band there was a band exhibiting λ_{max} 300 mμ. Combination of the fractions of the main band yielded the sample of VI discussed above.

From a similar dehydrogenation of the mother liquors of XIII and similar chromatography there was obtained, from the elution band with λ_{max} 300 mμ, 5 mg. of substance believed to be **3′,4′,10-trimethyl-1,2-benzanthracene** (**XVI**). Crystallization from ethanol gave colorless plates, m.p. 164–166°. Several recrystallizations raised the melting point to 167–169°; $\nu_{max}^{CCl_4}$ 3070, 2930, 2865, 876 and 683 cm.$^{-1}$; $\nu_{max}^{CS_2}$ 816, 738 and 803 cm.$^{-1}$. For ultraviolet data see Table I. Insufficient material was available for combustion analysis which we felt was less valuable than the spectroscopic characterization for which our sample was used.

Total Synthesis of 4′,10-Dimethyl-1,2-benzanthracene (VI).—The sequence used was that previously reported[28] from 4′-bromobenzanthraquinone,[27] except that it was found preferable to modify the reduction[27,28] of the latter in the following way.

A mixture of 20 g. of 4′-bromobenzanthraquinone in 2 l. of glacial acetic acid and 200 ml. of concd. hydrochloric acid containing 40 g. of stannous chloride was refluxed 75 min. After cooling and addition of 3 l. of ice, the precipitated bromobenzanthrone was dried under a vacuum over P_2O_5 for 3 days. One-half of the product (19.3 g.) was dissolved in 500 ml. of tetrahydrofuran, and then 1 l. of glacial acetic acid and 100 g. of zinc dust was added. The mixture was refluxed with stirring for 2.5 hr. (which, from rough kinetic studies, proved to be an optimal time), cooled and filtered. The filtrate was then diluted with a large volume of water and extracted several times with ether. The ether extract was washed with H_2O and then with 10% aq. NaOH. The residue from the ether extracts was chromatographed on 750 g. of neutral alumina in *warm* benzene. Seventy fractions of 20 ml. were collected. The residue from fractions 31–70 upon crystallization from glacial acetic acid yielded colorless **4′-bromo-1,2-benzanthracene** as hexagonal plates, m.p. 213–215°, lit.[27] m.p. 210–211°. The yield of crystallized material was 10.2 g. after both halves of the crude bromobenzanthrone were carried through the zinc reduction and chromatography. Several alternatives, *e.g.*, reduction with metal hydrides, to the zinc reduction did not prove satisfactory.

The 4′-bromo-1,2-benzanthracene by bromination[28] at position 10 and replacement[28] of the halogens with lithium from butyllithium and then with methyl iodide yielded 4′,10-dimethyl-1,2-benzanthracene (VI), m.p. 154.5–156.0°, lit.[28] m.p. 154–154.5°. The ultraviolet spectrum of VI prepared in this way is given in Table I, and the polymorphism and behavior on heating were identical to the sample prepared from the anthrasteroid. Table I also records the spectra of the brominated intermediates.

Spectroscopic Correlations.—From known spectra of methyl- and dimethyl-1,2-benzanthracenes, the bathochromic shift associated with new substitution can be anticipated for the so-called D- and H-bands.[39,40] The change from no substitution (1,2-benzanthracene, D = 287.5 mμ, H = 341.0 mμ) to 4′-methyl substitution is +5.5 mμ for the D-band and +3.5 mμ for the H-band. For 10-methyl substitution it is +4.0 and +13.5 mμ, respectively. For disubstitution, the values for the D-band are known to be additive plus 0.5–1.5 mμ for the 5,10-, 8,10- and 9,10-dimethyl derivatives. For the H-band they are additive minus 1–3 mμ. Thus, the calculated values for the D-band of **4′,10-dimethyl-1,2-benzanthracene** are 287.5 + 5.5 + 4.0 + (0.5 to 1.5) = 297.5–298.5 mμ. The observed value is 298 mμ. For the H-band calculation gives 341.0 + 3.5 + 13.5 − (1 to 3) = 355 to 357 mμ. The observed value is 354.5 mμ.

The dehydrogenation of the crystalline diacetate XIII also gave in yields of *ca.* 0.7% two benzanthracenes, one of which chromatographed ahead of and one behind VI. The faster moving had an ultraviolet spectrum identical with **4′-methyl-1,2-benzanthracene** (Table I), and the slower possessed a spectrum indicating, on the basis of the D-band at 300 mμ and the H-band at 355 mμ, that it was at least 4′,10-disubstituted. Since it was different from VI, we assign to it the structure of **3′,4′,10-trimethyl-1,2-benzanthracene** (**XVI**) in keeping with the observation that the yield was increased tenfold (to 5–9%) when mother liquor material (in which the 17aα-acetoxy compound XV was enriched) from the crystalline diacetate was dehydrogenated. 1,2-Diaxial orientation of the angular methyl and 17a-acetoxyl groups of XV would be expected to favor rearrangement. From the known shift for 3′-substitution[41] for the D-band (+1.5 mμ) and H-band (+2.5), the calculated positions (uncorrected for multiple substitution) for XVI are 298 + 1.5 = 299.5 and 354.5 + 2.5 = 357 mμ, respectively, in excellent agreement with observation when it is remembered (foregoing paragraph) that for multiple substitution the D-band is generally at a wave length slightly greater than calculated and the H-band slightly less than calculated. Trisubstitution was verified from the infrared spectrum (in CCl_4) of XVI which exhibited an increased ratio of alkyl C–H stretching to aromatic C–H stretching absorption. For the dimethyl (VI) and trimethyl (XVI) derivatives, the ratio of alkyl to aromatic H-atoms is 6/10 = 0.60 and 9/9 = 1.0, respectively, and the first ratio divided by the second is 0.60. Experimentally, the ratio of the integrated intensities of the respective bands (near 2935 and 2870 cm.$^{-1}$ and near 3071 cm.$^{-1}$) for VI was 2.3 and for XVI was 3.6, and 2.3/3.6 = 0.64 in excellent agreement with theory.

(39) R. N. Jones, *J. Am. Chem. Soc.*, **62**, 148 (1940).

(40) G. M. Badger, R. S. Pearce and R. Pettit, *J. Chem. Soc.*, 1112 (1952).

(41) For the data for this and other substituted 1,2-benzanthracenes see ref. 39, 40 and *h* in Table I.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA, MINNEAPOLIS 14, MINN.]

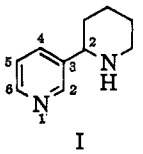
Biosynthesis of the Nicotiana Alkaloids. IX. The Non-random Incorporation of Acetate-2-C^{14} into the Pyridine Ring of Anabasine[1]

BY ALAN R. FRIEDMAN[2] AND EDWARD LEETE[3]

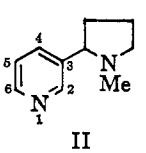
RECEIVED FEBRUARY 22, 1963

Radioactive anabasine (2-(3-pyridyl)-piperidine) produced when sodium acetate-2-C^{14} was injected into the stems of intact *Nicotiana glauca* plants had 37% of its activity located in the pyridine ring. Using a new degradative scheme it was established that all this activity was located at C_2 and C_3 and was divided approximately equally between these positions. The significance of this result and its relation to studies on the biosynthesis of nicotine and ricinine is discussed.

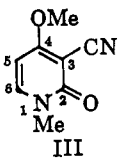
It has been established that the pyridine ring of anabasine (I)[4] and nicotine (II)[5] and the pyridone ring of ricinine (III)[6,7] are derived from nicotinic acid. However, until recently, the biosynthesis of nicotinic acid in the plants which produce these alkaloids has remained a mystery. It was established[8–10] some time



I



II



III

ago, that tryptophan, the precursor of nicotinic acid in animals and some microörganisms, is apparently not converted to nicotinic acid in higher plants. Five years ago we[11] and Byerrum and Griffith[12] showed that

(1) This investigation was supported by a research grant (MY-02662) from the National Institutes of Health, U. S. Public Health Service. Part VIII in this series: E. Leete and V. M. Bell, *J. Am. Chem. Soc.*, **81**, 4358 (1959).

(2) Eastman Kodak Predoctoral Fellow, 1961–1962.

(3) Alfred P. Sloan Fellow, 1962–1964.

(4) M. L. Solt, R. F. Dawson and D. R. Christman, *Plant Physiol.*, **35**, 887 (1960).

(5) R. F. Dawson, D. R. Christman, A. D'Adamo, M. L. Solt and A. P. Wolf, *J. Am. Chem. Soc.*, **82**, 2628 (1960).

(6) E. Leete and F. H. B. Leitz, *Chem. Ind.* (London), 1572 (1957).

(7) G. R. Waller and L. M. Henderson, *J. Biol. Chem.*, **336**, 1186 (1961).

(8) E. Leete, *Chem. Ind.* (London), 1270 (1957).

(9) L. M. Henderson, J. F. Someroski, D. R. Rao, P. L. Wu, T. Griffith and R. U. Byerrum, *J. Biol. Chem.*, **234**, 93 (1959).

(10) R. F. Dawson, private communication.

(11) E. Leete, *Chem. Ind.* (London), 1477 (1958).

(12) T. Griffith and R. U. Byerrum, *Science*, **129**, 1485 (1959).

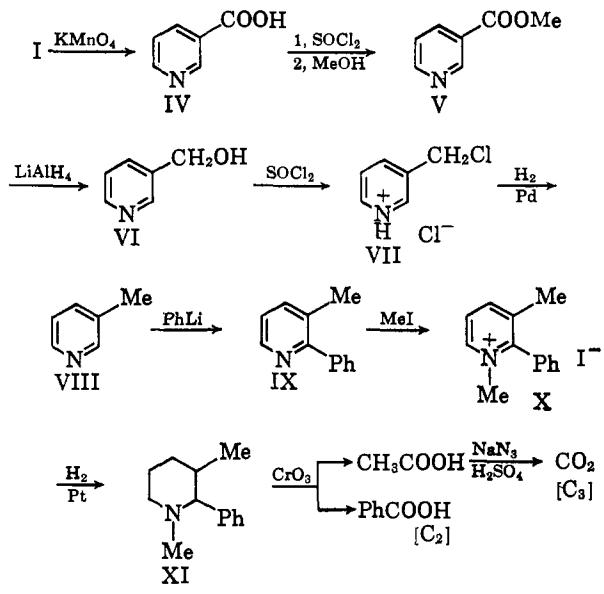


Fig. 1.—Degradative scheme for radioactive nicotinic acid to determine activity at C_2 and C_3.

acetate-2-C^{14} and compounds which could be metabolized to acetic acid-2-C^{14} were incorporated into the pyridine ring of anabasine and nicotine. The significance of these results could not be evaluated until methods were developed for the systematic degradation of the pyridine ring to determine activity on each of the carbon atoms. Griffith, *et al.*,[13] showed that approximately one-half of the C^{14} in the pyridine ring of nicotine derived from acetate-2-C^{14} was located at C_3. The degradation they used involved the oxidation of nicotine to 1-methylpyrrolidine-2-carboxylic acid (hygrinic acid) and subsequent decarboxylation. More recently[14] they used the same degradation on nicotine derived from aspartic acid-3-C^{14} and also found that C_3 contained half the activity of the pyridine ring. Dawson and Christman[15] have recently published a degradative scheme by which they could determine the activity at C_2 of the pyridine ring of nicotine. They showed that nicotine derived from β-alanine-2-C^{14} had 25% of the pyridine ring activity at C_2.

We have now developed a degradative scheme, illustrated in Fig. 1, whereby activity at C_2 and C_3 of nicotinic acid can be determined unambiguously.

Anabasine diperchlorate was oxidized with alkaline potassium permanganate yielding nicotinic acid (IV). The optimum yield of methyl nicotinate (V) was obtained by treating nicotinic acid with thionyl chloride followed by methanol. Reduction of this ester with lithium aluminum hydride afforded 3-hydroxymethylpyridine (VI) which was treated with thionyl chloride to give the hydrochloride of 3-chloromethylpyridine (VII). Hydrogenation of this compound over palladium-on-calcium carbonate afforded 3-methylpyridine (VIII) which was purified as the oxalate. It has been shown by Abramovitch, *et al.*,[16] that reaction of 3-methylpyridine with phenyllithium afforded 3-methyl-2-phenylpyridine (IX) and 3-methyl-6-phenylpyridine in the ratio of 19:1. Using our experimental conditions we obtained exclusively the 2-phenyl isomer, none of the 6-isomer being detected by vapor phase chromatography. The 3-methyl-2-phenylpyridine was converted to its methiodide X which was hydrogenated over platinum to give 1,3-dimethyl-2-phenylpiperidine (XI). Oxidation of this piperidine derivative with chromium trioxide in dilute sulfuric acid yielded a mixture of acetic and benzoic acids which were separated by simple countercurrent fractionation between ether and water. The acetic acid was collected as sodium acetate which was subjected to the Schmidt reaction affording carbon dioxide which was assayed as barium carbonate. The activity of this barium carbonate and the benzoic acid thus represent the activity at C_3 and C_2, respectively. The total activity of the pyridine ring was determined by heating the nicotinic acid with barium hydroxide at 325° when pyridine distilled and was collected as the picrate. In a separate experiment the nicotinic acid was decarboxylated by refluxing in quinoline with copper chromite, the liberated carbon dioxide being assayed as barium carbonate, its activity being that of C_2 of the piperidine ring.

We have carried out this degradation on radioactive anabasine which was produced when sodium acetate-2-C^{14} was fed to four-month old *Nicotiana glauca* plants. In our previous work[11] we fed sodium acetate-2-C^{14} to excised shoots of this plant and obtained a 0.03% incorporation of tracer into the anabasine. In the present work a solution of the tracer was introduced into the stems of intact plants by means of a cotton wick.[17] There was a high incorporation (2.0%) of tracer into the anabasine which was isolated from the plants two weeks later. The activities of the degradation products of the anabasine are shown in Table I. It was found that 37% of the radioactivity was located in the pyridine ring. Furthermore the activity in this ring was located entirely at C_2 and C_3 and was approximately equally divided between these positions. Our results are thus in agreement with the previous observations of Griffith, *et al.*[13] We suggest that the acetate-2-C^{14} enters the Krebs cycle leading to the formation of succinic acid-2,3-C^{14} which is then incorporated into the pyridine ring of nicotinic acid. Recent work of Juby and Marion[18] on the biosynthesis of ricinine is consistent with this hypothesis. They fed sodium acetate-2-C^{14} to *Ricinus communis* plants and found that the pyridone ring of the resultant radioactive ricinine was labeled only at C_2 and C_3, activity being equally divided between these two positions. They found that succinic acid-2,3-C^{14} led to an almost identical pattern of labeling. Waller and Henderson[19] found that succinic acid-1,4-C^{14} afforded radioactive ricinine in which most of the activity was located on the nitrile carbon, a result which is also consistent with the direct participation of succinic acid or closely related metabolite in the biosynthesis of nicotinic acid. Marion and coworkers[20] found that glycerol-1,3-C^{14} and glycerol-2-C^{14} were incorporated into the pyridone ring of ricinine, the pattern of labeling strongly suggesting that the three-carbon chain of glycerol became C_4, C_5 and C_6 of ricinine. It has been previously shown[14,15] that glycerol is a good precursor of the pyridine ring of nicotine. We have also found that the administration of glycerol-2-C^{14} to *N. glauca* affords anabasine labeled in the pyridine ring, and we are currently developing a scheme to determine the activity at C_4, C_5 and C_6.

In the present work the anabasine derived from acetate-2-C^{14} was found to have considerable activity (63%) in the piperidine ring. We have previously

(13) T. Griffith, K. P. Hellman and R. U. Byerrum, *J. Biol. Chem.*, **235**, 800 (1960).

(14) T. Griffith, K. P. Hellman and R. U. Byerrum, *Biochemistry*, **1**, 336 (1962).

(15) D. R. Christman and R. F. Dawson, *ibid.*, **2**, 182 (1963).

(16) R. A. Abramovitch, G. C. Seng and A. D. Notation, *Can. J. Chem.*, **38**, 761 (1960).

(17) C. L. Comar, "Radioisotopes in Biology and Agriculture," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p. 151.

(18) P. F. Juby and L. Marion, *Can. J. Chem.*, **41**, 117 (1963).

(19) G. R. Waller and L. M. Henderson, *Biochem. Biophys. Research Commun.*, **6**, 398 (1961).

(20) J. Essery, P. F. Juby, L. Marion and E. Trumbull, *J. Am. Chem. Soc.*, **84**, 4597 (1962); *Can. J. Chem.*, **41**, 1142 (1963).

TABLE I

ACTIVITIES OF THE DEGRADATION PRODUCTS OF ANABASINE

	Activity, d.p.m./mmole × 10^{-6}	Percentage of total
Anabasine diperchlorate	3.88	
Nicotinic acid	1.95	
Pyridine picrate	1.42	36.6
$BaCO_3$[a] [C_2 of piperidine ring]	0.45	11.6
3-Chloromethylpyridine hydrochloride	1.78	
3-Methylpyridine oxalate	2.12	
3-Methyl-2-phenylpyridine methiodide	2.03	
Benzoic acid [C_2 of pyridine ring]	0.74	19.1
Barium carbonate[b] [C_3 of pyridine ring]	0.68	17.5
Activity in piperidine ring (by diff.)		63.4

[a] Obtained by the decarboxylation of the nicotinic acid. [b] Obtained by the Schmidt reaction on acetic acid produced by the Kuhn–Roth oxidation of 1,3-dimethyl-2-phenylpiperidine.

shown that lysine is a precursor of this ring.[21] In molds, lysine is derived from acetate and the Krebs cycle intermediate, α-ketoglutarate.[22] If it is assumed that the same biosynthesis occurs in higher plants, prolonged feeding with acetate-2-C^{14} would be expected to yield essentially uniformly labeled lysine which would lead to a uniformly labeled piperidine ring. The degradation used in the present work only yielded information on the activity at C_2 in the piperidine ring, which was, however, approximately one-fifth of the total activity of the ring.

Experimental[23]

Assay of the Radioactive Compounds.—Some of the radioactive compounds were assayed on aluminum planchets in a Nuclear Chicago model C 115 low background Q gas flow counter, making corrections for self absorption and geometry. More recently we have counted samples in a Nuclear Chicago model 724 liquid scintillation spectrometer using as solvents either (a) toluene containing 0.5% 2,5-diphenyloxazole (PPO) and 0.03% 1,4-bis-2-(5-phenyloxazolyl)-benzene (POPOP); or (b) dioxane–water mixtures containing 10% naphthalene, 0.7% PPO and 0.05% POPOP. Barium carbonate was counted with high precision by decomposing with sulfuric acid in a closed system, collecting the liberated carbon dioxide in methanolic Hyamine-10 X[24] solution which was then diluted with the previously mentioned toluene solution containing the scintillators. Absolute counting efficiencies of 50 to 65% with a background of 22 to 30 c.p.m. were obtained with this liquid scintillation counter.

Administration of Sodium Acetate-2-C^{14} and Isolation of the Anabasine.—Sodium acetate-2-C^{14} (5.60 mg., 9.0 × 10^8 d.p.m.)[25] dissolved in water (5 ml.) was divided equally between ten 4-month-old *Nicotiana glauca* plants growing in soil in a greenhouse (April, 1962).[26] The stems of each plant were threaded by means of a sewing needle with cotton (Coates and Clark's Darning Cotton, 4 ends 2 ply, plain finish) about 10 cm. above the soil level, and the ends of the cotton dipped into the solution of tracer. Two weeks after the feeding the plants (wet wt. 1208 g.) were harvested and extracted with chloroform and aqueous ammonia as previously described.[21] The aqueous ammoniacal layer contained 15% of the total activity fed to the plants. Pure anabasine (738 mg.) was obtained by a final distillation *in vacuo* (120°, 0.1 mm.) and was converted to the diperchlorate (1.48 g.) having an activity of 1.07 × 10^4 d.p.m./mg. (2.0% incorporation).

Degradation of the Radioactive Anabasine.—Since the anabasine had a high specific activity, we were able to dilute at various stages in this degradation with inactive intermediates when the amounts available became so small that subsequent steps were impractical. Activities reported in Table I are calculated for undiluted material.

Nicotinic Acid.—Anabasine diperchlorate (701 mg.) was dissolved in water (50 ml.) and the solution made alkaline to litmus by the addition of potassium hydroxide. Potassium permanganate (1.8 g.) was added in 0.1-g. portions to the stirred solution at room temperature during 4 hr. The solution was then refluxed for 1 hr., more permanganate (1.0 g.) being added during this period. Excess permanganate was decomposed by the addition of a little methanol. The manganese dioxide was filtered off and washed well with hot water. The combined filtrates were evaporated to dryness, redissolved in water (10 ml.) and the *p*H of the solution adjusted to 8 by adding dilute hydrochloric acid. A saturated aqueous solution of cupric acetate (25 ml.) was added and the resultant precipitate of copper nicotinate filtered off and washed with water. The green copper salt was suspended in water and decomposed with hydrogen sulfide. The mixture was filtered and the residue washed with hot water. The residue obtained on evaporation of the combined filtrates was sublimed *in vacuo* yielding nicotinic acid (143 mg., 60%).

Methyl Nicotinate.—Nicotinic acid (1.318 g.) was refluxed with thionyl chloride (6 ml.) for 4 hr. and then the excess thionyl chloride removed *in vacuo*. Methanol (5 ml.) was added cautiously to the residue and the mixture warmed at 60° for 20 min. Excess methanol was removed *in vacuo*, the residue dissolved in water, made basic with sodium carbonate and extracted with ether. Evaporation of the dried ether extract afforded colorless crystals of methyl nicotinate (1.378 g., 94%), m.p. 38–40° (lit.[27] m.p. 38°).

3-Chloromethylpyridine.—Methyl nicotinate (1.378 g.) dissolved in dry ether (15 ml.) was added during 30 min. to a stirred solution of lithium aluminum hydride (0.75 g.) in ether (20 ml.) maintained at 0°. The mixture was stirred for an additional hour and then water (1.2 ml.) added to decompose the excess lithium aluminum hydride. Sodium hydroxide solution (20%, 1.0 ml.) was then added and the granular precipitate of sodium aluminate filtered off. The residue was washed with methylene chloride and the combined organic filtrates dried over magnesium sulfate, evaporated and distilled *in vacuo* (110°, 0.1 mm.) yielding 3-hydroxymethylpyridine (0.854 g.). This alcohol was added dropwise to thionyl chloride (5 ml.) cooled to −70°. The mixture was allowed to warm to room temperature and stirred for 17 hr. Excess thionyl chloride was removed under reduced pressure, final traces being removed by adding dry benzene to the residue and continuing the distillation. Crystallization of the residue from ethanol and ether yielded 3-chloromethylpyridine hydrochloride as colorless needles (0.827 g., 53%), m.p. 125–127°. Some of the 3-chloromethylpyridine was characterized as the picrate, m.p. 133.5–135° (lit.[28] m.p. 133°).

3-Methylpyridine.—3-Chloromethylpyridine hydrochloride (1.25 g.) dissolved in absolute ethanol (50 ml.) was hydrogenated in the presence of 5% palladium-on-calcium carbonate catalyst (5.0 g.) for 90 min. at a pressure of 2 atmospheres. The catalyst was filtered off, the filtrate acidified with concd. hydrochloric acid (1.0 ml.) and evaporated to dryness. The residual 3-methylpyridine hydrochloride was dissolved in a small amount of water, made strongly alkaline with sodium hydroxide, and the solution then extracted with ether. The ether extract was dried over potassium hydroxide and then evaporated to yield 3-methylpyridine (0.52 g., 73%). This 3-methylpyridine (0.423 g.) was dissolved in ether (25 ml.) and mixed with a solution of oxalic acid (0.60 g.) in acetone (5 ml.). After standing overnight, colorless crystals separated out, and crystallization from a mixture of acetone and ether afforded colorless prismatic needles of the acid oxalate salt of 3-methylpyridine (0.698 g.), m.p. 119–120°. Pure dry 3-methylpyridine (n^{26}D 1.5035, lit.[29] n^{24}D 1.5043) was obtained by heating an intimate mixture of the oxalate salt with freshly prepared calcium oxide under reduced pressure.

3-Methyl-2-phenylpyridine Methiodide.—3-Methylpyridine (96.5 mg., 1.04 moles) dissolved in dry ether (5 ml.) was added to a stirred solution of phenyllithium (87.5 mg., 1.04 moles) in ether (2 ml.) at room temperature. A yellow precipitate was immediately formed which dissolved on the addition of dry toluene (5 ml.). Ether was distilled out of the reaction mixture which was then refluxed at 120° for 20 hr. Water (5 ml.) was then added to the cooled solution and the organic layer separated. This was combined with ether extracts of the aqueous layer, dried over potassium hydroxide, evaporated, and the residue distilled *in vacuo* (110°, 0.1 mm.) yielding 3-methyl-2-phenylpyridine. The product was dissolved in methanol (5 ml.) and methyl iodide (0.2 g.) added. After 18 hr., ether was added when 3-methyl-2-phenylpyridine methiodide (68.4 mg., 21%) separated. Crystallization from a mixture of methanol and ether afforded colorless needles, m.p. 178–179°.

Anal. Calcd. for $C_{13}H_{14}NI$: C, 50.18; H, 4.53; N, 4.50. Found: C, 50.22; H, 4.57; N, 4.33.

1,3-Dimethyl-2-phenylpiperidine.—The 3-methyl-2-phenylpyridine methiodide (220 mg.) was dissolved in methanol (15 ml.) and hydrogenated at atmospheric pressure in the presence of platinum oxide (30 mg.). After 7 hr., 96% of the theoretical

(21) E. Leete, *J. Am. Chem. Soc.*, **78**, 3520 (1956).

(22) M. Strassman and S. Weinhouse, *ibid.*, **75**, 1680 (1953).

(23) Melting points are corrected. We thank Mrs. Olga Hamerston and her assistants at the University of Minnesota for the analyses.

(24) Registered trademark of Rohm and Haas; *p*-(diisobutylcresoxyethoxyethyl)-dimethylbenzylammonium hydroxide.

(25) Purchased from Research Specialities, California.

(26) We thank Robert C. McLeester of the Botany Department of the University of Minnesota for the cultivation of splendid specimens of *N. glauca* plants.

(27) A. Kirpal, *Monatsh.*, **27**, 365 (1906).

(28) Z. J. Vejdělek and M. Protiva, *Chem. Listy*, **45**, 451 (1951).

(29) J. W. Brühl, *Z. physik. Chem.*, **16**, 216 (1895).

amount of hydrogen had been absorbed. Evaporation of the filtered reaction mixture afforded a pale yellow oil, which on distillation *in vacuo* (115°, 0.1 mm.) yielded 1,3-dimethyl-2-phenylpiperidine as a colorless oil (118 mg., 88%). The base was characterized as its methiodide, obtained a colorless needles from methanol and ether; m.p. 176–177°.

Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.76; H, 6.70; N, 4.23. Found: C, 50.46; H, 6.71; N, 4.32.

Oxidation of 1,3-Dimethyl-2-phenylpiperidine.—The piperidine derivative (71.3 mg.) dissolved in 10% sulfuric acid (2 ml.) was added to a refluxing solution of chromium trioxide (5.0 g.) in 10% sulfuric acid (12 ml.). Distillation was commenced immediately, distilled water being added from a dropping funnel to maintain the volume of the reaction mixture at about 12 ml. Distillation was continued for 3 hr. during which time 60 ml. of distillate was collected. This aqueous distillate was extracted with ether (2 × 40 ml.). The combined ether extracts were then extracted with water (2 × 40 ml.). These two water extracts were then back-extracted with ether (2 × 40 ml.). The combined ether extracts were then dried over sodium sulfate and evaporated, yielding crude benzoic acid (14.8 mg.). Sublimation twice afforded pure benzoic acid (4.8 mg.), m.p. 120–122°, not depressed on admixture with an authentic sample. The combined aqueous extracts were titrated to *p*H 8 with 0.0985 *N* sodium hydroxide solution (2.73 ml. required) and then evaporated to dryness. The white residue was refluxed with absolute ethanol, filtered and sodium acetate (11.1 mg.) precipitated by the addition of ether.

Schmidt Reaction on the Sodium Acetate.—Sodium acetate (6.1 mg.) was dissolved in warm concd. sulfuric acid (0.1 ml.). The mixture was then cooled to 0° and sodium azide (10 mg.) added. The reaction vessel was swept with carbon dioxide-free nitrogen, which was then passed through a 5% solution of potassium permanganate in 5% sulfuric acid (to remove sulfur dioxide) and then through a solution of barium hydroxide. The reaction flask was heated to 80° and maintained at this temperature for 1 hr. during which time barium carbonate (9.4 mg.) was precipitated in the barium hydroxide solution.

Decarboxylation of Nicotinic Acid. (a) With Barium Hydroxide.—Nicotinic acid (49.1 mg.) was intimately mixed with anhydrous barium hydroxide (110 mg.) and heated in a nitrogen stream. At about 325° pyridine distilled out of the reaction mixture and was collected as the picrate (32 mg., 26%).

(b) With Copper Chromite.—Nicotinic acid (34.3 mg.) was refluxed in quinoline (1 ml.) containing copper chromite catalyst (38.5 mg.) in a stream of nitrogen. The liberated carbon dioxide was passed into barium hydroxide solution yielding barium carbonate (53 mg., 98%).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS, AMHERST, MASS.]

Synthesis and Oxidation of 2-Amino-2,3-dihydro-1H-benz[de]isoquinoline and 1,2,3,4-Tetrahydronaphtho[1,8-de][1,2]diazepine and Related Cyclic 1,2-Dibenzylhydrazines[1]

BY LOUIS A. CARPINO

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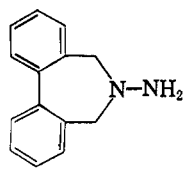
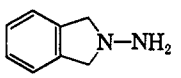
Contrary to expectations based on previous studies of the oxidation of cyclic 1,1-disubstituted hydrazines such as 6-amino-5,7-dihydrodibenzo[ce]azepine (I) and 2-aminodihydroisoindole (II), neither oxidation of 2-amino-2,3-dihydro-1H-benz[de]isoquinoline (III) nor alkaline degradation of the corresponding sulfonhydrazide led to the formation of acenaphthene. A general method for the synthesis of the three corresponding hydrazo compounds, 5,6,7,8-tetrahydrodibenzo[df][1,2]diazocine (XV), 1,2,3,4-tetrahydrophthalazine (XVI) and 1,2,3,4-tetrahydronaphtho[1,8-de][1,2]diazepine (X) was developed involving reaction of *t*-butyl hydrazodiformate with an appropriate bis-halomethyl derivative followed by cleavage of the carbo-*t*-butoxy group by means of hydrogen chloride. The oxidation of X gave a stable azo compound (XX), whereas the azo compound XXII derived from XV proved to be an unstable, heat-sensitive material. No stable azo compound could be isolated from the mercuric oxide oxidation of XVI. Thermal decomposition of 1,4-dihydronaphtho[1,8-de][1,2]diazepine (XX) yielded acenaphthene.

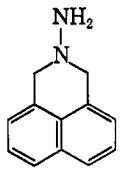
Just as 1,1-dibenzylhydrazine, on oxidation with mercuric oxide[2] and other oxidizing agents or alkaline degradation of the corresponding sulfonhydrazides,[3] yields bibenzyl, it would be expected that oxidation of the analogous cyclic systems I, II and III would yield 9,10-dihydrophenanthrene (IV), benzocyclobutene (V) and acenaphthene (VI), respectively. Indeed,



I

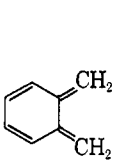


II

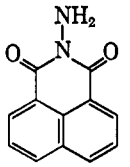


III

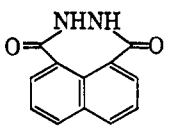
compound I gave IV in 95% yield on sulfonhydrazide degradation. Similarly, sulfonhydrazide degradation of II was shown by Baker, McOmie and Preston[4] to give benzocyclobutene in 14% yield along with some *o*-xylene and dibenzocycloöctadiene. It was subsequently shown[5] that this reaction as well as the corresponding mercuric oxide oxidation yields, in addition to V, the Errede dimer[6] of *o*-quinodimethane (VII). The present paper reports a study of the oxidation of the naphthalene derivative III. Contrary to expectations, neither the oxidation of III nor the alkaline degradation of the corresponding sulfonhydrazide yielded any acenaphthene.



VII



VIII



IX

A synthesis of III was described in an earlier paper[7] utilizing two methods which implied the correctness of the structure indicated, namely (a) sodium borohydride–lithium bromide reduction of a hydrazide described as N-aminonaphthalimide (VIII) and (b) alkylation of *t*-butyl carbazate by means of 1,8-bis(chloromethyl)-naphthalene followed by hydrogen chloride cleavage of the carbo-*t*-butoxy group. Neither method, however, is unequivocal and in view of the unexpected lack of conversion of III to acenaphthene on oxidation it was considered desirable to obtain further evidence for the structure of III.

The most likely alternative structure is the 7-ring hydrazo compound X. Although it is unlikely, method b could have led to the formation of X. The structure of the precursor hydrazide used in method a appears well established as VIII. An isomeric naphthalic hy-

(1) Supported by a grant from the National Science Foundation (NSF G-19506).

(2) M. Busch and B. Weiss, *Ber.*, **33**, 270 (1900).

(3) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957).

(4) W. Baker, J. F. McOmie and D. R. Preston, *Chem. Ind.* (London), 1305 (1960); *J. Chem. Soc.*, 2971 (1961).

(5) L. A. Carpino, *J. Am. Chem. Soc.*, **84**, 2196 (1962).

(6) L. A. Errede, *ibid.*, **83**, 949 (1961).

(7) L. A. Carpino, A. A. Santilli and R. W. Murray, *ibid.*, **82**, 2728 (1960).