Oxidation of Benzothiophene-1-dioxide.—A mixture of 0.3 g. (0.0018 mole) of benzothiophene-1-dioxide, 1.4 g. (0.0065 mole) of potassium permanganate and 25 ml. of water was heated on the steam-bath for five hours, acidified with concentrated hydrochloric acid, and the solution clarified with 30% hydrogen peroxide. Addition of a solution of benzylthiouronium chloride to this solution yielded 0.6 g. (60%) of the dibenzylthiouronium salt of *o*-sulfobenzoic acid, m. p. 205–206°, which did not depress the melting point of an authentic sample.[11]

(11) Veibel, *Bull. soc. chim.*, [5] **5**, 1153 (1938); Campaigne and Suter, THIS JOURNAL, **64**, 3040 (1942).

Summary

The 2–3 bond in benzothiophene-1-dioxide (I) was found to be readily hydrogenated and oxidized, and was shown to undergo addition reactions with a variety of reagents. These reactions are typical of an α,β-unsaturated sulfone, and no indication of aromatic character in the 2–3 bond was revealed.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Some α-Substituted β-Pyridylethylamines

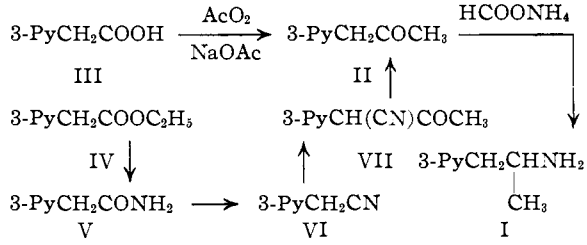
BY ALFRED BURGER AND C. ROBERT WALTER, JR.[1,2]

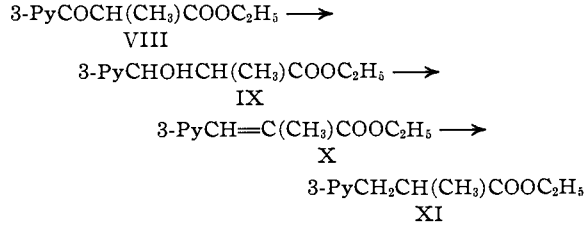
The three isomeric β-pyridylethylamines exhibit characteristic differences in their physiological activity depending on the position of the side-chain in the pyridine ring. The 2-isomer resembles histamine, while the 3- and 4-isomers are pressor amines,[3,4] perhaps because only the β-(2-pyridyl)-ethylammonium ion can exist in a chelated form like the histamine ion.[3]

It could be expected that these properties would be more pronounced in the corresponding β-pyridylisopropylamines since these compounds should be more refractory to enzymatic deamination than the unbranched ethylamine derivatives. In fact, β-(2-pyridyl)-isopropylamine has been found to have pronounced histamine-like activity.[5] We are now reporting the synthesis of β-(3-pyridyl)-isopropylamine (I). This compound was obtained from 3-pyridylacetone (II) by the Leuckart reaction.

Two different routes were used in preparing 3-pyridylacetone. The more rewarding one was patterned on the preparation of phenylacetone from phenylacetic acid, sodium acetate and acetic anhydride.[6] 3-Pyridylacetic acid[7] (III) furnished the ketone under analogous conditions. The second method started with 3-pyridylacetamide[7a] (V), which we prepared by the action of ammonia on ethyl 3-pyridylacetate (IV). Dehydration of the amide led to 3-pyridylacetonitrile (VI) which, when condensed with ethyl acetate, produced 3-pyridylacetylacetonitrile (VII). The latter yielded 3-pyridylacetone on acid hydrolysis.

Another series of experiments designed to lead to I began with ethyl α-nicotinoylpropionate (VIII) which we hoped to reduce to ethyl α-methyl-β-(3-pyridyl)-propionate (XI). However, this reduction could not be forced beyond ethyl α-methyl-β-hydroxy-β-(3-pyridyl)-propionate (IX) which proved singularly hard to dehydrate; only its acetate was pyrolyzed to ethyl α-methyl-β-(3-pyridyl)-acrylate (X). This unsaturated ester absorbed one mole of hydrogen but the reaction product, presumably XI, could not be characterized, and its degradation to I was not pursued further.





It was also considered pertinent to prepare pyridine analogs of α-phenyl substituted phenethylamines ($C_6H_5CH_2CH(C_6H_5)NH_2$] since some of the latter possess marked analgetic properties.[8] Two pyridine derivatives of this type (XIV and XVI) were therefore prepared by way of the corresponding ketones.

Ethyl nicotinate was condensed with phenylacetonitrile, and the resulting α-(3-nicotinoyl)-phenylacetonitrile (XII) was hydrolyzed and decarboxylated to benzyl-(3-pyridyl) ketone (XIII). The latter was converted to α-(3-pyridyl)-phenethylamine (XIV).

(1) Smith, Kline and French Laboratories Fellow, 1947–1949.

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(3) Nieman and Hays, THIS JOURNAL, **64**, 2288 (1942).

(4) Walter, Hunt and Fosbinder, *ibid.*, **63**, 2771 (1941).

(5) Burger and Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

(6) Magidson and Garkusha, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 339 (1941); *Chem. Abstr.*, **35**, 5868[6] (1941).

(7) (a) Hartman and Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941); *Soc. pour l'ind. Chim. à Bâle*, British Patent 558,774 (1944); (b) Malan and Dean, THIS JOURNAL, **69**, 1797 (1947).

(8) Dodds, Lawson and Williams, *Nature*, **151**, 614 (1943); **154**, 514 (1944); *Proc. Roy. Soc.* (*London*), **132B**, 119 (1944).

$$3\text{-PyCOOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{CH}_2\text{CN} \longrightarrow \text{C}_6\text{H}_5\text{CH(CN)CO(3-Py)} \longrightarrow$$
XII

$$\text{C}_6\text{H}_5\text{CH}_2\text{CO(3-Py)} \longrightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CH(NH}_2\text{)(3-Py)}$$
XIII XIV

The second ketone in this group, (3-pyridyl 2-picolyl) ketone (XV) was prepared from 3-cyanopyridine and 2-picolyllithium. The Leuckart reaction with this ketone led to the secondary amine XVI.

$$2\text{-PyCH}_2\text{Li} + 3\text{-PyCN} \longrightarrow 2\text{-PyCH}_2\text{CO(3-Py)} \longrightarrow$$
XV

$$[2\text{-PyCH}_2\text{CH(3-Py)}]_2\text{NH}$$
XVI

A pharmacological study of compounds I and XIV will be reported elsewhere.

Experimental[9]

3-Pyridylacetamide (V).—3-Pyridylacetic acid hydrochloride[7b] was obtained in a yield of 58%, m. p. 149–156°. A solution of 37 g. of the salt in a mixture of 63.8 g. of concentrated sulfuric acid and 63.8 g. of absolute ethanol was heated at 95° for four hours, poured into 300 g. of crushed ice, and worked up in analogy to the directions for the preparation of ethyl nicotinate.[10] The yield of colorless ethyl 3-pyridylacetate (IV) of b. p. 102–104° (2 mm.) was 22.5 g. (64%).

Ten grams of this ester was agitated with 50 cc. of 28% ammonium hydroxide for six hours, and the clear solution was evaporated at 25°. The colorless crystalline amide was obtained in near-quantitative yield. After recrystallization from dioxane it melted at 121–123°. The literature reports m. p. 123° for 3-pyridylacetamide prepared by a different route.[7a]

3-Pyridylacetonitrile (VI).—A mixture of 26.2 g. of 3-pyridylacetamide and 170 cc. of freshly distilled phosphorus oxychloride was refluxed for 90 minutes, excess reagent was removed under reduced pressure, and the cooled viscous residue was decomposed with ice-water. The acid solution was cleared with Darco, the dark-red filtrate was made alkaline with sodium carbonate and extracted with ether. The nitrile from the extract distilled as a colorless liquid, b. p. 107–108° (0.5 mm.). The yield was 7.8 g. (34%).

The yellow **picrate** crystallized from ethanol, m. p. 160.5–161.5°.

Anal. Calcd. for $C_{13}H_9N_5O_7$: N, 20.17. Found: N, 20.05.

α-(3-Pyridyl)-acetylacetonitrile (VII).—Sodium (1.2 g.) was dissolved in 20 cc. of boiling absolute ethanol, and a mixture of 5 g. of 3-pyridylacetonitrile and 5.4 g. of dry ethyl acetate was added dropwise. The color of the reaction mixture deepened through yellow to red. After refluxing for four hours and standing overnight, the viscous mass was treated with a saturated sodium chloride solution, extracted with ether, and acidified with acetic acid to *p*H 7. A yellow precipitate appeared. It was filtered and recrystallized from ethanol. The material melted at 194.5–195.5° and weighed 3.8 g. (56%).

Anal. Calcd. for $C_9H_8N_2O$: N, 17.49. Found: N, 18.14.

3-Pyridylacetone (II).—(a) A mixture of 53.4 g. of 3-pyridylacetic acid,[7b] 88.5 g. of acetic anhydride and 26.7 g. of anhydrous sodium acetate was heated to reflux for nineteen hours. After dilution with 150 cc. of water and clearing it with charcoal, the dark-red acid solution was concentrated, made alkaline with sodium carbonate and extracted exhaustively with ether. The oily residue from the ether extract boiled at 119–123° (1 mm.) as an almost colorless oil. The yield was 20.8 g. (39.6%).

The **semicarbazone** was prepared in aqueous acetic acid solution, m. p. 184.5–185°.

Anal. Calcd. for $C_9H_{12}N_4O$: N, 29.15. Found: N, 29.37.

The **oxime** melted at 117.5–119°.

Anal. Calcd. for $C_8H_{10}N_2O$: N, 18.66. Found: N, 18.78.

(b) A solution of 3.2 g. of α-(3-pyridyl)-acetylacetonitrile in 40 cc. of 48% hydrobromic acid was refluxed for eight hours, diluted with 35 cc. of water, made alkaline with sodium carbonate and extracted exhaustively with ether. The oily residue from the ether extract was used for the preparation of two derivatives.

The **semicarbazone** melted at 181.5–182.5° and did not depress the melting point of a sample of 3-pyridylacetone semicarbazone prepared by method (a).

The **oxime** melted at 115.5–117°. A mixture with a sample prepared as described under (a) had the same melting point.

β-(3-Pyridyl)-isopropylamine (I).—Fifteen grams of 3-pyridylacetone was dropped into molten ammonium formate which had been made from 33.9 g. of 26% ammonium hydroxide and 27.8 g. of 98% formic acid with subsequent dehydration at 160°. The temperature of the mixture was maintained at 160–170° for seventeen hours, and the reaction mixture was then hydrolyzed by boiling it with 65 cc. of 20% hydrochloric acid for eight to nine hours. It was diluted with 20 cc. of water, saturated with potassium hydroxide, and extracted with ether continuously for eight days. The yield of colorless oil from this extract was 5.5 g. (36.4%), b. p. 83–88° (1 mm.), or 74–77° (0.5 mm.).

The yellow *m*-**nitrobenzenesulfonamide** prepared by standard directions crystallized from dilute ethanol, m. p. 167–168.5°.

Anal. Calcd. for $C_{14}H_{15}N_3O_4S$: N, 13.08. Found: N, 12.64.

The yellow **dipicrate** crystallized from ethanol containing a little acetone, m. p. 186–187.5°.

Anal. Calcd. for $C_{20}H_{18}N_8O_{14}$: C, 40.41; H, 3.05; N, 18.85. Found: C, 40.49; H, 3.14; N, 18.61.

Ethyl α-Nicotinoylpropionate (VIII).—This ester was prepared in a yield of 33% by the procedure of Burrus and Powell.[11] It boiled at 131–134° (1 mm.). The **oxime** was formed by warming a neutral dilute alcoholic solution of hydroxylamine with the keto ester for 15 minutes. It crystallized from water, m. p. 96.5–97.5°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.20; H, 6.30; N, 12.63.

Ethyl α-Methyl-β-hydroxy-β-(3-pyridyl)-propionate (IX).—Hydrogenation of ethyl α-nicotinoylpropionate under ordinary pressure in glacial acetic acid in the presence of palladized barium sulfate, or in absolute ethanol under the influence of Adams catalyst, was complete after absorption of one mole of hydrogen. The solution was neutralized, or the ethanol evaporated, the hydroxy ester was extracted into ether, and the crystalline residue from the ether extract was recrystallized from xylene. Colorless crystals, m. p. 94.5–96°, were obtained in yields up to 63%.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69; mol. wt., 209.24. Found: C, 63.39; H, 6.83; N, 6.79; mol. wt., 211.

The **hydrochloride** crystallized from ethanol–ethyl acetate, m. p. 131–131.5°.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: N, 5.70. Found: N, 5.71.

Ethyl α-Methyl-β-acetoxy-β-(3-pyridyl)-propionate was prepared by refluxing a mixture of 2.5 g. of the hydroxy ester (IX) and 9 cc. of acetic anhydride for three hours and

(9) All melting points are corrected. Many of the microanalyses have been performed by Clark Microanalytical Laboratory, Urbana, Illinois.

(10) LaForge, THIS JOURNAL, **50**, 2477 (1928).

(11) Burrus and Powell, *ibid.*, **67**, 1468 (1945).

working it up by hydrolysis of excess reagent and extraction into ether. The colorless acetoxy ester boiled at 130–131° (1 mm.) and weighed 1.4 g. (61.5%).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.58. Found: C, 61.69; H, 6.53; N, 5.76.

Ethyl α-Methyl-β-pyridyl acrylate (X).—When the crude acetoxy ester prepared from 15.5 g. of the hydroxy ester (IX) was distilled at atmospheric pressure, a pale red liquid was obtained which, on redistillation, boiled at 115–117° (0.5 mm.). The yield was 12.3 g. (86.6%).

The **picrate** crystallized as yellow needles from ethanol, m. p. 148.5–150°.

Anal. Calcd. for $C_{17}H_{16}N_4O_8$: C, 48.57; H, 3.84. Found: C, 48.10; H, 4.00.

α-Nicotinoylphenylacetonitrile (XII).—A mixture of 26 g. (0.172 mole) of ethyl nicotinate and 13.3 g. (0.119 mole) of phenylacetonitrile was dropped into a solution of sodium ethoxide prepared from 3.4 g. (0.148 mole) of sodium and 50 cc. of absolute ethanol. The yellow mixture was heated under reflux for four hours, the color deepening to orange-red as the reaction progressed. The product was poured into water, unreacted starting materials were extracted with ether, the alkaline solution was acidified to *p*H 7, and the heavy yellow precipitate which formed was collected. It weighed 18 g. (71%). Recrystallization from dilute ethanol furnished almost colorless crystals, m. p. 142–143°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: N, 12.61. Found: N, 12.69.

3-Pyridyl Benzyl Ketone (XIII).—A solution of 5 g. of α-nicotinoylphenylacetonitrile in 50 cc. of 48% hydrobromic acid was refluxed for eight hours and then poured into 150 cc. of water. A heavy white precipitate of 3-pyridyl-benzyl ketone hydrobromide appeared. A sample of the salt was recrystallized from ethanol. The colorless needles melted at 225–228° (dec.).

Anal. Calcd. for $C_{13}H_{12}BrNO$: N, 5.04. Found: N, 5.09.

The colorless **base** was liberated from the hydrobromide with sodium carbonate solution and recrystallized from dilute methanol. The yield was 3 g. (66.7%), m. p. 58–59°.

Anal. Calcd. for $C_{13}H_{11}NO$: N, 7.10. Found: N, 7.21.

The **oxime**, obtained in neutral dilute alcoholic medium by refluxing for two hours, crystallized from dilute ethanol as bright colorless crystals, m. p. 124.5–125.5°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: N, 13.20. Found: N, 13.15.

α-(3-Pyridyl)-phenethylamine (XIV).—To ammonium formate obtained from 20.5 g. of 88% formic acid was added 15.4 g. of 3-pyridyl-benzyl ketone at 160°, and the temperature was kept at 160–170° for fifteen hours while water formed in the reaction was distilled off.

The crude formyl derivative was hydrolyzed by refluxing with 45 cc. of 20% hydrochloric acid for eight hours. The reaction mixture was diluted with 40 cc. of water and extracted with ether. The acid solution was then saturated with potassium hydroxide, and the oily precipitate extracted into chloroform. The solvent was removed and the amine distilled. The almost colorless distillate weighed 6.2 g. (40%), b. p. 155–160° (0.5 mm.).

The colorless *dihydrochloride* crystallized from ethanol, m. p. 270–274° (dec., evacuated tube).

Anal. Calcd. for $C_{13}H_{16}Cl_2N_2$: C, 57.55; H, 5.95; N, 10.33. Found: C, 57.44; H, 5.90; N, 10.33.

(3-Pyridyl) (2-Picolyl) Ketone (XV).—A solution of 2-picolyllithium was prepared by adding 127.2 g. (1.36 moles) of 2-picoline to a solution of 114.2 g. (1.36 moles) of phenyllithium in 600 cc. of anhydrous ether. To this solution was added slowly, with stirring under an atmosphere of nitrogen, a suspension of 80 g. (0.72 mole) of 3-cyanopyridine in 275 cc. of ether. The mixture grew very thick and dark. It was refluxed for three hours after completion of the initial reaction, and then allowed to stand overnight. This was followed by hydrolysis with a solution of 550 cc. of 37% hydrochloric acid in 2 l. of ice water, separation of the acid layer, and refluxing for one hour to complete the reaction. The cooled, dark red solution was neutralized with ammonium hydroxide to *p*H 7, and the heavy black oil which separated was extracted into chloroform. The residue from the dried extract was fractionated, and 38 g. of an orange-red oil, b. p. 167–170° (1 mm.), which solidified on standing was collected. This fraction was recrystallized from benzene–petroleum ether and finally from dilute methanol. The bright greenish-yellow crystals melted at 71.5–73°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08. Found: C, 72.56; H, 4.87.

The **oxime** crystallized from dilute ethanol, m. p. 135–136.5°.

Anal. Calcd. for $C_{12}H_{11}N_3O$: N, 19.71. Found: N, 19.64.

Bis-[α-(3-pyridyl)-β-(2-pyridyl)-ethyl]-amine (XVI).—From the Leuckart reaction with the ketone XV, 25% of an intensely yellow, viscous oil boiling at 153–157° (0.5 mm.) was obtained. The colorless **pentahydrobromide**, prepared in alcohol solution, crystallized from ethanol–acetone, m. p. 286–293° (dec., uncor.).

Anal. Calcd. for $C_{24}H_{28}Br_5N_5$: C, 36.67; H, 3.59; N, 8.91. Found: C, 36.60; H, 3.70; N, 8.88.

Summary

3-Pyridylacetone was synthesized from 3-pyridylacetic acid (a) through 3-pyridylacetonitrile and 3-pyridylacetylacetonitrile, and (b) by the Magidson and Garkusha reaction. β-(3-Pyridyl)-isopropylamine was obtained from the ketone by the Leuckart method.

A synthesis of ethyl α-methyl-β-(3-pyridyl)-acrylate was performed.

Condensation of ethyl nicotinate with benzyl cyanide gave α-(3-nicotinoyl)-phenylacetonitrile which was converted to (3-pyridyl) benzyl ketone. From the reaction between 2-picolyllithium and 3-cyanopyridine, (2-picolyl) (3-pyridyl) ketone was isolated. These ketones furnished corresponding amines by the Leuckart reaction.

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