at pH 5.0 with a mobility relative to histidine of 0.72. Any phenistidine which might have been formed was thus readily detected. Small amounts were formed when the acetylamidine hydrochloride and the chloro ketone were fused without solvent at 110°. Maximal yield was obtained after 24 hr., but it never exceeded 2%, and much decomposition occurred during such long periods of reaction. Small amounts were also formed when the two reactants (the acetylamidine hydrochloride and the chloro ketone) were dissolved in refluxing acetic acid for 20 hr. or in formamide at 100° for 1 hr., but the yield did not exceed 1%.

Phenistidine.—The free amino acid was obtained either by hydrolysis of the pure derivatives described above, or by hydrolysis of crude reaction mixtures of the acylamidine and the chloromethyl ketone. The pure free amino acid was isolated from a fusion reaction (110°, 18 hr.) of acetyl-L-phenylalanineamidine hydrochloride (0.735 g., 3 mmoles) and ethyl 2-carbobenzoxyamino-4-keto-5-chloro-L-valerate (0.990 g., 3 mmoles). The crude reaction mixture was hydrolyzed in refluxing 6 *N* hydrochloric acid for 3 hr., and, after removal of excess hydrogen chloride by repeated evaporation under reduced pressure, the hydrolysate was neutralized with ammonia and distributed countercurrently for 294 transfers in the system 1-butanol–ethanol–water–concentrated aqueous ammonia, 45:5:49:1. Monitoring by paper electrophoresis showed that the phenistidine was maximal in tube 50. The contents of tubes 40–60 were freed of solvents and distributed countercurrently in the system 1-butanol–water–acetic acid, 10:9:1, for the 146 transfers. Phenistidine was maximal in tube 8. It was obtained pure as the monoacetate salt (23 mg.) by evaporation of the contents of tubes 1–14 and precipitation with alcohol.

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: N, 16.8. Found: N, 16.9.

In paper electrophoresis it gave a single spot with the characteristic gray color when heated with ninhydrin and moved relative to histidine 0.72 at pH 5.0 in 0.1 *M* pyridine acetate. In ascending paper chromatography it gave a single spot with R_f 0.39 in *sec*-butyl alcohol–water–concentrated aqueous ammonia, 25:9:1; R_f 0.86 in phenol–0.1 *N* hydrochloric acid, 9:2; and R_f 0.55 in 1-propanol–water, 2:1.

When hydrolyzed for 20 hr. in refluxing 6 *N* hydrochloric acid it was not entirely stable. Paper electrophoresis of the hydrolysate at pH 5.0 showed, in addition to the characteristic gray spot, small amounts of a neutral spot which was identified as phenylalanine by paper chromatography and of aspartic acid.

2-Alkylidene-2H-indole Intermediates. The Lithium Aluminum Hydride Hydrogenolysis of 2-Indolecarbinol Derivatives[1]

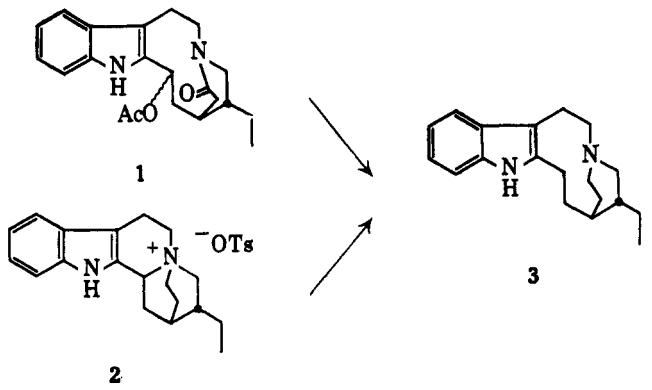
LLOYD J. DOLBY AND DAVID L. BOOTH[2]

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

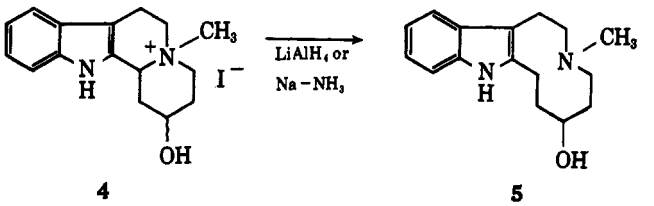
Received November 9, 1964

The action of lithium aluminum hydride results in hydrogenolysis of the oxygen function of several 2-indolecarbinol derivatives. We propose that these reactions proceed by an elimination–addition sequence involving 2-alkylidene-2H-indole intermediates. The observation that methylation of the indole nitrogen inhibits the hydrogenolysis reaction is taken as firm evidence for this hypothesis.

We recently reported that lithium aluminum hydride reduction of the acetoxylactam **1** and the quaternary ammonium salt **2** gives rise to the same tetracyclic base **3**.[3] It was suggested that these lithium aluminum hydride reductions involve 2-alkylidene-2H-indole intermediates. We wish to present further results which indidate the intervention of these intermediates.



The generality of this type of cleavage reaction is shown by the lithium aluminum hydride reduction of the tetracyclic quaternary ammonium salt **4**, prepared by reduction and methylation of 1,2,3,4,6,7,12,12b-octahydro-2-ketoindolo[2,3-*a*]pyridocoline.[4] The action of lithium aluminum hydride in refluxing N-methylmorpholine converts the quaternary ammonium salt **4** to the tricyclic alcohol **5**, obtained in 45% yield The same tricyclic alcohol is obtained in 76% yields from the Birch reduction of **4** as anticipated from previous studies.[5] The structure of the tricyclic alcohol **5** is supported by its proton magnetic resonance spectrum which shows an N-methyl group at τ 7.77 but no signal which could be ascribed to a C-methyl group.



We propose that these reactions take place by an elimination–addition sequence involving an intermediate 2-alkylidene-2H-indoles. Similar mechanisms have been advanced to account for the hydrogenolysis of 3-indolecarbinol derivatives[6] and 2- and 3-pyrrolecarbinols.[7] A consequence of this hypothesis is that N-methylation prevents the hydrogenolysis reaction by blocking the elimination which undoubtedly proceeds *via* the indole anion. The effect has been observed with 3-indolecarbinol derivatives[6] and also in the pyrrole series.[7a]

(1) Supported by a grant from the National Institutes of Health (Grant NB 03232-03).

(2) U. S. Public Health Service Predoctoral Fellow.

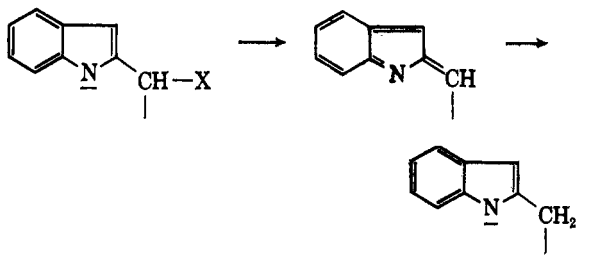
(3) L. J. Dolby and S. Sakai, *J. Am. Chem. Soc.*, **86**, 1890 (1964).

(4) G. B. Kline, *ibid.*, **81**, 2251 (1959).

(5) E. Leete, *Chem. Ind.* (London), 692 (1960).

(6) E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).

(7) R. L. Hinman and S. Theodropulos, *J. Org. Chem.*, **28**, 3052 (1963); (b) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954); (c) A. Treibs and H. Derra-Scherer, *Ann.*, **589**, 188 (1954); (d) A. Treibs and H. Scherer, *ibid.*, **577**, 139 (1952).



It should be noted that 2-hydroxymethylindole is stable to lithium aluminum hydride in ether solution.[6] However, we find that 2-acetoxymethylindole does yield a small amount (3%) of 2-methylindole upon exposure to lithium aluminum hydride, while we could not detect any 1,2-dimethylindole from the reduction of N-methyl-2-acetoxymethylindole. These results are not very conclusive, although 1% of the hydrogenolysis product could be detected by thin layer chromatography. Isogramine appears to be stable toward hydrogenolysis by lithium aluminum hydride since it has been prepared in good yield by the lithium aluminum hydride reduction of the dimethylamide of indole-2-carboxylic acid in refluxing ethyl ether.[8] However, we find that isogramine methotosylate gives 2-methylindole in 33% yield upon lithium aluminum hydride reduction in refluxing tetrahydrofuran, and that no isogramine could be detected.

The difference in reactivity between 1-hydroxytetrahydrocarbazole derivatives and the corresponding N-methyl-1-hydroxytetrahydrocarbazoles is quite striking. All of the N–H compounds suffer extensive reduction to tetrahydrocarbazole, while the N-methylated compounds yield only N-methyl-1-hydroxytetrahydrocarbazole. These results are summarized in Table I.

TABLE I

PRODUCTS FROM THE LITHIUM ALUMINUM HYDRIDE REDUCTION OF 2-INDOLECARBINOL DERIVATIVES

Compd.	% alcohol	% hydrogenolysis product
2-Acetoxymethylindole	80	3
N-Methyl-2-acetoxymethylindole	95	0
1-Benzoyloxytetrahydrocarbazole	49	49
N-Methyl-1-(2-naphthoyloxy)tetrahydrocarbazole	95	0
1-Ketotetrahydrocarbazole	75	20
N-Methyl-1-ketotetrahydrocarbazole	98	0
1-Hydroxytetrahydrocarbazole	44	49

The lithium aluminum hydride reductions were performed in ether or tetrahydrofuran solution using excess lithium aluminum hydride. The reduction products of the N-methyl series did not show any hydrogenolysis products by thin layer chromatography. The reduction products from the N–H series were separated by chromatography over alumina and the yields recorded in Table I refer to isolated material.

Some of the lithium aluminum hydride reductions were also carried out under more drastic conditions. We find that lithium aluminum hydride reduction of N-methyl-1-hydroxytetrahydrocarbazole in boiling dioxane gives N-methyltetrahydrocarbazole in 21% yield. Under these severe conditions, methyl β-naphthoate is reduced to β-methylnaphthalene in 86% yield, and β-acetylnaphthalene affords β-ethylnaphthalene in 34% yield. With this procedure 1-hydroxytetrahydrocarbazole is reduced to tetrahydrocarbazole in almost quantitative yield.

The hydrogenolysis of N-methyl-1-hydroxytetrahydrocarbazole observed under drastic conditions appears to be simple nucleophilic displacement. It seems unlikely that N–H compounds are hydrogenolyzed by a displacement reaction because the formation of the indole anion should make them less reactive toward nucleophilic attack. The marked difference in reactivity between the N–H compounds and the N-methyl series provides good evidence for 2-alkylidene-2H-indole intermediates. The fact that 2-hydroxymethylindole is not reduced under conditions that convert 2-hydroxymethylpyrrole to 2-methylpyrrole indicates that formation of the 2-methylene-2H-pyrrole intermediate is more favorable than the formation of the corresponding intermediate in the indole series. This is not unreasonable since the formation of such intermediates must disrupt the benzene resonance to some extent.

Experimental[9]

1,2,3,4,6,7,12,12b-Octahydro-2-hydroxyindolo[2,3-*a*]pyridocoline.—A sample of 1,2,3,4,6,7,12,12b-octahydro-2-ketoindolo[2,3-*a*]pyridocoline (1.50 g., 0.00625 mole), prepared by the method of Kline,[4] was treated with sodium borohydride (0.30 g., 0.0079 mole) in isopropyl alcohol (50 ml.). The mixture was stirred at room temperature for 3 hr. An equal volume of water was added and the isopropyl alcohol was removed *in vacuo*. The aqueous solution was extracted with five 200-ml. portions of chloroform. The chloroform solution was dried and evaporated *in vacuo* to give 1.17 g. (78%) of the tetracyclic alcohol: infrared spectrum, 3420 and 3200 cm.$^{-1}$. The analytical sample had m.p. 144–145° after several crystallizations from ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.01; H, 7.67; N, 11.62.

Tetracyclic Alcohol Methiodide 4.—A solution of the tetracyclic alcohol (0.562 g., 0.00232 mole) and methyl iodide (0.500 g., 0.00352 mole) in 25 ml. of nitromethane was stored at room temperature for 48 hr. Ether was added and the precipitate was collected to give 0.844 g. (95%) of the tetracyclic alcohol methiodide **4**. Crystallization from methanol–ether gave white needles, m.p. 230–231° dec.

Anal. Calcd. for $C_{16}H_{21}IN_2O$: C, 50.01; H, 5.52; I, 33.02; N, 7.29. Found: C, 50.32; H, 5.78; I, 32.54; N, 7.11.

Lithium Aluminum Hydride Cleavage of the Tetracyclic Alcohol Methiodide 4.—The tetracyclic alcohol methiodide salt (0.916 g., 0.0024 mole) was suspended in 100 ml. of dry N-methylmorpholine (freshly distilled from lithium aluminum hydride). The suspension was cooled to 0° while lithium aluminum hydride (3.50 g., 0.092 mole) was added after which the mixture was refluxed for 15 hr. The mixture was cooled in an ice bath and the excess lithium aluminum hydride was decomposed with 1 ml. of water, 2 ml. of aqueous 5 *N* sodium hydroxide, and 3 ml. of water. The N-methylmorpholine solution was decanted off and the aluminum salts were washed with two 100-ml. portions of chloroform. The chloroform and N-methylmorpholine solutions were combined, washed with two 100-ml. portions of water, and dried. Evaporation of the solvent gave an oil which was chromatographed over 18 g. of alumina to give two fractions: fraction I, 0.143 g., eluted with 100 ml. of benzene; and fraction II, 0.276 g. (45%) of the tricyclic alcohol,

(8) E. C. Kornfield, *J. Org. Chem.*, **16**, 806 (1951).

(9) All melting points are uncorrected. Infrared spectra were determined with a Beckman IR-5 infrared spectrophotometer and ultraviolet spectra were measured with a Cary Model 11 spectrophotometer. Proton magnetic resonance spectra were determined in deuteriochloroform solution using tetramethylsilane as an internal standard with a Varian A-60 spectrometer. Silica gel was used as absorbent in thin layer chromatography with benzene as the eluent. Petroleum ether refers to the fraction of b.p. 30–60°. Sodium sulfate was used as the drying agent. Grade III Woelm alumina was employed in all column chromatography. Microanalyses were by Pascher and Pascher Laboratories, Bonn, Germany.

eluted with 150 ml. of ether. The infrared spectrum had peaks at 3410 and 3240 cm.$^{-1}$; the n.m.r., τ 7.77 (N-CH_3); and ultraviolet, λ_{max}^{EtOH} 229 mμ (ϵ 32,500), 285 (7100), and 292 (6500). The analytical sample showed m.p. 143–145° after crystallization from benzene.

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.45; H, 8.68; N, 11.13.

Sodium and Ammonia Cleavage of the Tetracyclic Alcohol Methiodide 4.—The tetracyclic alcohol methiodide **4** (2.50 g., 0.0065 mole) was placed in a three-necked round-bottom flask fitted with a Dry Ice condenser, a soda lime drying tube, and an ammonia inlet tube. Ammonia (175 ml.) was distilled into the flasks and sodium (3.10 g., 0.135 g.-atom) was added. The ammonia solution was stirred for 15 min. and then the blue color was extinguished with ammonium chloride. The ammonia was allowed to evaporate and the residue was taken up in chloroform, washed with water until neutral, and dried. The oil remaining after removal of the chloroform was crystallized from benzene to yield 1.28 g. (76%) of the tricyclic alcohol **5**, m.p. 143–145°, identical in every respect with the material obtained from the lithium aluminum hydride reduction of **4**.

Reduction of 2-Acetoxymethylindole.—A sample of 2-acetoxymethylindole[10] (0.700 g., 0.0037 mole) in 20 ml. of dry tetrahydrofuran was added dropwise to a slurry of lithium aluminum hydride (1.50 g., 0.0395 mole) in 75 ml. of dry tetrahydrofuran. The mixture was refluxed for 3 hr. and then cooled in an ice bath. The excess lithium aluminum hydride was decomposed with water, aqueous 5 *N* sodium hydroxide, and water. The ether solution was dried and evaporated to yield 0.450 g. (*ca.* 82%) of crystalline material. The proton magnetic resonance spectrum of this material was that of 2-hydroxymethylindole, except for a signal at τ 7.78 which indicated the presence of about 3% of 2-methylindole. The crude reaction product was chromatographed over 15 g. of alumina to afford 0.010 g. of 2-methylindole eluted with 100 ml. of 50% benzene–petroleum ether. The 2-methylindole was identical in every respect with an authentic sample prepared as previously described.[11]

N-Methyl-2-acetoxymethylindole.—Treatment of a pyridine solution of N-methyl-2-hydroxymethylindole[12] with acetic anhydride gave N-methyl-2-acetoxymethylindole, m.p. 63.5–64°, after sublimation and crystallization from pentane.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.23; H, 6.53; N, 6.89.

Reduction of N-Methyl-2-acetoxymethylindole.—The reaction conditions and work-up for the reduction of N-methyl-2-acetoxymethylindole (0.304 g., 0.0015 mole) were identical with the reduction of 2-acetoxymethylindole. Only N-methyl-2-hydroxymethylindole (0.230 g., 95%) was isolated. Thin layer chromatography did not reveal any 1,2-dimethylindole, although 1% of 1,2-dimethylindole could be easily detected in synthetic mixtures.

1-Benzoyloxytetrahydrocarbazole was obtained in 98% yield by the action of benzoyl chloride on 1-hydroxytetrahydrocarbazole[13] in pyridine solution. The pure material had m.p. 121–122° after crystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.09; H, 6.09; N, 4.98.

Reduction of 1-Benzoyloxytetrahydrocarbazole.—A solution of the ester (0.524 g., 0.0018 mole) in 20 ml. of ether was added slowly to a stirred slurry of lithium aluminum hydride (0.300 g., 0.0079 mole) in 30 ml. of ether at 0°. The reaction mixture was stirred at 0° for 1 hr. and at room temperature for 2 hr. The products were isolated as previously described. Chromatography of the crude products over 15 g. of alumina afforded tetrahydrocarbazole (0.151 g., 49%) eluted with 150 ml. of 25% benzene–petroleum ether. Continued elution with this solvent removed benzyl alcohol (0.129 g.) and elution with 200 ml. of ether yielded 1-hydroxytetrahydrocarbazole (0.166 g., 49%).

N-Methyl-1-ketotetrahydrocarbazole.—A modification of the method of Stevens and Tucker[14] was used to methylate 1-ketotetrahydrocarbazole. To a solution of 1-ketotetrahydrocarbazole (1.84 g., 0.01 mole) and 6 ml. of 66% aqueous potassium hydroxide in 10 ml. of acetone was added dimethyl sulfate (5.00 g., 0.04 mole) during 15 min. Water (20 ml.) was added and the mixture was extracted with 100 ml. of ether. The ether layer was washed with dilute ammonia and water. Evaporation of the ether afforded 1.90 g. of crude material which was crystallized from benzene–petroleum ether to yield 1.60 g. (80%) of pure N-methyl-1-ketotetrahydrocarbazole (needles), m.p. 102.5–103°.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.28; H, 6.60; N, 6.80.

N-Methyl-1-hydroxytetrahydrocarbazole.—The N-methyl-1-ketotetrahydrocarbazole (1.211 g., 0.0061 mole) was reduced with lithium aluminum hydride (0.600 g., 0.0158 mole) in ether solution to yield N-methyl-1-hydroxytetrahydrocarbazole (1.203 g., 0.0060 mole, 97%). Recrystallization from benzene–petroleum ether gave m.p. 107–109°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.47; H, 7.56; N, 6.86.

N-Methyl-1-(β-naphthoyloxy)tetrahydrocarbazole.—The acetate, benzoate, and *p*-nitrobenzoate of N-methyl-1-hydroxytetrahydrocarbazole were obtained as oils and could not be purified. A solution of N-methyl-1-hydroxytetrahydrocarbazole (0.400 g., 0.0021 mole) in 2 ml. of pyridine was cooled in an ice bath and β-naphthoyl chloride (0.500 g., 0.0026 mole) was added. The solution was stirred in the cold for 3 hr. Ether (100 ml.) was added and the solution was washed with three 50-ml. portions of 10% phosphoric acid, two 50-ml. portions of sodium bicarbonate, and two 50-ml. portions of water. The ether layer was dried and concentrated to give 0.537 g. of crystalline material. Recrystallization from benzene gave a compound, m.p. 134–136° which was β-naphthoic anhydride. Concentration of the mother liquors gave N-methyl-1-(β-naphthoyloxy)tetrahydrocarbazole, 0.300 g. (42%), m.p. 101–103.5°.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.24; H, 5.87; N, 4.03.

Reduction of N-Methyl-1-(β-naphthoyloxy)tetrahydrocarbazole.—A solution of N-methyl-1-(α-naphthoyloxy)tetrahydrocarbazole (0.450 g., 0.00127 mole) in 20 ml. of ether was added dropwise to a slurry of lithium aluminum hydride (0.300 g., 0.0079 mole) in 20 ml. of ether. Reaction conditions and work-up were identical with the 1-benzoyloxytetrahydrocarbazole case. Only N-methyl-1-hydroxytetrahydrocarbazole was isolated in 95% yield. N-Methyltetrahydrocarbazole could not be detected by thin layer chromatography of the crude product, although 1% of N-methyltetrahydrocarbazole was easily detected in synthetic mixtures. Authentic N-methyltetrahydrocarbazole was prepared as previously described.[14a]

Reduction of 1-Ketotetrahydrocarbazole. A. In Diethyl Ether Solution.—The conditions employed in the reduction of 1-ketotetrahydrocarbazole were identical with those used in the reduction of 1-benzoyloxytetrahydrocarbazole. A 20% yield of tetrahydrocarbazole and an 75% yield of 1-hydroxytetrahydrocarbazole were obtained from the reduction of 1-ketotetrahydrocarbazole.

B. In Dioxane Solution.—A solution of 1-ketotetrahydrocarbazole (0.496 g., 0.00268 mole) in dioxane (20 ml.) was added to a slurry of lithium aluminum hydride (1.007 g., 0.026 mole) in dioxane (20 ml.). The resulting mixture was refluxed for 20 hr. and worked up in the usual manner. Only tetrahydrocarbazole (0.436 g., 95%) was obtained and 1-hydroxytetrahydrocarbazole could not be detected by thin layer chromatography.

Reduction of 1-Hydroxytetrahydrocarbazole.—A sample of 1-hydroxytetrahydrocarbazole was reduced with lithium aluminum hydride in ether solution under the conditions described for the reduction of 1-ketotetrahydrocarbazole except that the reaction time was extended to 18 hr. Tetrahydrocarbazole (49%) and 1-hydroxytetrahydrocarbazole (44%) were isolated as previously described.

Lithium Aluminum Hydride Reductions in Dioxane Solution. A. N-Methyl-1-hydroxytetrahydrocarbazole.—N-methyl-1-hydroxytetrahydrocarbazole (0.252 g., 0.00135 mole) in dioxane (10 ml.) was added dropwise to a slurry of lithium aluminum hydride (0.401 g., 0.01055 mole) in dioxane (20 ml.). The resulting mixture was heated under reflux for 20 hr. and worked up in the usual manner. The crude product was chromatographed on 12 g. of alumina. Elution with petroleum ether (b.p. 60–68°) afforded N-methyltetrahydrocarbazole (0.050 g., 21%) and elution with ether yielded N-methyl-1-hydroxytetrahydrocarbazole (0.190 g., 75%). Both products were identical in all respects with authentic samples.

(10) W. I. Taylor, *Helv. Chim. Acta*, **33**, 164 (1950).

(11) H. M. Kissman, D. W. Farnsworth, and B. Witkop, *J. Am. Chem. Soc.*, **74**, 3948 (1952).

(12) K. Eiter and O. Svierak, *Monatsh.*, **83**, 1453 (1952).

(13) R. J. S. Beer, L. McGrath, and A. Robertson, *J. Chem. Soc.*, 2118 (1950).

(14) (a) T. S. Stevens and S. H. Tucker, *ibid.*, **123**, 2140 (1923); (b) private communication from Dr. Manfred Reinecke.

B. Methyl β-Naphthoate.—A solution of methyl β-naphthoate (1.004 g., 0.00540 mole) in dioxane (20 ml.) was added to a slurry of lithium aluminum hydride (2.20 g., 0.057 mole) in dioxane (30 ml.). The reaction mixture was refluxed for 20 hr. and processed in the usual manner. Chromatography over 32 g. of alumina afforded β-methylnaphthalene, 0.670 g. (86%), m.p. 34–35° (lit.[15] m.p. 31–32°), eluted with petroleum ether, and β-hydroxymethylnaphthalene, 0.010 g. (1%), m.p. 81–82° (lit.[15] m.p. 80–81°), eluted with ether.

C. β-Acetylnaphthalene.—β-Acetylnaphthalene (1.096 g., 0.00645 mole) was reduced with lithium aluminum hydride (2.20 g., 0.058 mole) exactly as described above to afford β-ethylnaphthalene (0.342 g., 34%), identified from its proton magnetic resonance spectrum which exhibited a quartet (2H) at τ 7.36, a triplet (3H) at 8.79, and a multiplet (7H) at 2.2–3. The expected alcohol, 1-(β-naphthyl)ethanol, 0.702 g. (64%), showed m.p. 69–70° (lit.[16] m.p. 67–68.5°).

Reduction of Isogramine Methotosylate.—Isogramine methotosylate, m.p. 149–151° dec., was prepared in the usual manner and crystallized from acetone. The salt (2.75 g., 0.0076 mole) was added to a slurry of lithium aluminum hydride (1.18 g., 0.031 mole) in 75 ml. of tetrahydrofuran. The reaction mixture was heated under reflux for 24 hr. and worked up in the usual manner. Sublimation of the crude product afforded 2-methylindole (0.333 g., 33%), identical in all respects with an authentic sample. Isogramine could not be detected by thin layer chromatography of the crude reduction product.

Anal. Calcd. for $C_{19}H_{24}N_2O_3S$: C, 63.30; H, 6.72; N, 7.77; S, 8.89. Found: C, 63.08; H, 6.88; N, 7.51; S, 8.80.

(15) H. Adkins and E. E. Burgoyne, *J. Am. Chem. Soc.*, **71**, 3528 (1949).

(16) H. Adkins and H. R. Billica, *ibid.*, **70**, 695 (1948).

Novel Synthesis of a Tetrahydropyranylalkanol

R. C. BLUME, DEREK PLANT, AND W. P. O'NEILL

The Pioneering Research Division, Textile Fibers Department, E. I. du Pont de Nemours and Company, Inc. Wilmington, Delaware

Received November 27, 1963
Revised Manuscript Received February 4, 1965

Condensation of 3-methyl-3-buten-1-ol at −65° with BF_3 gave the terpenoid 2-(2,4,4-trimethyltetrahydro-2-pyranyl)ethanol. The structure was proven by n.m.r. data and relationship to 3,3,5-trimethylhexanol prepared from the known 3,3,5-trimethyl-5-hexenoic acid. In similar condensations 3-ethyl-3-buten-1-ol and 2,3-dimethyl-3-buten-1-ol gave products assumed by analogy to be more highly substituted tetrahydropyranylalkanols.

Early workers[1–5] showed that the three unsaturated alcohols derived from isoprene, 3-methyl-3-buten-1-ol, 3-methyl-2-buten-1-ol, and 2-methyl-3-buten-2-ol, may be condensed in acidic systems at room temperature to give mixtures of terpenes. Much more recently it has been shown that these same compounds are involved in the biosynthesis of terpenes.[6]

A cursory chromatographic examination of the products obtained under conditions used by the earlier investigators showed that as many as twelve products were present in fractions boiling from 40 to 100° at 1 mm. Exploratory work of this sort indicated that the product mixture became markedly less complex as the reaction temperature was decreased. At a temperature of −65°, condensation of 3-methyl-3-buten-1-ol using boron trifluoride as the condensing agent and methylene chloride as solvent led to a single predominant C_{10} compound which proved to be the saturated ether–alcohol terpenoid ($C_{10}H_{20}O_2$), 2-(2,4,4-trimethyltetrahydro-2-pyranyl)ethanol (I).

The pyranylethanol I was readily oxidized to the $C_{10}H_{18}O_3$ acid II. The n.m.r. spectrum of the acid (Table I) was most helpful in assigning the structure as 2,4,4-trimethyltetrahydro-2-pyranylacetic acid. The singlet at δ 2.55 appeared clearly that of a $-CH_2$ adjacent to -COOH; the triplet at δ 3.75 was that due to $-O-CH_2-CH_2-CR_3$. The adjacent methylene ($-O-CH_2-CH_2-CR_3$) was confirmed as present in the 7-proton complex at δ 1.25–1.5 by spin decoupling[7] from the triplet at δ 3.75. This spin decoupling yielded two signals at δ ~1.5 and 1.4. The remainder of the 7-proton complex at δ 1.25–1.5 was evidently due to an isolated methylene group and a methyl group in the situation $O-CR_2CH_3$. The remaining methyl absorptions at δ 1.0 and 1.05 appeared then to be those of a *gem*-dimethyl group.

The n.m.r. data for the alcohol II was rendered interpretable only by double resonance. The 2-proton complex at δ 1.6–1.95 was collapsed to a singlet by

TABLE I

N.M.R. ABSORPTION DATA[a]

	Alcohol I			Acid II		
Assignment[b]	No. of H's[c]	Band position	Band multiplicity[d]	No. of H's	Band position	Band multiplicity[d]
COOH	..	...	..	1	11.2	s
-OH	1	~3.7	..			
>C-CH_2-CH_2O-	4	3.55–3.9	c	2	3.75	t[e]
>C-CH_2COOH	..	...	..	2	2.55	s
>C-CH_2-CH_2-O-	2	1.6–1.95	c	2	1.4	t[e]
	2	1.35	t[e]			
>C-CH_2-C<	2	1.25	s	2	~1.5	..
H_3C-C-CH_3	3	1.0	s	3	1.02	s
	3	1.05	s	3	1.04	s
H_3C-C-O-	3	1.25	s	3	1.4	s
	20			18		

[a] Determined on a Varian A-60 high-resolution n.m.r. spectrometer in $CDCl_3$ solution and reported as p.p.m. downfield from TMS included as internal standard. [b] Proton assigned is italic. [c] Determined by integration. [d] m = multiplet, c = complex, s = singlet, t = triplet. [e] J = ~5 c.p.s.

(1) T. Wagner-Jauregg, *Ann.*, **496**, 52 (1932).

(2) A. E. Favorsky and A. J. Lebedeva, *Chem. Abstr.*, **33**, 1298 (1939); *Bull. soc. chim. France*, [5] **6**, 1347 (1939); *J. Gen. Chem. USSR*, **8**, 879 (1938).

(3) T. Lennarts, *Chem. Ber.*, **76**, 831 (1943).

(4) T. Lennarts, *Z. Naturforsch.*, **1**, 684 (1946).

(5) A. Laforque, *Compt. rend.*, **227**, 352 (1948).

(6) F. Lynen, B. W. Agranoff, H. Eggerer, U. Henning, and E. M. Moselein, *Angew. Chem.*, **71**, 657 (1959).

(7) Method described by L. F. Johnson in "Proton–Proton Spin Decoupling Using the Varian V-3521 Integrator," Varian Associates, Palo Alto, Calif., 1962. The other equipment used in the decoupling experiments included the Varian V-4311 60 n.m.r. instrument and the Hewlett-Packard 200 ABR audio oscillator.