The pure product gave no depression of melting point when mixed with Compound A. 2-Amino-5-chlorobenzimidazole is therefore the correct representation of the structure of the monochlorination product of 2-aminobenzimidazole and of the condensation product of *p*-chloro-*o*-phenylenediamine with cyanogen bromide.

2-Amino-5-chloro-1-(*m*-nitrobenzenesulfonyl)-benzimidazole (VII).—2-Amino-5-chlorobenzimidazole (28.5 g., 0.170 mole) and *m*-nitrobenzenesulfonyl chloride (39.0 g., 0.175 mole) were shaken overnight in 70 ml. of dry pyridine. The pasty mass was poured into 400 ml. of water, and 51.1 g. of yellow, alkali-insoluble solid was isolated following cooling, filtration and drying. The material was recrystallized from ethanol and methyl cellosolve repeatedly, with great loss. After seven recrystallizations, the platelets melted at 216–218°.

Anal. Calcd. for $C_{13}H_9ClN_4O_4S$: C, 44.29; H, 2.57. Found: C, 44.47; H, 2.70.

Summary

Some arylsulfonate salts of substituted benzimidazoles have been prepared by direct combination of the arylsulfonic acid and the amine.

2-Amino-5-chlorobenzimidazole has been identified as the monochlorination product of 2-aminobenzimidazole and the condensation product of *p*-chloro-*o*-phenylenediamine with cyanogen bromide.

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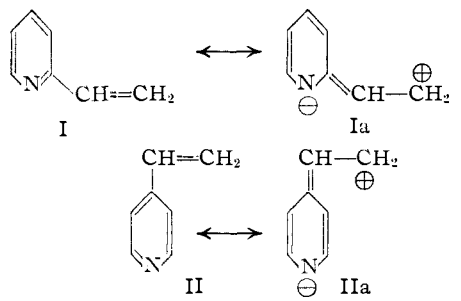
[CONTRIBUTION FROM CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

Electrophilic Reactions of 2- and 4-Vinylpyridines

BY WILLIAM E. DOERING AND RUTH ALICE N. WEIL[1]

Theoretical consideration of the electronic interaction of the pyridine nucleus with a conjugated double bond leads to the conclusion that 2-vinylpyridine (I) and 4-vinylpyridine (II) should react with nucleophilic reagents more rapidly than 3-vinylpyridine (III). The electron deficiency imposed on the α- and γ-positions of pyridine by the electronegative nitrogen inhibits substitution by electrophilic reagents, facilitates reaction with nucleophilic reagents, and would be expected to extend electron deficiency to a double bond conjugated in the α- and γ-positions. Such resonance interaction is apparent in I and Ia, II and IIa, pertinent pairs of the six resonance



structures comprising I and II. Similar resonance interaction of the double bond in III is impossible, only slight activation comparable to that in styrene[2] and involving higher energy structures with carbon bearing a negative charge being possible.[3]

Accordingly the α- or γ-pyridyl group should be classed with the carbonyl, carboxyl, carbalkoxyl, cyano, nitro and sulfonyl groups among others which activate a conjugated double bond to attack by nucleophilic reagents.[4]

No example of the predicted reaction involving vinylpyridines has been found. However, it is apparent from Vorländer's failure to add sodiomalonic ester to benzalquinaldine[5] that he has tried to realize a similar reaction, a single example of which is reported in the reaction of phenylmagnesium bromide with benzalquinaldine to give 2-(β,β-diphenyl)-ethylquinoline (with structure unproved).[6]

Of the wide variety of nucleophilic reagents that react with carbonyl compounds and α,β-unsaturated carbonyl compounds[7] a representative group has been chosen to demonstrate the general validity of the predicted reactivity of I and II. The group of reagents which react to form carbon to carbon bonds is exemplified by sodiomalonic ester, sodioacetoacetic ester and hydrogen cyanide. Diethylamine and piperidine represent the class of reagents forming carbon–nitrogen bonds; sodium ethoxide furnishes an example of the formation of a carbon–oxygen bond; and finally, sodium bisulfite exemplifies the class of reactive nucleophilic reagents giving rise to carbon–sulfur bonds.

Sodiomalonic ester reacts with I to give diethyl β-(2-pyridyl)-ethylmalonate (IV) in moderate yield. The ester is hydrolyzed to β-(2-pyridyl)-ethylmalonic acid (V), which loses carbon dioxide on heating to give γ-(2-pyridyl)-butyric acid (VI).

(1) Submitted in partial fulfilment of the requirements for the Degree, Doctor of Philosophy, in the Department of Chemistry, Columbia University. Present address: Hickrill Chemical Research Foundation, Katonah, New York.

(2) Styrene does not react with sodiomalonic ester [Herrmann and Vorländer, *Chem. Zentr.*, **70**, I, 730 (1899)] nor with sodium bisulfite, a powerful electron donor [v. Miller, *Ann.*, **189**, 340 (1877)], although with peroxide catalysis a complicated reaction occurs [Kharasch, Schenck and Mayo, THIS JOURNAL, **61**, 3092 (1939)].

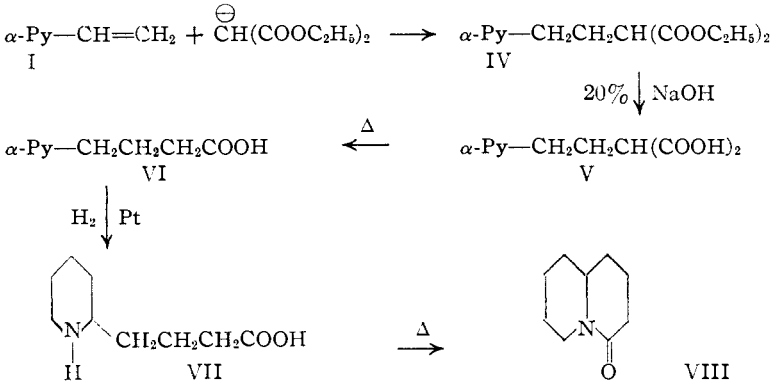
(3) In terms of the transition state theory, attack of a base at the end of the double bond in I and II leads to an activated state of lower energy, electronegative nitrogen bearing the negative charge, than is possible in similar intermediates derived from III or styrene in which carbon would bear a negative charge.

(4) Similar analysis of conjugated unsaturated quinolines, isoquinolines, acridines and other heterocycles of comparable electronic type leads to predictions analogous to those made for the vinylpyridines.

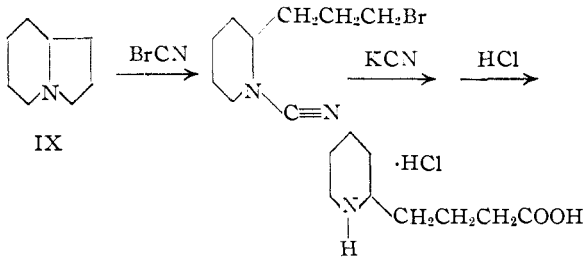
(5) Vorländer, *Ann.*, **320**, 66 (1902).

(6) Hoffmann, Farlow and Fuson, THIS JOURNAL, **55**, 2000 (1933).

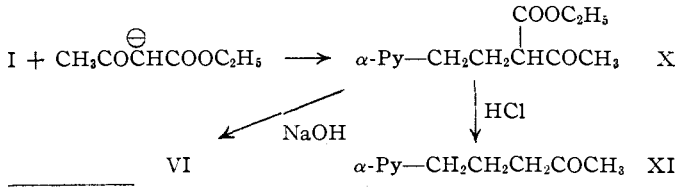
(7) Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1860.



The structures of compounds IV, V and VI follow from the conversion of VI to γ-(2-piperidyl)-butyric acid (VII), the melting point of the hydrochloride of which (191–192°) compares with that found for the hydrochloride of an acid (188–189°) prepared from indolizidine (IX).[8] Our series has been compared further with Ochiai's series by cyclizing VII to α-norlupinone (VIII), the hydrochloride of our sample (m. p. 144–146°) appearing to be identical with the sample of Ochiai, *et al.* (m. p. 146–147°).[9]



Sodioacetoacetic ester condenses with I to give an excellent yield of ethyl β-(2-pyridyl)-ethylacetoacetate (X). As a β-keto ester, X is decarboxylated on acid hydrolysis to give 1-(2-pyridyl)-pentanone-4 (XI) and is hydrolyzed by concentrated alkali to γ-(2-pyridyl)-butyric acid (VI). The additions of sodioacetoacetic ester and sodiomalonic ester therefore proceed in identical directions.



Hydrogen cyanide reacts with I in a sealed tube to give β-(2-pyridyl)-propionitrile (XII). The liquid XII has been prepared previously but has not been characterized by the preparation of a solid derivative.[10] Hydrolysis of the nitrile gives the known β-(2-pyridyl)-propionic acid, first prepared by Feist.[11]

Cyanide ion in large concentrations fails to react with 2-vinylpyridine under various conditions in contrast to the facile reaction of hydrogen cyanide. This behavior is consistent with the theory that some reactions of I with nucleophilic reagents of suitable basicity may be acid–base catalyzed in an easily observed range of *p*H.[12]

Diethylamine and I react incompletely at high temperature to give a low yield of α-diethylamino-β-(2-pyridyl)-ethane (XIII),[10,13,14] converted to a monopicrate, a dipicrate and a chloroplatinate, the melting points of which are identical with those of similar derivatives of XIII synthesized by a structurally unequivocal Mannich reaction.[14]

$$\text{I} + (C_2H_5)_2NH \longrightarrow \underset{\text{XIII}}{\alpha\text{-Py—CH}_2CH_2N(C_2H_5)_2} \longleftarrow \alpha\text{-Py—CH}_3 + CH_2{=}O + (C_2H_5)_2NH$$

The reaction of I with piperidine gives an excellent yield of N-β-(2-pyridyl)-ethylpiperidine (XIV), the structure of which is assigned by analogy with XIII. XIV forms a monopicrate, a dipicrate, and a monohydrochloride and is converted to 2-vinylpyridine when heated with one equivalent of *p*-toluenesulfonic acid.[15]

Catalyzed by sodium ethoxide, the reaction of I with ethanol proceeds slowly to give XV to which the structure, ethyl β-(2-pyridyl)-ethyl ether, is assigned by analogy with the previous reactions. An attempt to catalyze the addition of ethanol with boron trifluoride has failed, I being recovered unchanged. XV is characterized by a picrate and a deliquescent hydrochloride.

(8) Ochiai, Tsuda and Yokahoma, *Ber.*, **68**, 2291 (1935.)

(9) We have been obliged to rely on Ochiai's work to establish the structure of IV, V, and VI even though other workers have prepared identical or closely derived substances by structurally unequivocal methods. First, Clemo, Ramage and Raper [*J. Chem. Soc.*, 2959 (1932)] prepared VIII by an unequivocal synthesis involving intermediates one of which was the ethyl ester of VI. Later, Späth and Galinowsky [*Ber.*, **69**, 761 (1936)] repeated Clemo's work with the modification that they appear to have employed VI. Finally, Sugasawa and Lee [*J. Pharm. Soc. Japan*, **59**, 113 (1939)] prepared VIII by way of the ethyl esters of VI and VII. These three groups of workers reported no melting points for their solid intermediates nor did they prepare solid derivatives of their liquid intermediates or the liquid α-norlupinone. Repetition of Clemo's work for purposes of direct comparison seems superfluous since the synthesis of the same acid by Ochiai's method and by our method permits the assignment of a unique structure to VII.

(10) Walter, Hunt and Fosbinder, THIS JOURNAL, **63**, 2771 (1941).

(11) Feist, *Arch. Pharm.*, **240**, 185 (1902).

(12) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1940, pp. 329–341, discusses many examples of acid-base catalysis, of which the reaction of carbonyl compounds with semicarbazide seems closely related to the behavior of I with hydrogen cyanide.

(13) Löffler, *Ber.*, **37**, 161 (1904).

(14) Tseou Héou-Féo, *Compt. rend.*, **192**, 1242 (1931).

(15) This is an example of a general method for the preparation of olefins [Houben, "Die Methoden der organische Chemie," 3rd ed., Vol. II, Thieme, Leipzig, 1925, p. 955], the elimination presumably being facilitated by the activating effect of a pyridine nucleus on the hydrogen atoms attached to carbon atoms in the α or γ position.

α-Py—$CH_2CH_2OCH_2CH_3$ XV α-Py—$CH_2CH_2SO_3H$ XVI

Concentrated aqueous sodium bisulfite reacts rapidly, completely, and exothermically with 2-vinylpyridine[16] to give β-(2-pyridyl)-ethyl sulfonic acid (XVI). Resistance of XVI to hydrolysis both by acid and base indicates a sulfonic acid rather than a sulfite ester. The point of attachment of the sulfonic acid group is assigned by analogy.

In contrast to the remarkably rapid reaction of sodium bisulfite is the imperceptibly slow reaction of sodium sulfite. The difference is presumably due to the greater acidity of the bisulfite solution which activates I to attack by the still strongly nucleophilic bisulfite ion.[17] Because of its pronounced reactivity, behavior toward sodium bisulfite has been chosen to diagnose the reactivity of other vinylpyridines.

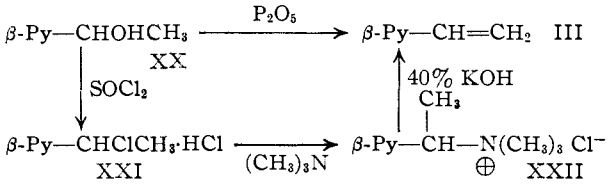
4-Vinylpyridine (II) is prepared from β-(4-pyridyl)-ethanol by the convenient method of Meisenheimer.[18] II reacts with sodium bisulfite as characteristically as does I, giving rapidly and in excellent yield a sulfonic acid which, by analogy, is assumed to be β-(4-pyridyl)-ethyl sulfonic acid (XVII). With liquid hydrogen cyanide, II re-

γ-Py—$CH_2CH_2SO_3H$ XVII γ-Py—$CH_2CH_2C{\equiv}N$ XVIII

γ-Py—CH_2CH_2COOH XIX

acts to give β-(4-pyridyl)-propionitrile (XVIII), the structure of which is proved by hydrolysis to the known β-(4-pyridyl)-propionic acid (XIX).[19] The analogous course of these two reactions of II suggests that the type of reaction established for I is also general for 4-vinylpyridine, as predicted by theory.

3-Vinylpyridine (III) has been prepared by Iddles, Lang and Gregg[20] from β-pyridylmethylcarbinol (XX).[21] Iddles, *et al.*, convert XX to the corresponding chloride hydrochloride XXI which



is dehydrochlorinated with alcoholic potassium hydroxide to give III in 18–20% yield. With this method we have encountered unresolved difficulties. The alternate method of Iddles, *et al.*, involves dehydration of XX by phosphorus pentoxide, a method which has been repeated by Woodward, Eisner and Haines[22] and by us, who have obtained crude III in 13% yield. In an effort to improve the method of preparation, XXI is converted by trimethylamine to the corresponding quaternary ammonium salt XXII, which, without isolation, gives III in 46% yield when boiled with concentrated sodium hydroxide. The picrate of III prepared in this way melts at 146.5–147.5° whereas Iddles, *et al.*,[20] and Woodward[22] report and we find m. p. 143–144° for the picrate of III prepared by the phosphorus pentoxide dehydration. The two picrates do not depress. Further to prove the identity of the two samples of III, the hydrochlorides have been compared. III hydrochloride from III prepared according to Iddles is deliquescent, soluble in water, soluble in absolute ethanol, and on crystallization from dry acetone melts at 118–120°.[23] This hydrochloride is identical with the purer hydrochloride obtained from III prepared from XXII.

3-Vinylpyridine is found to be unreactive toward concentrated aqueous sodium bisulfite in striking contrast to 2- and 4-vinylpyridines which undergo their most rapid additions with this reagent.

The theoretical prediction that olefinic groups at the α and γ carbon atoms in pyridine should show electrophilic properties at the end of the double bond has been substantiated while the single reaction attempted with a β-vinyl compound has failed.

Experimental[24]

Diethyl β-(2-Pyridyl)-ethylmalonate (IV).—An absolute ethanolic solution of sodium (3 g.), 2-vinylpyridine (44 g.), diethyl malonate (100 g.) and hydroquinone (0.1 g.) was refluxed for six hours. Ether extraction of the acidified residue remaining after removal of the alcohol *in vacuo* separated unreacted diethyl malonate. Treatment of the acidic aqueous solution with excess 5 *N* sodium hydroxide precipitated an oil which was extracted with ether. After being washed with water, shaken with concentrated sodium bisulfite and charcoal for one hour, and filtered, the ethereal solution was concentrated to a pale yellow oil weighing 37.75 g. (33% yield); b. p. 125–144° at 0.15–0.3 mm.

Anal. Calcd. for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22. Found: C, 63.65; H, 7.36.

In an alternate procedure, freshly distilled 2-vinylpyridine (5.25 g.) was added to a solution of sodium (0.37 g.) in diethyl malonate (16.0 g.). After refluxing for six hours, the reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The oil which separated on treating the aqueous solution with excess 5 *N* alkali was extracted with ether, recovered from the dried ethereal solution by evaporation, and distilled to give 3.1 g. of recovered 2-vinylpyridine and 2.6 g. of

(16) The reaction is useful for effecting the quantitative separation of unreacted 2-vinylpyridine from reaction products which are extractable from water.

(17) We are indebted to Professor L. P. Hammett for his suggestions concerning this reaction.

(18) Meisenheimer, *Ann.*, **420**, 199 (1920).

(19) Stevens and Beutel, THIS JOURNAL, **65**, 449 (1943).

(20) Iddles, Lang and Gregg, *ibid.*, **59**, 1945 (1937).

(21) Strong and McElvain, *ibid.*, **55**, 816 (1933).

(22) C. F. Woodward, Eisner and Haines, *ibid.*, **66**, 911 (1944).

(23) Iddles, *et al.*,[20] report 3-vinylpyridine hydrochloride to be insoluble in water, crystallizable from absolute ethanol, and to melt at 114–115°. They report a mercuric chloride addition product, m. p. 145–150°, whereas we find the decomposition point to be above 250°.

(24) Microanalyses were performed by the Misses F. Marx, L. May and L. Baker. Melting points are corrected. The purity of the 2-vinylpyridine, obtained from Reilly Tar and Chemical Corporation, was confirmed by boiling point and quantitative conversion to the picrate.

β-(2-pyridyl)-ethylmalonate (84% of theoretical yield based on 2-vinylpyridine recovered).

β-(2-Pyridyl)-ethylmalonic Acid (V).—The reaction mixture obtained by refluxing an excess of 5 *N* sodium hydroxide with crude diethyl β-(2-pyridyl)-ethylmalonate (37.75 g.) was extracted with ether, acidified with hydrochloric acid, and cooled. A first crop of needles (14.25 g.) was collected; a second crop (6.5 g.) was obtained from the concentrated mother liquor. Evaporation of the second mother liquor to dryness left a mixture from which additional product (3.25 g.) was obtained by leaching with 95% ethanol. The crude β-(2-pyridyl)-ethylmalonic acid (81% yield) was recrystallized from water and from absolute ethanol; m. p. 138° with gas evolution.

Anal. Calcd. for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30. Found: C, 57.29; H, 5.14.

β-(2-Pyridyl)-ethylmalonic Acid Hydrochloride.—In another procedure, the hydrolysis product was saturated with hydrogen chloride gas. The precipitated sodium chloride was filtered from the acidic solution which was then evaporated to dryness leaving a residue which was extracted with a small amount of boiling absolute alcohol. On cooling or diluting with ether, the filtered solution deposited V hydrochloride as needles; m. p. 80° with evolution of gas, after being dried *in vacuo* at room temperature.

Anal. Calcd. for $C_{10}H_{12}O_4NCl \cdot H_2O$: C, 45.54; H, 5.35. Found: C, 45.73; H, 5.44.

γ-(2-Pyridyl)-butyric Acid (VI).—V (11.2 g.) was decarboxylated at 160°. The benzene solution of the dark reaction product, refluxed with charcoal for a few minutes and filtered, deposited on cooling large colorless crystals (7.5 g.) of γ-(2-pyridyl)-butyric acid, m. p. 84–85°.

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.43; H, 6.71. Found: C, 65.39; H, 6.60.

γ-(2-Pyridyl)-butyric Acid Hydrochloride.—Upon heating V hydrochloride, carbon dioxide (identified as calcium carbonate) was evolved vigorously. The product, VI hydrochloride, was recrystallized from water and absolute ethanol; m. p. 111.5–112°.

Anal. Calcd. for $C_9H_{12}O_2NCl$: C, 53.60; H, 6.00. Found: C, 53.45; H, 5.96.

γ-(2-Piperidyl)-butyric Acid Hydrochloride.—Dissolved in 100 cc. of 5% hydrochloric acid, 2.0 g. of VI was hydrogenated in an Adams–Parr apparatus with 0.09 g. of platinum oxide catalyst.[25] The filtered solution was evaporated almost to dryness and on being diluted with acetone deposited needles of VII hydrochloride in 97% yield. Recrystallized from water and acetone, the hydrochloride had an m. p. 191–192°, whereas Ochiai, *et al.*,[8] reported 194.5–195°.

Anal. Calcd. for $C_9H_{18}O_2NCl$: C, 52.04; H, 8.73. Found: C, 52.47; H, 8.77.

γ-(2-Piperidyl)-butyric Acid (VII).—An aqueous solution of 1.56 g. of VII hydrochloride was neutralized with sodium hydroxide and evaporated almost to dryness. The product VII, freed of sodium chloride by leaching with benzene and absolute ethanol, was obtained in 99% yield and was recrystallized from absolute ethanol; m. p. 170–171° (dec.).

Anal. Calcd. for $C_9H_{17}O_2N$: C, 63.12; H, 10.01. Found: C, 62.61; H, 10.07.

α-Norlupinone (VIII) Hydrochloride.—When 1.03 g. of VII was heated in a molecular still under reduced pressure at 168°, VIII, contaminated with starting material, distilled. Pure α-norlupinone obtained colorless on redistillation was converted by hydrogen chloride to a deliquescent hydrochloride which, after crystallization from benzene, melted at 144–146°. Ochiai, *et al.*,[8] reported m. p. 146–147°.

Anal. Calcd. for $C_9H_{16}ONCl$: C, 56.98; H, 8.50. Found: C, 56.73; H, 8.57.

(25) Späth and Galinowsky, *Ber.*, **69**, 761 (1936).

Ethyl β-(2-Pyridyl)-ethylacetoacetate (X).—A solution of 2-vinylpyridine (I) (10.5 g.) in ethyl acetoacetate (26 g.) containing sodium (0.3 g.) was refluxed for six hours. The dark red oil which precipitated on addition of water and acidification to *p*H 3 was removed by ether extraction. Addition of sodium carbonate to the acidic solution precipitated the crude product, the ethereal solution of which was dried and concentrated. Distillation at 1.3 mm. of the crude dark liquid gave recovered I (1.5 g.) and yellow X, b. p. 135–145° (13.7 g., 58.2% yield).

Anal. Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.29. Found: C, 66.60; H, 7.41.

γ-(2-Pyridyl)-butyric Acid (VI).—Having been refluxed for eight hours with potassium hydroxide (4.0 g.) an absolute ethanolic solution (4 cc.) of X (2.0 g.) was diluted with water, freed of ethanol by distillation *in vacuo*, extracted with ether to remove 0.79 g. of non-acidic material, acidified with concentrated hydrochloric acid, and finally evaporated to dryness. After being heated to 150° to decarboxylate β-(2-pyridyl)-ethylacetoacetic acid, the residue was dissolved in 50% potassium hydroxide, separated from 0.3 g. of non-acidic material by ether extraction, and brought to *p*H 5 with hydrochloric acid. The filtered acidic solution was evaporated to dryness. The benzene extract of the residue was treated with charcoal, filtered, and evaporated to dryness giving 0.35 g. of crude VI, m. p. 84–85° after being recrystallized from benzene. The m. p. was not depressed upon admixture with a sample of VI prepared from V.

1-(2-Pyridyl)-pentanone-4 (XI).—A solution of 3.0 g. of X in 15 cc. of 20% hydrochloric acid was refluxed for four hours, brought to *p*H 10 with sodium hydroxide, and concentrated *in vacuo* until two liquid phases appeared. Ether extraction gave 1.75 g. (84%) of crude XI, purified for analysis by evaporative distillation in a molecular still at 114°.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.37; H, 8.00; N, 8.72.

The *picrate*, yellow needles, was crystallized from acetone; m. p. 111.0–111.5°.

Anal. Calcd. for $C_{16}H_{16}O_8N_4$: C, 48.98; H, 4.11. Found: C, 48.85; H, 4.37.

The *2,4-dinitrophenylhydrazone hydrochloride*, glistening orange needles, was crystallized from absolute ethanol; m. p. 189–190°.

Anal. Calcd. for $C_{16}H_{18}O_4N_5Cl$: C, 50.69; H, 4.78; N, 18.44. Found: C, 50.57; H, 4.47; N, 18.42.

The *oxime monohydrate* was prepared by refluxing a solution of XI (1.0 g.), hydroxylamine hydrochloride (1.0 g.), and potassium hydroxide (4.0 g.) in absolute ethanol (20 cc.) for two hours. The oxime was isolated by dilution with 150 cc. of water, removal of alcohol under reduced pressure, precipitation with carbon dioxide, and extraction with ether. Crystallized from ethanol–water, XI oxime monohydrate melted at 55–56° (0.72 g., 60% yield). When dried *in vacuo* the oxime liquefied, but resolidified on standing in air.

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: C, 61.20; H, 8.22. Found: C, 61.24; H, 8.45.

β-(2-Pyridyl)-propionitrile (XII).—Heated in a sealed tube for twenty hours at 77°, I (0.1 mole) and hydrogen cyanide (0.2 mole) gave a black reaction mixture. The filtered ether extract was washed with water, dried and concentrated to give 7.9 g. of crude product. On distillation pure XII, b. p. 93–96° at 1.25–1.5 mm., was obtained (5.5 g., 42% yield).

Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10. Found: C, 72.80; H, 6.11.

The *picrate*, pale yellow leaflets, was crystallized from water, m. p. 140–142° (dec.).

Anal. Calcd. for $C_{14}H_{11}O_7N_5$: C, 46.54; H, 3.07. Found: C, 46.72; H, 3.10.

β-(2-Pyridyl)-propionic Acid.—The solution obtained by refluxing 1.0 g. of XII with excess dilute hydrochloric acid was neutralized and evaporated to dryness. From

the filtered benzene extract of the residue, 0.85 g. (75%) of pure β-(2-pyridyl)-propionic acid crystallized; m. p. 141° (Fiest[11] reported 141°).

Anal. Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00. Found: C, 63.81; H, 5.90.

2-(β-Diethylamino)-ethylpyridine (XIII).—The red liquid resulting when 6.5 g. of I and 13 cc. of diethylamine were heated in a sealed tube for fifteen hours at 165° was distilled *in vacuo* to give 2.22 g. of recovered I and 0.64 g. of XIII, b. p. 79–80° at 2 mm. An additional 0.22 g. obtained on evaporative distillation of the residual tar raised the yield to 12% based on I consumed.

The yellow *monopicrate* was obtained in 97% yield by crystallizing equivalents of XIII and picric acid from ethanol; m. p. 97–98°. Löffler[13] reported the monopicrate, m. p. 96–97°.

Anal. Calcd. for $C_{17}H_{21}O_7N_5$: C, 50.12; H, 5.20. Found: C, 50.13; H, 5.30.

The yellow *dipicrate* formed from equivalents of picric acid and the monopicrate was crystallized from water–acetone; m. p. 164–164.5°. Löffler[13] reported the dipicrate, m. p. 163–164°.

Anal. Calcd. for $C_{23}H_{24}O_{14}N_8$: C, 43.40; H, 3.80. Found: C, 43.55; H, 4.22.

The *chloroplatinate*, crystallized from ethanol, began darkening at 205°, finally decomposing at 215–222°.

Anal. Calcd. for $C_{11}H_{20}N_2Cl_6Pt$: Pt, 33.2. Found: Pt, 32.8.

N-β-(2-Pyridyl)-ethylpiperidine (XIV).—Distillation of the product of refluxing 10.5 g. of I with 17 g. of piperidine for six hours gave 16.5 g. of XIV (86% yield) b. p. 121–127° at 4 mm., 108° at 1 mm. XIV was sparingly soluble in water.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53. Found: C, 75.83; H, 9.48.

The hygroscopic *hydrochloride* was crystallized from water; m. p. 173°.

Anal. Calcd. for $C_{12}H_{19}N_2Cl$: C, 63.56; H, 8.45. Found: C, 63.27; H, 8.98.

The *monopicrate* was crystallized from acetone; m. p. 126–127°.

Anal. Calcd. for $C_{18}H_{21}O_7N_5$: C, 51.55; H, 5.05. Found: C, 51.52; H, 5.11.

The orange *dipicrate* crystallized from acetone; m. p. 159–160°.

Anal. Calcd. for $C_{24}H_{23}O_{14}N_8$: C, 44.45; H, 3.73. Found: C, 44.55; H, 3.74.

When a mixture of 5.0 g. of XIV and 5.1 g. of *p*-toluenesulfonic acid was heated to 175° a mixture of water and I distilled, the latter being separated by ether extraction and isolated in 66% yield as the picrate. Recrystallized from water and alcohol, *2-vinylpyridine picrate* melted at 157.5–158.5°.

Anal. Calcd. for $C_{13}H_{10}O_7N_4$: C, 46.71; H, 3.02; N, 16.75. Found; C, 46.55; H, 3.05.

Authentic I picrate crystallized from ethanol; m. p. 157.5–158.5°.

Anal. Found: C, 46.55; H, 3.02; N, 16.66.

A mixture of the two picrates showed no depression of m. p.

β-(2-Pyridyl)-ethyl Ethyl Ether (XV).—A solution of 2.50 g. of sodium in 250 cc. of absolute ethanol containing 21.0 g. of I was refluxed for fourteen hours, treated with excess hydrochloric acid, and evaporated to dryness. An ether extract of the suspension of the residue in sodium hydroxide solution was dried, concentrated and separated into three fractions by distillation: (a) 9.88 g., b. p. 65–75° (25 mm.); (b) 3.18 g., b. p. 75–104° (25 mm.); (c) 7.46 g., b. p. 104–107° (25 mm.). An additional 0.40 g., identical with (c), was obtained by extracting (b) with concentrated sodium bisulfite and raised the total yield of XV to 25% or 65% if based on I consumed. Pure XV was obtained by redistillation of material treated with sodium bisulfite; b. p. 74–75° (3 mm.) or 106–107° (19 mm.).

Anal. Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.28; H, 8.93; N, 8.67.

XV forms a strongly deliquescent *hydrochloride*, m. p. 83.5–84.5°, which can, when dry, be crystallized from dry acetone.

The *picrate* crystallized from absolute ethanol in heavy needles, m. p. 105–106°, *ca.* 85° after resolidification.

Anal. Calcd. for $C_{15}H_{16}O_8N_4$: C, 47.37; H, 4.24. Found: C, 47.40; H, 3.91.

From the reaction of boron trifluoride etherate (0.2 mole) and I (0.2 mole) in 200 cc. of absolute ethanol at reflux for four hours, about 80% I was recovered.

β-(2-Pyridyl)-ethyl Sulfonic Acid (XVI).—On shaking a suspension of 12 cc. of I in 25 cc. of water with 25 cc. of saturated sodium bisulfite, the temperature rose from 18° to 60°. The resulting homogeneous solution was treated with concentrated hydrochloric acid and evaporated to dryness. The 90% alcoholic extract of the residue deposited needles of XVI, m. p. 265–266.5° (dec.) after darkening at about 245°. Working the mother liquor raised the total yield to 97%.

Anal. Calcd. for $C_7H_9O_3NS$: C, 44.91; H, 4.85. Found: C, 44.85; H, 4.95.

I (5.0 g.), shaken for one hour with saturated sodium sulfite, was recovered in 95% of the theoretical amount.

β-(4-Pyridyl)-ethyl Sulfonic Acid (XVII).—4-Vinylpyridine (II) (0.5 g.), prepared from β-(4-pyridyl)-ethanol by the method of Meisenheimer,[18] was suspended in 1 cc. of water and shaken with 1 cc. of saturated sodium bisulfite to give a rapid exothermic reaction. The solution was made strongly acidic with concentrated hydrochloric acid and evaporated to dryness. The residue was dissolved in concentrated hydrochloric acid, filtered from sodium chloride, evaporated to dryness, and leached with boiling 95% ethanol. XVII crystallized in clusters of needles and after two recrystallizations melted at 284–285° (dec.) with darkening beginning at 245°. The yield was 0.73 g. (86%).

Anal. Calcd. for $C_7H_9O_3NS$: C, 44.91; H, 4.85; S, 17.12. Found: C, 44.64; H, 4.87; S, 17.81.

β-(4-Pyridyl)-propionitrile (XVIII).—The cake of tar and carbon obtained when II (3 g., 0.035 mole) was heated for two hours at 145° in a sealed tube with hydrogen cyanide (0.2 mole) was extracted with ether. The ethereal solution was filtered, dried with potassium hydroxide, and concentrated *in vacuo* to yield 1.85 g. (40%) of yellow liquid which was evaporatively distilled at 103° at 20–30 mm. giving 1.21 g. (26%) of colorless XVIII.

Anal. Calcd. for $C_8H_8N_2$: C, 72.68; H, 6.10; N, 21.20. Found: C, 72.60; H, 6.20; N, 21.13.

The yellow *picrate* crystallized from ethanol; m. p. 171–171.5°.

Anal. Calcd. for $C_{14}H_{11}O_7N_5$: C, 46.54; H, 3.07. Found: C, 46.55; H, 3.14.

β-(4-Pyridyl)-propionic Acid Hydrochloride.—XVIII was hydrolyzed with boiling 20% sodium hydroxide and isolated as the hydrochloride by treating the reaction mixture with concentrated hydrochloric acid, evaporating to dryness, and leaching with absolute ethanol. Recrystallized from absolute ethanol–ether, *XIX hydrochloride* was obtained in 80% yield; m. p. 202–204°.

Anal. Calcd. for $C_8H_{10}O_2NCl$: C, 51.21; H, 5.37. Found: C, 51.33; H, 5.02.

Free *β-(4-pyridyl)-propionic acid* (XIX) was obtained quantitatively by neutralizing the hydrochloride and crystallizing from benzene; m. p. *ca.* 220°.

Anal. Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00. Found: C, 63.38; H, 6.17.

3-Vinylpyridine (III).—III was prepared by the method of Iddles, *et al.*,[20] by heating 5.00 g. of β-pyridylmethylcarbinol made according to Strong and McElwain[21] with 30 g. of phosphorus pentoxide in boiling xylene for three

hours. Crude III obtained in 13% yield (0.56 g.) was evaporatively distilled to give a purer product (0.28 g., 6.5%), from which a *picrate, ca.* 1 g. soluble in 100 cc. of boiling benzene, was obtained, m. p. 140–143° (on recrystallization, m. p. 143–144°). Occasionally a rapidly cooled benzene solution of the picrate deposited fluffy needles which gradually changed to heavier needles.

Treatment of III with dry hydrogen chloride gave an oil which was miscible with water and cold ethanol in contrast to the report of Iddles, *et al.*[20] A filtered solution of the dried, crude hydrochloride in acetone deposited on concentration prismatic needles of a deliquescent hydrochloride, m. p. 118–120°. Iddles[20] reported a water-insoluble hydrochloride, m. p. 114–115°.

In a different preparation, 5.0 g. of β-pyridylmethylcarbinol (XX) was converted to α-(3-pyridyl)-ethyl chloride hydrochloride (XXI) with 10 cc. of purified thionyl chloride.[26] After removal of excess reagent *in vacuo*, addition of water, and filtration with the aid of charcoal, the red solution was evaporated to dryness, treated with absolute ethanol, and evaporated to dryness again. After several recrystallizations from dry acetone colorless XXI was obtained; m. p. 109–110°; deliquescent; easily sublimable.

A mixture of 2.60 g. of crude XXI and 4 cc. of trimethylamine[27] in methanol was heated ten hours in a sealed tube at 125°. A solution of the solvent-free residue in 8% sodium hydroxide was thrice extracted with ether (0.66 g. removed). After the addition of sufficient sodium hydroxide to raise the concentration to 30–40%, the solution of the quaternary salt XXII was boiled, 0.70 g. of crude III being extractable from the steam distillate with ether. Evaporative distillation gave 0.58 g. of purer III (38% yield).

The *picrate* of this sample crystallized from benzene, m. p. 146.5–147.5°; m. p. 143–145° in admixture with the picrate prepared above according to Iddles, *et al.*[20]

(26) Cottle, THIS JOURNAL, **68**, 1380 (1946).

(27) Trimethylamine was purified by treating with phenyl isocyanate.

Anal. Calcd. for $C_{13}H_{10}O_7N_4$: C, 46.71; H, 3.02; N, 16.75. Found: C, 46.67; H, 3.10; N, 16.71.

The *hydrochloride* was identical with III hydrochloride prepared above according to Iddles[20] (mixed m. p. 119–121°).

The *mercurichloride* of III was crystallized from absolute ethanol; darkened but did not melt when heated to 250°. Iddles reported m. p. 145–150°.

In another preparation of III *via* XXII in which inadequately purified trimethylamine was used, the large amount of oil extracted from the alkaline solution of the reaction product was evaporatively distilled at 60° and 25 mm., 2.68 g. of *α-(3-pyridyl)-ethyldimethylamine* being obtained from 5.00 g. of XX.

The *monopicrate* crystallized from water; m. p. 147–148°; mixed m. p. with III picrate, 130–180°.

Anal. Calcd. for $C_{15}H_{17}O_7N_5$: C, 47.49; H, 4.52; N, 18.46. Found: C, 47.76; H, 4.85; N, 18.13.

The *dipicrate*, very sparingly soluble in organic solvents, crystallized from water (1 g./100 cc.); m. p. 223–224°.

Anal. Calcd. for $C_{21}H_{20}O_{14}N_8$: C, 41.45; H, 3.31. Found: C, 42.16; H, 3.66.

The deliquescent *monohydrochloride* crystallized from absolute ethanol in large prismatic needles, m. p. 220–221°.

Anal. Calcd. for $C_9H_{15}N_2Cl$: N, 15.01; Cl, 18.95. Found: N, 15.08; Cl, 18.50.

After having been shaken with a saturated solution of aqueous sodium bisulfite for one hour, 300 mg. of III was recovered in 78% yield as the picrate (740 mg.).

Summary

In accordance with resonance theory, 2- and 4-vinylpyridines react with a variety of electron donating reagents. 3-Vinylpyridine fails to react with sodium bisulfite.

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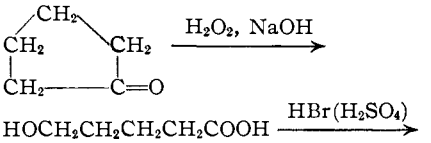
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Prolyl and Phthalyl Derivatives of Enantiomorphs of Valine and Leucine[1,2]

BY MARGUERITE FLING,[3] FREDERICK N. MINARD[4] AND SIDNEY W. FOX

The present report concerns the preparation of derivatives of D- and L-amino acids. Gramicidin[4a] and penicillin[5] have been shown to be derivatives of D-amino acids; D-amino acids inhibit bacterial growth under experimental conditions,[6–8] and the D-amino acid residue is one of a number of critical structural features in penicillin.[9] Attempts to synthesize some powerful D-amino acid derivatives as conceivable models of antibiotics are therefore of interest.

Partly since gramicidin contains no free primary amino groups,[10] prolyl derivatives of D- and L-forms of valine and leucine were prepared. These were obtained by the same general procedure employed by Fischer and Suzuki,[11] except that the necessary α,δ-dibromovaleric acid was made by a more direct synthesis. The reactions for the synthesis of these peptides are illustrated below.



(1) Journal Paper No. J-1458 of the Iowa Agricultural Experiment Station, Project 897, in coöperation with the Veterinary Research Institute, and Project 980.

(2) Taken in part from the thesis submitted by Marguerite Fling to the Graduate School of Iowa State College in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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(4a) Lipmann, Hotchkiss and Dubos, *J. Biol. Chem.*, **141**, 163 (1941).

(5) Committee on Medical Research, O. S. R. D., Washington, and the Medical Research Council, London, *Science*, **102**, 627 (1945).

(6) Fox, Fling, and Bollenback, *J. Biol. Chem.*, **155**, 465 (1944).

(7) Fling and Fox, *ibid.*, **160**, 329 (1945).

(8) Fox, Fling, Kobayashi and Minard, *Proc. Fed. Am. Soc. Exp. Biol.*, **6**, 253 (1947).

(9) du Vigneaud, Carpenter, Holley, Livermore and Rachele, *Science*, **104**, 431 (1946).

(10) Hotchkiss, *J. Biol. Chem.*, **141**, 171 (1941).

(11) Fischer and Suzuki, *Ber.*, **37**, 2842 (1904).