovered two components in the initial 1:1 molar ratio. Benzophenone and benzhydrol afforded a 21% yield of benzopinacol when irradiated under the same experimental conditions.

Irradiation 2-benzoylpyridine in ethanol resulted in unchanged starting ketone. Neither a one electron nor a two electron reduction occurred as judged from the absence of hydroxyl absorption in the infrared spectrum.

Results of our limited experiments did not furnish an explanation of the finding that, under analogous conditions, 3-benzoylpyridine was reduced by a one electron process to the corresponding pinacol, 4-benzoylpyridine was reduced by a two electron process to the secondary alcohol, while 2-benzoyl-

(6) W. E. Bachmann, "Org. Synthesis," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, 71.

(7) C. Weizmann, E. Bergmann, and Y. Hirschberg, *J. Am. Chem. Soc.*, **60**, 1530 (1938).

(8) M. R. Kegelman and E. V. Brown, *ibid.*, **75**, 4649 (1953).

(9) J. N. Pitts, R. L. Lesinger, R. P. Taylor, J. M. Patterson, G. Reckenwald, and R. B. Martin, *ibid.*, **81**, 1068 (1959).

(10) G. S. Hammond and W. M. Moore, *ibid.*, **81**, 6334 (1959).

(11) G. O. Schenck, G. Koltzenburg, and H. Grossman, *Angew. Chem.*, **69**, 177 (1957).

(12) A. Y. Drummond and W. A. Waters, *J. Chem. Soc.*, 3119 (1953).

(13) V. Franzen, *Ann.*, **633**, 1 (1960).

pyridine failed to yield either pinacol or secondary alcohol.

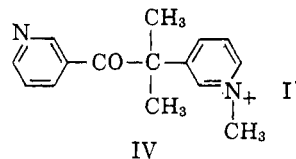
Another effect arising from the position of the ring nitrogen atom in the pyridine ring is the considerably lower rate of the photochemical reduction of 3-acetylpyridine compared with that of 2- and 4-acetylpyridine. The greater electron density at carbon 3 of the pyridyl residue is assumed to require a higher excitation energy for the uncoupling of one electron pair in the neighboring carbonyl bond. This circumstance is equivalent to the statement that the same light source acts less efficiently in the bimolecular reduction of 3-acetylpyridine than in the case of 2- and 4-acetylpyridine.

A more subtle effect of the different positions of the ring nitrogen on the photochemical reduction of a steric nature. The combination of two *b* type radicals to form a pinacol generally results in a mixture containing the *meso* and the racemic forms of the symmetrical pinacols, usually designated merely as the higher and lower melting forms. In the course of our experiments we have repeatedly observed that the reduction of 3-acetylpyridine yields the higher melting form of the pinacol with only a small amount of the lower melting form present. On the other hand, under the same conditions, the reduction of 2-acetylpyridine gave approximately equal amounts of the lower and higher melting form. Hence the configurational behavior of the *b* radicals, in the case of the photochemical reduction of 3-acetylpyridine is similar to that of desoxybenzoin<sup>14</sup> yielding only the higher melting form of the pinacols, whereas 2-acetylpyridine resembles acetophenone with both forms of pinacols emerging from the bimolecular light-induced reduction.

As ultraviolet light source we have tested several lamps and sunlight, especially in the case of the bimolecular reduction of 3-acetylpyridine. Light sources emitting at 3125 and 3650 Å. were just as useful as the more powerful 2537-Å. wave length. Moreover, sunlight passing through Pyrex glass proved to be most adequate. On the other hand, common incandescent lamps or fluorescent tubes were found to be rather ineffective.

**Rearrangement.**—Both ketones II and III were produced simultaneously upon pinacol pinacolone rearrangement of glycol I due to concomitant migration of the methyl and 3-pyridyl residues.<sup>1</sup> In order to eliminate the tedious separation of the two isomeric ketones the rearrangement was carried out in sulfuric acid containing sulfur trioxide. This medium ensured the rearrangement and also oxidized ketone III which contains the reactive methyl ketone grouping. It is noteworthy that in spite of the very different chemical nature

of ketones II and III their biological activities have so far proved to be indistinguishable.<sup>15</sup> Whereas the two pyridyl groups of ketone III possess equal basicities, those of ketone II are distinctly different. This could be demonstrated in the ready formation of the monoquaternary salt (IV).<sup>16</sup>



Kegelman and Brown did not report the isolation of the ketone which was obtained upon rearrangement of 1,2-diphenyl-1,2-di-3-pyridylethylene glycol.<sup>8</sup> Rearrangement of this glycol in concentrated sulfuric acid resulted exclusively in phenyl migration to give 1,1-diphenyl-1,2-di-3-pyridylethanone, the structure of which was proven by hydrolysis with methanolic potassium hydroxide to nicotinic acid and diphenyl-3-pyridylmethane.

Dehydration of pinacol type glycols is much more dependent on the reaction conditions than the pinacol-pinacolone rearrangement of the same glycols.<sup>17</sup>

Dehydration of the pinacol type glycols formed upon bimolecular reduction of 2- and 4-acetylpyridine occurred as a side reaction in the course of the rearrangement effected by sulfuric acid.<sup>1</sup> However, the rearrangement of glycol I in the same medium resulted merely in the two isomeric ketones (II and III); on the other hand, when the rearrangement was carried out in polyphosphoric acid above 200° only dehydration and cyclodehydration occurred. Further elevation of the temperature diminished the amount of butadiene (V) formed and increased the yield of the ring-closed product (VI). Ring closure in 2-position of the pyridine nucleus to give pyrindine VI was proved by oxidative degradation followed by the isolation of nicotinic and pyridine-2,3-dicarboxylic acids. The pyrindine derivative corresponding to a ring closure in the 4-position of the pyridine ring could not be isolated. Both dehydration

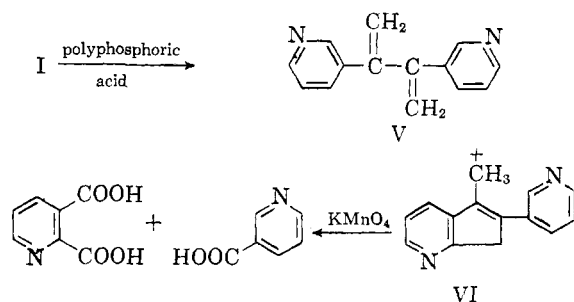
(15) (a) W. L. Benze and M. J. Allen, *J. Med. Pharm. Chem.*, **1**, 395 (1959); (b) J. J. Chart and H. Sheppard, *ibid.*, **1**, 407 (1959).

(16) In the quaternary pyridinium salts contribution of the pyridine ring to the carbonyl conjugation is blocked. Therefore, carbonyl absorption of 3-acetylpyridine N-methyl iodide appeared at 1702 and 1710  $\text{cm}^{-1}$  as a doublet and absorption of the N,N'-dimethyl diiodide salt of ketone II or 1702  $\text{cm}^{-1}$ . On the other hand, compound IV exhibited the normal absorption band of a conjugated carbonyl group at 1690  $\text{cm}^{-1}$ .

(17) Frazer-thesis, 1939, University of Illinois—found that the pinacol obtained from the reduction of acetophenone afforded the dehydration product, 2,3-diphenylbutadiene in optimal yields when the pinacol and equal weight of acetylchloride was refluxed for 7 min. C. C. Price and G. P. Mueller did not succeed in the dehydration of the pinacol derived from *p*-methoxyacetophenone, *J. Am. Chem. Soc.*, **66**, 634 (1944).

(14) F. Bergmann and Y. Hirschberg, *J. Am. Chem. Soc.*, **65**, 1429 (1943).

products (V and VI) possessed biological activities similar to that of ketone II.



### Experimental<sup>18</sup>

**Photochemical, Bimolecular Pinacol Reduction.**—(A). Gates Raymaster multipurpose desk type ultraviolet lamp equipped with a 12 in. long,  $\frac{5}{8}$  in. diameter Black Raymaster bulb. This lamp provides long wave ultraviolet radiation with an energy peak close to 3,600 Å., and consumes 8 watts of power.

Yields and analytical data of the pinacol type glycols as obtained by photochemical reduction of the three isomeric methyl pyridyl ketones with the application of the above lamp have been published previously.<sup>1</sup>

The following descriptions of various irradiation assemblies, as well as the yields of pinacols, are presented mainly to illustrate the efficiency of the light sources.

(B). **Hanovia 550-Watt Lamp.**—A solution of 3-acetylpyridine (1800 g.) in isopropyl alcohol (3 l.) was placed in a 5-l. three-neck flask equipped with stirrer and two large-capacity reflux condensers. The flask was also equipped with a standard taper 60/50 female joint, fused at an oblique angle, through which was inserted a similarly ground single wall quartz finger of sufficient size to accommodate a 550-watt high pressure mercury vapor lamp (Hanovia lamp A. Cat. No. 673A) with an arc length of 4.5 in.

After irradiation under reflux for 23.25 hr., the suspension of precipitated pinacol was cooled to room temperature and the product filtered and washed with isopropyl alcohol. Dried in vacuum at 100° for 16 hr. it weighed 477 g. and melted at 224–240°. Removal of isopropyl alcohol from the filtrate afforded an additional amount of pinacol (43 g.) which melted 215–222°. The total yield of pinacol was 28.7%. The quantum yield of the photochemical reaction, as determined by the uranyl oxalate method<sup>19</sup> was found to be 0.32. Recovery of 1192 g. of unchanged 3-acetylpyridine gave a net conversion of 85%.

(C). **Hanovia 200-Watt Lamp.**—The lamp was operated inside a double-jacketed vycor glass well 16 in. long and 2 in. outer diameter, which was cooled with tap water. The lamp assembly was immersed in a beaker or in a dewar type flask of 2  $\frac{3}{4}$  in. inside diameter and 12 in. length. This latter container made it possible to irradiate a reaction mixture of 300–350 ml. whereas the well was designed by the manufacturer to be operated in a 5-l. flask.

Acetophenone (125 g.) in 1150 ml. of isopropyl alcohol irradiated for 90 hr. afforded 98.3 g. of crystalline chromatographically separated pinacol. The yield was 78%.

A 3.00-g. sample of the crude pinacol was chromatographed on aluminum oxide (100 g., Woelm, neutral, activity 3) with an eluant mixture of benzene–petroleum either 1:1 to give 0.55 g. of the low-melting pinacol, m.p.

115–117°; 1.02 g. of the high-melting pinacol, m.p. 122–125° and 0.63 g. of an unseparated mixture of the two forms, m.p. 100–115°.

2-Acetylpyridine (93 g.) in 1 ml. of acetic acid and 250 ml. of isopropyl alcohol was irradiated for 40 hr. The precipitated pinacol was collected and dried (40.7 g.). Evaporation of the filtrate under reduced pressure gave 22 g. of unreacted 2-acetylpyridine and 25.7 g. of pinacol. The total yield was 71.4%.

3-Acetylpyridine (318 g.) in 240 ml. of benzene and 1060 ml. of isopropyl alcohol was irradiated for 71 hr. Filtration and distillation afforded 91.6 g. of pinacol and 208 g. of unchanged ketone. The recovered methyl 3-pyridyl ketone was irradiated again for 79 hr. under the above conditions to give pinacol and unchanged ketone (98.7 g.). The latter was subjected to irradiation once more (160 hr.). The total irradiation time was 310 hr. and the total yield was 282.4 g. (88%).

4-Acetylpyridine (104 g.) in 1 ml. of acetic acid and 350 ml. of isopropyl alcohol was irradiated for 70 hr. The crystalline pinacol was collected (17.5 g., m.p. 182–189°) and the filtrate irradiated for 20 hr. Recovered methyl 4-pyridyl ketone weighed 64.0 g. The total yield of pinacol was 29.2 g. (61%).

(D). **Pen-Ray Quartz, Low Pressure, Mercury Gaseous Discharge Lamp.**—Tube length 2  $\frac{1}{8}$  in., 14 watts power consumption. 3-Acetylpyridine (10 g.) in 70 ml. of isopropyl alcohol was irradiated for 135 hr. The above quartz lamp was immersed in the reaction mixture, the temperature of which did not rise above 40° during irradiation. Ether and hexane were added to the reaction mixture and the colorless, crystalline pinacol was collected, washed twice with ether and dried. The yield was 900 mg., 9%, m.p. 245–248°.

4-Benzoylpyridine (5.0 g.) in 60 ml. of 95% ethanol was irradiated for 168 hr. Upon removal of the solvent a reddish brown viscous oil was obtained. Addition of ether and hexane afforded a crystalline material (2.35 g.) which, after distillation at 140/0.1 mm. and two recrystallizations from a mixture of benzene and pentane, melted at 125–126.5°. On admixture with an authentic sample of phenyl-4-pyridylcarbinol (prepared from 4-pyridine carboxaldehyde and phenylmagnesium bromide) the melting point was undepressed.

4-Benzoylpyridine (2.0 g.) and phenyl-4-pyridylcarbinol (2.0 g.) in 75 ml. of benzene were irradiated for 168 hr. A small amount of a solid material was collected, washed three times with benzene, and dried (100 mg.). The infrared absorption spectrum of this material in Nujol mull showed broad diffuse bands in the hydroxy and carbonyl regions. This product could not be melted or crystallized and had the appearance of a polymer. Evaporation of the filtrate to dryness afforded a solid material (3.9 g.), the infrared absorption spectrum of which was identical to that of a 1:1 mixture of the starting ketone and carbinol.

Benzophenone (2.0 g.) and benzhydrol (2.0 g.) in 75 ml. of benzene were irradiated for 168 hr. After addition of ether and hexane to the reaction mixture a crystalline solid precipitated which was collected and dried (880 mg., m.p. 133–179°). After recrystallization from aqueous ethanol, it melted at 184–185°, and was found to be benzpinacol.

2-Benzoylpyridine (5.0 g.) in 60 ml. of 95% ethanol was irradiated for 168 hr. The reaction mixture turned dark on the first day. The quartz finger of the lamp was cleaned daily. After 1 week of irradiation 40 mg. of a dark amorphous material was filtered off and the filtrate evaporated to dryness. The residual dark oil was distilled at 120–130°/0.1 mm. to give 4.3 g. of a colorless oil which crystallized spontaneously and melted at 41–50°. The infrared absorption spectrum of the distillate indicated the presence of a carbonyl and the absence of a hydroxyl group. The distillation residue was an intractable black tar (0.6 g.).

(E). **Sunlight.**—3-Acetylpyridine (10.0 g.) in 0.2 ml. of acetic acid and 120 ml. of isopropyl alcohol was irradiated for 2 months in a 125 ml. Pyrex flask closed with a glass stopper. After 30 days of irradiation 2.3 g. of pinacol was

(18) The melting points are uncorrected.

(19) W. G. Leighton and G. S. Forbes, *J. Am. Chem. Soc.*, **52**, 3139–3152 (1930); C. R. Masson, V. Boekelheide, and W. A. Noyes, Jr., in A. Weissberger, ed., "Technique of Organic Chemistry," Vol. II, 2nd ed., Interscience, New York, 1956, pp. 294–298; F. Daniels, J. H. Mathews, and J. W. Williams, "Experimental Physical Chemistry," 4th ed., McGraw-Hill, New York, 1949, pp. 282–284.

filtered off. The filtrate was subjected to continued irradiation. On the 40th, 50th, and 60th days additional amounts (3.4, 0.6, and 0.1 g.) of pinacol were collected. The combined crops (6.4 g.) melted at 220–226°. Upon evaporation to dryness the final filtrate afforded a tan-colored crystalline mass, which was triturated with ether to give 3.4 g. of crude pinacol, m.p. 198–216°. The yield was 98%.

(F). **Fluorescent Tube**.—2-Acetylpyridine (30.0 g.) in 120 ml. of isopropyl alcohol was placed in a Pyrex tube 2 cm. wide, 40 cm. long. This container was placed on top of the light fixture approximately 2 cm. from the light bulb. The reaction mixture was irradiated 10 hr./day for 1 month and then distilled at 14 mm. and 1 mm. pressure to remove solvent and unreacted ketone. The distillation residue of 2.96 g. crystallized completely. One crystallization from methanol gave a small amount of the high-melting form of the pinacol (0.2 g. m.p. 142–143°) while the remainder of the product was a mixture of the high- and low-melting forms of the pinacol.

(G). **Common Incandescent Lamp, 100 Watt**.—2-Acetylpyridine (100 g.) in 400 ml. of isopropyl alcohol was placed in a 500-ml. Pyrex flask. The light source was placed about 5 cm. below the flask and operated for 10 days. The heat from the light bulb maintained the reaction temperature between 55° and 60°. Fractionation by distillation yielded 660 mg. of pinacol, containing primarily the higher melting form, m.p. 140–142°.

**Pinacol-Pinacolone Type Rearrangement. 2-Methyl-1,2-di-3-pyridyl-1-propanone**.—To a mixture of 133 g. each of concd. sulfuric acid and 20% fuming sulfuric acid was added 2,3-di-3-pyridyl-2,3-butanediol (43.5 g.) during 50 min. with stirring, keeping the temperature below 75°. After heating on a steam bath at 94–97° for 3.5 hr., the clear solution was cooled to 25°, poured over 550 g. of ice and made alkaline (pH 8.5) with 425 ml. of concentrated ammonium hydroxide. The liberated oily base was extracted into toluene and the extract clarified with charcoal and evaporated to dryness. The oily residue (22.5 g.) was dissolved at 60° in 225 ml. of a mixture of methylcyclohexane and toluene, 9:1. The solution was filtered from 5.1 g. of insoluble material and then passed through a short column of 10 g. of aluminum oxide. The filtrate was stirred and cooled very slowly to the point of slight turbidity (24°) and then seeded with a slurry of the crystalline product prepared by cooling and scratching a small sample of the same solution. Once crystallization was well advanced, the slurry was cooled more rapidly to 5° and then allowed to stand at –15° for 15–20 hr. The product was filtered without washing and dried *in vacuo* at room temperature for 15–20 hr. The yield was 13.4 g., 33.3%, (m.p. 52–53°).

The above procedure greatly simplifies the preparation of ketone (II) because it avoids the tedious separation of ketones II and III.<sup>1</sup>

**3-Pyridyl Diphenyl-3-pyridylmethyl Ketone**.—1,2-Di-pyridyl-1,2-diphenylethanediol<sup>8</sup> (5.0 g.) was dissolved in 20 ml. concentrated sulfuric acid and allowed to stand at room temperature for 60 hr. The reaction mixture was poured onto ice and made slightly basic with a 20% aqueous sodium hydroxide solution. The product was extracted three times into ethyl acetate and the combined extracts were washed with a saturated solution of sodium chloride and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the crude product (3.02 g.), m.p. 166–172°. Twice recrystallized from aqueous ethanol, it melted at 175–177°.

*Anal.* Calcd. for C<sub>24</sub>H<sub>18</sub>N<sub>2</sub>O: C, 82.26; H, 5.18; N, 8.00. Found: C, 82.43; H, 5.35; N, 7.86.

Carbonyl absorption at 1690 cm.<sup>-1</sup> (Nujol mull).

**Diphenyl-3-pyridylmethane**.—The above ketone (1.0 g.) was heated under reflux in methanolic (25 ml.) potassium hydroxide (5 g.) for 24 hr. The solvent was exchanged for water under reduced pressure and the product extracted three times with ether. The combined extracts were washed with saturated aqueous sodium chloride solution and dried

over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product which, after recrystallization from a mixture of ether and petroleum ether (1:5), melted at 76–78° (570 mg., 81%).

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>N: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.30; H, 6.30; N, 5.67.

**Dimethiodide of Ketone (II)**.—A solution of ketone II (4.5 g.) and methyl iodide (6.0 g.) in 40 ml. of ethanol was left to stand at room temperature for 15 hr. and then heated under reflux on a steam bath for 1 hr. On cooling to room temperature, yellow crystals deposited which were collected, (7.7 g., m.p. 225–231°). After recrystallization from methanol, the diquaternary salt melted at 228–231° (6.29 g.).

*Anal.* Calcd. for C<sub>18</sub>H<sub>20</sub>I<sub>2</sub>N<sub>2</sub>O: C, 37.67; H, 3.96. Found: C, 37.42; H, 3.88.

Carbonyl absorption at 1704 cm.<sup>-1</sup> (Nujol mull).

**Monomethiodide of Ketone (II)**.—A solution of ketone II (4.5 g.) and methyl iodide (2.8 g.) in 20 ml. of acetone was allowed to stand at room temperature for 20 hr. The yellow crystals which formed were collected, washed with acetone, and dried (5.9 g., m.p. 159–168°). Recrystallized four times from a mixture of ethanol and hexane, it melted at 184–185.5°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>17</sub>IN<sub>2</sub>O: C, 48.93; H, 4.65. Found: C, 48.59; H, 4.75.

Carbonyl absorption at 1690 cm.<sup>-1</sup> (Nujol mull).

**Dehydration of the Pinacol 2,3-Di(3-pyridyl)-2,3-butanediol**.—Polyphosphoric acid (100 g., Victor Chemical Co.) was preheated to approximately 200° in a three-neck flask equipped with a glass stirrer and calcium chloride tube. The pinacol (10 g.) was added in portions to the hot acid and stirred manually until a clear colorless solution resulted. The external temperature of a silicone oil bath was raised to 275–280° and maintained in this range for 10 min., then lowered to 260° and kept there for an additional 40 min. The reaction mixture was straw colored at this point. After cooling to about 100°, it was poured into ice water and stirred. The resultant clear solution was neutralized below 25° with a 40% sodium hydroxide solution and then extracted once with ether and three times with small amounts of ethyl acetate. No resinous material was formed if the starting pinacol was a pure recrystallized sample. The combined extracts were washed with a saturated aqueous sodium chloride solution dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The residual tan oil, 8.4 g., was dissolved in 25 ml. of benzene and placed on an aluminum oxide column (300 g.) Woelm, neutral, activity (3) which was prewashed with hexane.

**2,3-Bis(3-pyridyl)-2,3-butadiene**.—Elution of the above column with benzene afforded a partly crystalline, oily product (2.42 g.). Distillation at 130–140°/0.1 mm. gave a colorless, viscous oil. Upon crystallization from a mixture of ether and hexane, the product melted at 51–52°. A mixture of this compound and ketone II melted below room temperature. The infrared absorption spectrum in chloroform, showed a strong absorption band for a =CH<sub>2</sub> group at 922 cm.<sup>-1</sup> and its overtone at 1828 cm.<sup>-1</sup>. In the ultraviolet absorption spectrum, maximal absorption was observed at 235 mμ, ε 17,460, in ethanol.

*Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>: C, 80.74; H, 5.82. Found: C, 80.46; H, 5.93.

**6-(3-Pyridyl)-7-methyl-5-H-4-pyridine**.—Further elution of the above aluminum oxide column with a mixture of ether and benzene produced fractions which, after removal of the solvent, crystallized spontaneously. The combined crystalline fractions weighed 2.65 g. Twice recrystallized from benzene and pentane, the compound melted at 88–89°. Maximal ultraviolet absorption was noted at 300 mμ, due to the stilbene-type double bond. The compound darkens in daylight; it can be stored for several months, however, in the cold if protected from light.

*Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>: C, 80.74; H, 5.82. Found: C, 80.57; H, 5.83.

Continued elution of the aluminum oxide column with ethyl acetate and methanol afforded an oily product, 2.94 g., which proved to be unstable even in the cold and in the absence of light. The total recovery was 8.01 g.

In the experiment described above, the ratio of the butadiene to the ring-closed pyridine derivative was approximately 1:1. In another experiment which was carried out in the same manner, except that the dehydration in polyphosphoric acid was performed at 240–250° for 30 min., the ratio of butadiene to pyridine was approximately 2:1 (3.74 g. and 1.70 g., respectively). In a third experiment, in which the dehydration was allowed to proceed at 240° for 20 min., the ratio of the open and ring closed products was found to be about 10:1.

**Oxidative Degradation of 6-(3-Pyridyl)-7-methyl-5H-4-pyridine.**—To a stirred, hot suspension of the above pyridine (416 mg., 2 mmoles) in water was added in portions 1.90 g. (0.012 mole) of potassium permanganate. Manganese dioxide began to precipitate immediately. Boiling and stirring were continued for 15 min. after the addition of the oxidizing agent, the excess of which was then decomposed by the addition of 1 ml. of methanol. The hot reaction mixture was filtered and the manganese dioxide washed twice with warm water. The clear, straw-colored filtrate was acidified with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The salt-like residue was taken up in 3 ml. of water the acidity was adjusted to approximately

pH 2–3 with crystalline sodium carbonate, and the crystalline precipitate was collected, washed twice with 1 ml. of cold water, and dried. The product weighed 35 mg. and melted with decomposition at 233–240°. After one recrystallization from water, the melting point was 235–241°. A paper chromatogram of this material indicated only one spot, inseparable from that of pyridine-2,3-dicarboxylic acid,  $R_f$  value 0.40, developed with a mixture of butanol-acetic acid-water (4:1:5) and stained with bromophenol blue indicator. The infrared absorption spectrum of the product was superimposable on that of an authentic specimen of pyridine-2,3-dicarboxylic acid in Nujol mull.

A second crop of product was obtained upon concentration of the aqueous filtrate. This material exhibited two spots on the paper chromatogram,  $R_f$  values 0.40 and 0.70, respectively, whereas the residue obtained after complete evaporation of the mother liquor showed only the rapidly migrating component, which proved to be inseparable from added nicotinic acid.

**Acknowledgment.**—We wish to express our appreciation to Dr. Emil Schlittler for his continued interest and encouragement throughout this project. We are grateful to Mr. Louis Dorfman and his staff for the microanalyses and the spectral data.

## Hydroxylamine Chemistry. II. The Abnormal Michael Reaction of N,N-Disubstituted Hydroxylamines with 2- and 4-Vinylpyridines<sup>1</sup>

LEO A. PAQUETTE

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

Received February 28, 1962

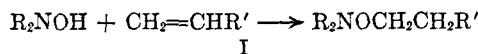
The application of the pyridylethylation reaction to N,N-disubstituted hydroxylamines affords unexpected products which do not contain oxygen. They have been identified as the compounds resulting from the addition of the corresponding amine (*i.e.*, the hydroxylamine without its oxygen atom) to the unsaturated system. Several different types of hydroxylamines have been investigated with consistent results.

The prediction by Doering and Weil<sup>2</sup> on theoretical grounds that the  $\alpha$ - and  $\gamma$ -pyridyl groups should be classified with the other well known electron-deficient systems ( $>C=O$ ,  $-CN$ ,  $-NO_2$ ,  $>SO_2$ , etc.) which activate a double bond to attack by nucleophilic reagents has been extensively substantiated. No report prior to 1947 on the pyridylethylation reaction had appeared, but in the last fourteen years this synthetic method has been widely exploited.

The facts that a wide variety of pyridylethylated products possess significant pharmacologic activity<sup>3–7</sup> and that N,N-disubstituted hydroxylamines

had never been subjected to the pyridylethylation reaction prompted us to investigate this area in an effort to obtain useful pharmacologic agents.

A number of N,N-disubstituted hydroxylamines have been successfully condensed in a Michael-type reaction with various electron-deficient systems to produce "normal" products such as I ( $R' = CN, COCH_3, COOR$ ).<sup>8</sup>



On the other hand, the reaction of N-hydroxypyrrolidine<sup>9</sup> and 2-vinylpyridine without solvent in the presence of a trace of Triton B does not give the expected Michael adduct but rather leads to 2-(2-pyrrolidinoethyl)pyridine, characterized as its dipicrate. This material was prepared by an

(1) E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. DaVanzo, and M. E. Greig, *J. Med. Pharm. Chem.*, **5**, 464 (1962), may be considered Part I of this series.

(2) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

(3) A. H. Sommers, M. Freifelder, H. B. Wright, and A. W. Weston, *ibid.*, **75**, 57 (1953).

(4) L. A. Walter, R. H. Barry, and J. R. Clark, U.S. Patent 2,713,051, July, 1955.

(5) A. R. Katritsky, *J. Chem. Soc.*, 2581 (1955).

(6) B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

(7) S. L. Shapiro and co-workers, *ibid.*, **79**, 2811 (1957); **80**, 1648 (1958); *J. Org. Chem.*, **26**, 1323 (1961); U.S. Patent 2,993,905 (July 25, 1961).

(8) G. Zinner, *Angew. Chem.*, **71**, 311 (1959); *cf.*, also, L. A. Paquette, *J. Org. Chem.*, to be published.

(9) J. Thesing and W. Sirrenberg, *Chem. Ber.*, **92**, 1748 (1959).