ethyl acetate to destroy the excess reducing agent. Addition of cold 5% sulfuric acid dissolved the precipitate. The resulting solution was extracted several times with ether. After washing with water and drying over magnesium sulfate, the extracts were evaporated to dryness to give a colorless oil (0.36 g.) which crystallized on trituration with benzene. Recrystallization from benzene-ethyl acetate yielded VII as a colorless product (0.26 g., 86% yield), m.p. 165–166°, which, after repeated recrystallizations, melted at 169–170°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 79.01; H, 5.77. An active hydrogen determination showed 0.84%, corresponding to 2.6 atoms.[10]

The infrared spectrum showed maxima at 3.00, 6.25, 6.82, 7.92, 8.57, and 8.85 μ. The ultraviolet spectrum is recorded in Fig. 1.

Reduction of 4-hydroxy-2-biphenylcarboxylic acid (0.080 g.) was performed essentially as described above. A crystalline white solid (0.045 g.) was obtained which was recrystallized several times from ether-benzene to yield VIII, m.p. 175–176°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.90; H, 5.87.

(10) Sample was incompletely soluble in the butyl ether.

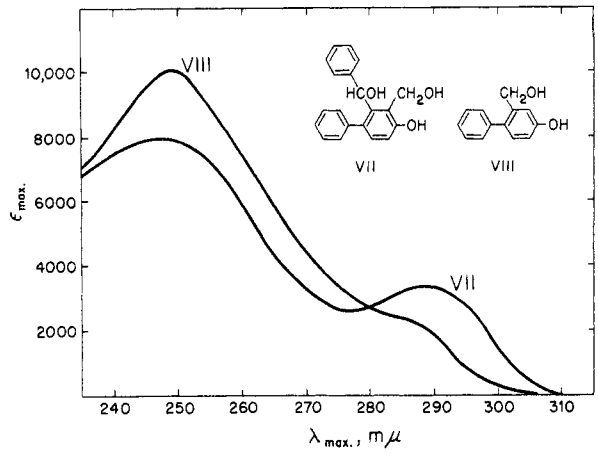

FIG. 1.—ULTRAVIOLET SPECTRA OF SUBSTITUTED 4-HYDROXYBIPHENYLS (IN 95% ETHANOL)

The ultraviolet spectrum is reproduced in Figure 1.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

Some Pyridylnitroalkenes, Nitroalkanols, and Alkylamines

ALFRED BURGER, M. LUISA STEIN,[1] AND JOHN B. CLEMENTS

Received July 19, 1956

Nicotinaldehyde condenses with nitroethane to 1-(3-pyridyl)-2-nitropropene which can be reduced stepwise to 3-pyridylacetoxime and 1-(3-pyridyl)-2-aminopropane. Pyridine-4-aldehyde and nitroethane furnish 1-(4-pyridyl)-2-nitropropanol-1, while isoquinoline-3-aldehyde and nitroethane give 1-(3-isoquinolyl)-2-nitropropene.

Considerable pharmacological interest has been attached to 2-aminoethyl and 2-aminopropyl derivatives of pyridine. 2-(2-Pyridyl)-ethylamine[2] and 1-(2-pyridyl)-2-aminopropane[3] resemble histamine in pharmacodynamic behavior whereas 1-(6-methyl-2-pyridyl)-2-aminopropane,[3] and especially 1-(5-ethyl-2-pyridyl)-2-aminopropane[3] produce marked analgesia in laboratory animals. 2-(3- or 4-Pyridyl)-ethylamines[2,4] are pressor amines, and 1-(3-pyridyl)-2-aminopropane[5] especially appears to have pronounced vasoconstrictor properties.[6] It became advisable to prepare this amine by a more rewarding route than described previously,[5] and the commercial availability of nicotinaldehyde invited a synthesis *via* 1-(3-pyridyl)-2-nitropropene. This compound was formed in 67% yield from nicotinaldehyde and nitroethane under the influence of *n*-butylamine at 90°, and could be reduced stepwise with lithium aluminum hydride. 3-Pyridylacetoxime[5] was obtained in high yields first. This reaction resembles the reduction of 1-phenyl-2-nitropropene which could be stopped at phenylacetoxime.[7] When four moles of the reducing agent was used in boiling ether for 10 hr., a mixture of 43% of 1-(3-pyridyl)-2-aminopropane and 40% of 3-pyridylacetoxime was formed. The latter could be separated and reduced in the same manner, but again only 48% of 1-(3-pyridyl)-2-aminopropane was obtained. No reduction of the pyridine ring was noted although this has been reported for certain other 3-substituted pyridine derivatives.[8,9]

Of the three pyridine aldehydes, only the 3-isomer reacts with nitromethane to give an α,β-unsaturated nitro derivative.[10] The 2- and 4-isomers furnish the corresponding 2-nitroethanols under analo-

(1) Consiglio Nazionale delle Ricerche Italia Fellow and Fulbright Grantee, 1955.

(2) L. A. Walter, W. H. Hunt, and R. J. Fosbinder, *J. Am. Chem. Soc.*, **63**, 2771 (1941).

(3) A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

(4) C. O. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, **64**, 2288 (1942).

(5) A. Burger and C. R. Walter, *J. Am. Chem. Soc.*, **72**, 1988 (1950).

(6) The pharmacological properties of the pyridylaminopropanes were studied by Smith, Kline and French Laboratories.

(7) R. T. Gilsdorf and F. F. Nord, *J. Am. Chem. Soc.*, **74**, 1837 (1952).

(8) V. M. Micovic and M. Lj. Mihailovic, *Rec. trav. chim.*, **71**, 970 (1952).

(9) F. Bohlmann and M. Bohlmann, *Chem. Ber.*, **86**, 1419 (1953).

(10) A. Dornow and F. Boberg, *Ann.*, **578**, 101 (1952).

gous conditions.[11] It has now been found that pyridine-4-aldehyde and nitroethane yield 80% of 1-(4-pyridyl)-2-nitropropanol-1 under the influence of *n*-butylamine or potassium hydroxide. This nitro alcohol could not be dehydrated by agitation with phosphorus pentoxide for 24 hr., and it was recovered unchanged when its solution in aqueous sodium hydroxide was treated with acid. Warming with acetic anhydride led to black tars with the evolution of oxides of nitrogen.

The formation of stable nitro alcohols α or γ to pyridine nitrogen has some analogies in related ring systems. Quinoline-4-aldehydes add nitroalkanes to give the corresponding 1-(4-quinolyl)-2-nitro-1-alkanols,[12,13] and isoquinoline-1-aldehyde yields 1-(1-isoquinolyl)-2-nitroethanol with nitromethane.[14] We have found that, by contrast, isoquinoline-3-aldehyde in which the formyl group is located at a slightly less reactive position[15] can be condensed with nitroethane to 1-(3-isoquinolyl)-2-nitropropene without difficulty.

These regularities may be explained on the basis of the higher inductive effect on the extraannular C—OH group exerted by the 2- and 4- positions of the pyridine ring, making an escape of hydroxide ions from the alcohol more difficult.

EXPERIMENTAL[16]

1-(3-Pyridyl)-2-nitropropene. A mixture of 3.2 g. (0.03 mole) of nicotinaldehyde, 2.67 g. (0.03 mole) of nitroethane, and 4–5 drops of *n*-butylamine was heated on a steam bath for 2.5 hr. or longer, cooled to −4°, and allowed to crystallize. The crystals were filtered and washed with petroleum ether. An additional batch of the material was obtained by extracting the filtrate with dilute acid and cautiously neutralizing the acid layer with sodium carbonate solution. Recrystallization from a small volume of ethyl acetate or from ligroin gave 3.2 g. (67%) of yellow prisms, m.p. 67.5–68°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91. Found: C, 58.56; H, 4.88.

The compound irritated the skin and caused severe dermatosis. The yellow *picrate* melted at 131° after crystallization from ethanol.

Anal. Calcd. for $C_{14}H_{11}N_5O_9$: C, 42.75; H, 2.92. Found: C, 42.59; H, 3.04.

About 17% of unchanged nicotinaldehyde was recovered by extraction of the aqueous alkaline filtrate of the nitropropene derivative with ether.

Reduction of 1-(3-pyridyl)-2-nitropropene. (*a*) To a stirred suspension of 1.7 g. (0.04 mole) of lithium aluminum hydride in 75 ml. of dry ether at 0° was added a solution of 2.2 g. (0.0135 mole) of the nitropropene derivative. The mixture was stirred at 0° for 10 min. and at 28° for 30 min., treated with 2.8 ml. of water, and filtered after 1 hr., and the precipitate was extracted exhaustively with ether. The colorless crystalline residue from the combined ether solutions melted at 115–117° and did not depress the melting point of an authentic sample of 3-pyridylacetoxime.[5] The yield was 80–90%.

(*b*) If the reduction was carried out with a four-molar excess of lithium aluminum hydride in boiling ether for 9–10 hr., and the residue from the ether extract was distilled, a 45% yield of 1-(3-pyridyl)-2-aminopropane, b.p. 70–73° (0.2 mm.) was obtained. The *dipicrate*, m.p. 187–187.5°, did not depress the melting point of an authentic sample.[5]

The hygroscopic *dihydrobromide* crystallized from absolute ethanol, m.p. 192–193°.

Anal. Calcd. for $C_8H_{12}N_2.2HBr$: C, 32.24; H, 4.73. Found: C, 32.13; H, 5.17.

About 40% of 3-pyridylacetoxime distilled as a higher boiling fraction, and was identified by its melting point characteristics.

(*c*) 3-Pyridylacetoxime could be reduced in the same manner with two moles of lithium aluminum hydride. The yield of amine after distillation was 48%.

1-(4-Pyridyl)-2-nitropropanol-1. (*a*) A mixture of 2.14 g. (0.02 mole) of pyridine-4-aldehyde, 1.65 g. (0.022 mole) of nitroethane, and 6 drops of *n*-butylamine was allowed to stand at 25° for 5 days. After trituration with 25 ml. of ether, 2.95 g. (80%) of pale brown needles was filtered which after recrystallization from ethanol melted at 153–153.5°, dec.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53. Found: C, 52.60; H, 5.44.

The yellow *picrate* crystallized from ethanol, m.p. 149–150°, dec.

Anal. Calcd. for $C_{14}H_{13}N_5O_{10}$: C, 40.88; H, 3.19. Found: C, 40.75; H, 3.27.

(*b*) To a stirred solution of 5 g. of potassium hydroxide and 80.9 g. (1.08 mole) of nitroethane in 200 ml. of absolute methanol at 10° was added 107.1 g. (1 mole) of pyridine-4-aldehyde at such a rate that the temperature did not rise over 35°. A white precipitate appeared. After standing overnight, the viscous mixture was filtered, and the colorless nitropropanol derivative (150.6 g., 82.5%, m.p. 150–151°, dec) was washed with water and methanol. After recrystallization from ethanol the substance melted at 151–152°, dec.

Anal. Found: C, 52.35; H, 5.42.

When ammonium acetate in hot acetic acid was used as a condensing agent, a high melting polymeric solid was formed. Attempts to reduce the pure nitropropanol derivative with nickel or platinum catalysts, or with lithium aluminum hydride, remained inconclusive.

1-(3-Isoquinolyl)-2-nitropropene. When a solution of 7.81 g. (0.05 mole) of isoquinoline-3-aldehyde,[17] 4.05 g. (0.054 mole) of nitroethane and 0.5 ml. of *n*-butylamine was allowed to stand at 25° for 5 days and worked up, 4.39 g. (41%) of brown needles was obtained which, after recrystallization from ethanol, melted at 113–114°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71. Found: C, 67.29; H, 4.64.

Like other β-nitrostyrenes,[18] 1-(3-isoquinolyl)-2-nitropropene inhibited the multiplication of a variety of pathogenic and agricultural fungi.

CHARLOTTESVILLE, VA.

(11) F. Zymalkowski, *Arch. Pharm.*, 289, 52 (1956).

(12) A. P. Phillips, *J. Am. Chem. Soc.*, 70, 452 (1948).

(13) M. Levitz and M. T. Bogert, *J. Org. Chem.*, 10, 341 (1945).

(14) R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, 64, 2430 (1942).

(15) W. J. Gensler, in *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley & Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 449–452.

(16) All melting points are corrected. Microanalyses by Miss Barbara J. Williamson.

(17) Generously supplied by Dr. James W. Wilson of Smith, Kline and French Laboratories.

(18) *See* A. C. Huitric, R. Pratt, Y. Okano, and W. D. Kumler, *Antibiotics & Chemotherapy*, 6, 290 (1956).