[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Heterocyclic Compounds. V. β-Pyridyl β-Styryl Ketone[1]

BY MILTON C. KLOETZEL AND FRANCIS L. CHUBB

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The base-catalyzed condensation of benzaldehyde with 3-acetylpyridine can be made to yield β-pyridyl β-styryl ketone (I) or 1,3,5-trinicotinoyl-2,4-diphenylpentane (VI). Michael type condensations of I with nitroalkanes, alkyl malonates, fluorene and 9-carboethoxyfluorene have been effected. The reaction with fluorene produced mixtures of the expected adduct XII and a trimolecular product. However the diethylamine-catalyzed condensation of I with 9-carboethoxyfluorene afforded a quantitative yield of the normal adduct XIII.

Reduction of γ-nitro ketones II–V by methods which have been explored in our laboratory[2,3] might be expected to yield a series of pyrrolidines and pyrrolines related to nicotine. Anticipating such studies, we have prepared the requisite β-pyridyl β-styryl ketone (I) and have investigated some of its reactions, including its conversion to the nitro ketones II–V.

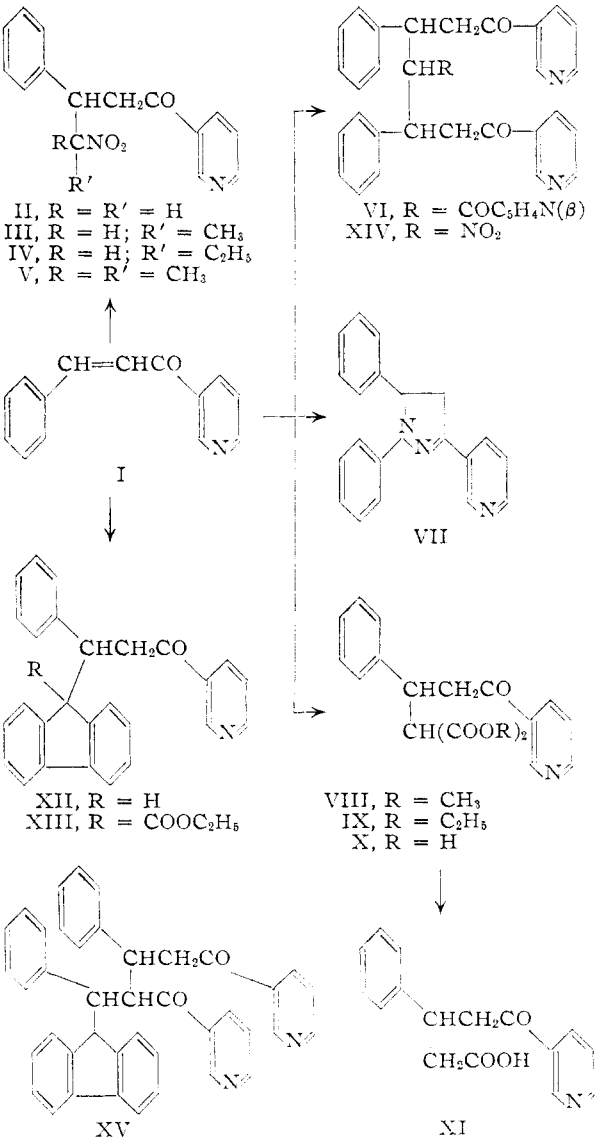
Ketone I was obtained in 92% yield when aqueous sodium hydroxide solution was added slowly to an equimolar mixture of benzaldehyde and 3-acetylpyridine in a large volume of water. Under more strongly basic conditions the condensation was more complex and yielded 1,3,5-trinicotinoyl-2,4-diphenylpentane (VI).[4] Effected in ethanol solution in the presence of benzyltrimethylammonium hydroxide, the reaction afforded two diastereoisomers of VI.

β-Pyridyl β-styryl ketone (I) reacted with phenylhydrazine in boiling acetic acid or in ethanol at room temperature under the catalytic influence of benzyltrimethylammonium hydroxide to yield the same product. Since hot acetic acid is known[5,6] to rearrange phenylhydrazones of α,β-unsaturated ketones, this substance has been designated 1,5-diphenyl-3-(3-pyridyl)-pyrazoline (VII). In dilute ethanolic acetic acid at room temperature, ketone I reacted with two molecules of phenylhydrazine, presumably producing the phenylhydrazone of 2-phenylhydrazino-2-phenylethyl 3-pyridyl ketone.

Diethylamine effectively catalyzed the Michael addition of nitro alkanes to β-pyridyl β-styryl ketone (I), affording nitro ketones II–V in 73–95% yields. Both nitroethane and 1-nitropropane yielded mixtures of diastereoisomeric nitro ketones.

The use of a 10:1 molar ratio of nitromethane to β-pyridyl β-styryl ketone effectively suppressed diketone formation and permitted the isolation of II in 75% yield. However, two diastereoisomers of 1,5-dinicotinoyl-3-nitro-2,4-diphenylpentane (XIV) resulted when the unsaturated ketone was employed in excess.

Diethylamine likewise promoted the reaction of β-pyridyl β-styryl ketone (I) with methyl and ethyl malonate to form adducts VIII and IX, respectively. These were hydrolyzed to the corresponding malonic acid X, which subsequently was decarboxylated at 180° to produce 5-oxo-3-phenyl-5-(3-pyridyl)-pentanoic acid (XI).



When fluorene and β-pyridyl β-styryl ketone (I), in molar ratio of 2 to 1, were allowed to react in aqueous pyridine containing sodium hydroxide (conditions which afforded[7] a quantitative yield of adduct in the case of benzalacetophenone), there was obtained 39% of the expected adduct XII, to-

(1) Abstracted from a portion of the Ph.D. dissertation of Francis L. Chubb.

(2) M. C. Kloetzel, THIS JOURNAL, **69**, 2271 (1947).

(3) M. C. Kloetzel, J. L. Pinkus and E. M. Washburn, *ibid.*, **79**, 4222 (1957).

(4) Compare (a) St. v. Kostanecki and G. Rossbach, *Ber.*, **29**, 1488 (1896); (b) C. Engler and A. Engler, *ibid.*, **35**, 4061 (1902); (c) D. B. Andrews and R. Connor, THIS JOURNAL, **57**, 895 (1935).

(5) K. Auwers and H. Voss, *Ber.*, **42**, 4411 (1909).

(6) L. C. Raiford and H. L. Davis, THIS JOURNAL, **50**, 156 (1928).

(7) L. A. Pinck and G. E. Hilbert, *ibid.*, **68**, 2014 (1946).

gether with 55% of a trimolecular condensation product. The yield of XII was increased to 62% when the molar ratio of fluorene to I was 10 to 1 but still 11% of the trimolecular product was formed.

Neither 9-ethylfluorene nor 9-benzylfluorene will add to the highly reactive acceptor, acrylonitrile, in the presence of a strongly basic catalyst.[8] Therefore it is not likely that our trimolecular condensation product results from addition of a second molecule of I at the 9-position of the fluorene nucleus in XII. Accordingly, XV is proposed as the more probable structure of the trimolecular product.

To circumvent the formation of trimolecular products in the Michael condensation, we examined the reaction of I with the more reactive addendum, 9-carboethoxyfluorene. 9-Carboalkoxyfluorenes have been reported to add to unsaturated nitriles[9,10] or ketones[11] but always in the presence of potassium hydroxide. We now have found that the condensation of 9-carboethoxyfluorene with β-pyridyl β-styryl ketone (I) is efficiently catalyzed by diethylamine and affords a quantitative yield of adduct XIII.

Experimental[12]

Ethyl nicotinate was obtained consistently in yields of 67%[13] by the following procedure. A mixture of nicotinic acid (200 g.), absolute ethanol (400 ml.) and sulfuric acid (120 ml.) was heated to reflux for 3 hours and then concentrated by distillation of 200 ml. of ethanol. The cooled solution was added slowly, with stirring, to 2000 g. of 20% aqueous sodium carbonate and the ester was extracted with ether. Distillation of the dried extract yielded 166 g. of ester, b.p. 132–133° at 14 mm.

3-Acetylpyridine.—Rapid evolution of hydrogen began soon after ethyl nicotinate (50 g.), ethyl acetate (44 g.) and sodium hydride (12 g.) were mixed by stirring under a nitrogen atmosphere. After the initial violence of the reaction had subsided the mixture was warmed on a steam-bath for 3 hours and excess sodium hydride was then decomposed by the cautious addition of 10 ml. of ethanol and 200 ml. of water. Concentrated hydrochloric acid (100 ml.) was added to the cooled solution and the mixture was then heated to reflux for 2 hours. After removal of excess ethyl acetate by distillation, the cooled solution was made alkaline by addition of 50% aqueous sodium hydroxide and the precipitated oil was extracted with ether. Distillation of the dried extract under reduced pressure yielded 33.6 g. (84%) of colorless 3-acetylpyridine, b.p. 80° at 2–3 mm.

A similar condensation was effected when a mixture of ethyl nicotinate (198 g.), ethyl acetate (176 g.) and commercial sodium methoxide (102 g.) was heated on a steam-bath for 3 hours with continuous stirring. To the cooled mixture was added 800 ml. of water and 400 ml. of concentrated acid and the afore-described procedure was followed; yield 130 g. (82%) of 3-acetylpyridine.

The use of sodium ethoxide to effect this condensation afforded 81–85% yields of 3-acetylpyridine.[13,14]

β-Pyridyl β-styryl ketone (I) was obtained in 92% yield from the reaction of 3-acetylpyridine with benzaldehyde, following a procedure described by Engler and Engler[4b] for the preparation of the α-pyridyl isomer. The product, after distillation under reduced pressure, separated from ethanol or heptane in green-yellow needles, m.p. 84–85°.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30. Found: C, 80.49; H, 5.27.

A picrate was formed in quantitative yield when equimolar ethanol solutions of ketone I and picric acid were mixed, and separated from ethanol in yellow needles, m.p. 199–200°.

Anal. Calcd. for $C_{20}H_{14}N_4O_8$: C, 54.79; H, 3.22. Found: C, 54.74; H, 3.56.

1,3,5-Trinicotinoyl-2,4-diphenylpentane (VI).—A solution of 3-acetylpyridine (6.0 g.) and benzaldehyde (5.4 g.) in ethanol (25 ml.), to which had been added 0.5 ml. of 40% benzyltrimethylammonium hydroxide solution, was allowed to stand at room temperature for 2 weeks. The solid precipitate was separated into two fractions by recrystallization from ethanol. The higher melting stereoisomer of VI (3.1 g.) formed colorless needles, m.p. 240–241°.

Anal. Calcd. for $C_{35}H_{29}N_3O_3$: N, 7.79. Found: N, 7.84.

A second isomer of VI (0.7 g.) also formed colorless needles but melted at 203–205°.

Anal. Calcd. for $C_{35}H_{29}N_3O_3$: N, 7.79. Found: N, 7.61.

When 10.8 g. of benzaldehyde and 12.1 g. of 3-acetylpyridine were allowed to react under the conditions employed by Kohler and Chadwell[15] for the preparation of benzalacetophenone, a yellow gum was obtained. Recrystallization from benzene afforded 8.1 g. of the stereoisomer of VI melting at 203–205°.

Reaction of β-Pyridyl β-Styryl Ketone with Phenylhydrazine.—Mild evolution of heat occurred when 0.1 ml. of 40% benzyltrimethylammonium hydroxide solution was added to a solution of ketone I (5.2 g.) and phenylhydrazine (2.7 g.) in ethanol (10 ml.). The solid which separated when the solution was allowed to stand for 12 hours at room temperature was crystallized from ethanol and afforded 5.4 g. (73%) of **1,5-diphenyl-3-(3-pyridyl)-pyrazoline** (VII) in green-yellow needles, m.p. 126–128°.

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.23; H, 5.72. Found: C, 80.18; H, 5.79.

The same compound was formed when a mixture of β-pyridyl β-styryl ketone (5.2 g.), phenylhydrazine (2.7 g.) and acetic acid (25 ml.) was heated to reflux for 2 hours. The solvent was evaporated under reduced pressure and 6 ml. of concentrated hydrochloric acid was added. Crystallization of the residue from aqueous ethanol yielded the pyrazoline hydrochloride (3.9 g.) in yellow plates, m.p. 224–240° dec., from which VII was obtained by neutralization in ethanol with dilute aqueous sodium hydroxide.

When equimolar quantities of VII and picric acid were combined in hot ethanol, the **picrate of 1,5-diphenyl-3-(3-pyridyl)-pyrazoline** was obtained in quantitative yield. This substance sometimes separated from ethanol in orange-red leaflets, m.p. 195–196°, but from a mixture of ethanol and acetone in red crystals, m.p. 193–194°.

Anal. Calcd. for $C_{26}H_{20}N_6O_7$: C, 59.09; H, 3.83. Found: C, 58.96; H, 4.18.

Upon standing at room temperature for 3 hours, a solution of ketone I (1 g.), phenylhydrazine (600 mg.) and acetic acid (0.15 ml.) in 95% ethanol (10 ml.) deposited 600 mg. of crystalline solid, m.p. 145–148°. Several crystallizations from ethanol raised the m.p. of the presumed phenylhydrazone of 2-phenylhydrazino-2-phenylethyl 3-pyridyl ketone to 153–155°.

Anal. Calcd. for $C_{26}H_{25}N_5$: C, 76.62; H, 6.18. Found: C, 76.42; H, 6.35.

Reaction of β-Pyridyl β-Styryl Ketone with Nitro Alkanes. (a) With Nitromethane.—When a mixture of ketone I (10.4 g.), nitromethane (61 g.), methanol (30 ml.) and diethylamine (7.3 g.) was allowed to stand at room temperature for 12 hours and the solvents were then removed under reduced pressure, there remained a solid residue which crystallized from a mixture of ethanol and petroleum ether (b.p. 63–69°) to give 10.1 g. (75%) of **4-nitro-3-phenyl-1-(3-pyridyl)-1-butanone** (II) in colorless needles, m.p. 93–95°. Further crystallization raised the m.p. to 97–99°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22. Found: C, 66.33; H, 5.04.

(8) N. Campbell and A. E. S. Fairfull, *J. Chem. Soc.*, 1239 (1949).
(9) S. H. Tucker, *ibid.*, 2182 (1949).
(10) A. Campbell and S. H. Tucker, *ibid.*, 2623 (1949).
(11) H. W. D. Stubbs and S. H. Tucker, *ibid.*, 3288 (1950).
(12) Microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, and by Mr. Joseph Pirie, formerly of the University of Southern California. Melting points are uncorrected.
(13) Compare H. O. Burrus and G. Powell, THIS JOURNAL, **67**, 1468 (1945).
(14) H. G. Kolloff and J. H. Hunter, *ibid.*, **63**, 490 (1941).
(15) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 78.

The oxime of II[16] formed colorless needles, m.p. 113–114°.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.23; H, 5.52; N, 14.52.

A solution of ketone I (5.2 g.), nitromethane (0.76 g.) and diethylamine (0.27 g.) in 95% ethanol (50 ml.) was allowed to stand at room temperature. After 4 days, the precipitate (2.1 g., m.p. 200–206°) was filtered and recrystallized from dioxane. **1,5-Dinicotinoyl-3-nitro-2,4-diphenylpentane (XIV)** formed colorless needles, m.p. 215–216° dec., containing one molecule of dioxane of crystallization.

Anal. Calcd. for $C_{33}H_{33}N_3O_6$: C, 69.82; H, 5.86. Found: C, 69.74; H, 5.80.

A sample dried at 75° in vacuum for 2 hours still contained one-half molecule of dioxane of crystallization.

Anal. Calcd. for $C_{31}H_{29}N_3O_5$: C, 71.11; H, 5.58. Found: C, 71.06; H, 5.20.

Dioxane of crystallization was removed completely by heating the crystals to constant weight at 95° in vacuum. The substance then melted at 220–222° dec.

Anal. Calcd. for $C_{29}H_{25}N_3O_4$: C, 72.63; H, 5.25. Found: C, 72.57; H, 5.31.

The original reaction mixture from which XIV had been filtered was evaporated under reduced pressure. Crystallization of the residue from chloroform and then from a mixture of acetone and benzene afforded 1.4 g. of a second diastereoisomer of XIV in colorless needles, m.p. 198–199°, containing one molecule of acetone of crystallization.

Anal. Calcd. for $C_{32}H_{31}N_3O_5$: N, 7.82. Found: N, 7.48.

Solvent of crystallization was removed by heating to constant weight at 95° in vacuum.

Anal. Calcd. for $C_{29}H_{25}N_3O_4$: C, 72.63; H, 5.25; N, 8.76. Found: C, 72.70; H, 5.26; N, 8.63.

(b) **With Nitroethane.**—After standing for 12 hours at room temperature, a mixture of ketone I (5.2 g.), nitroethane (5.6 g.), diethylamine (0.55 g.) and methanol (10 ml.) was evaporated under reduced pressure and the residual liquid mixture of nitro ketones was dissolved in a mixture of ethanol (20 ml.) and concentrated hydrochloric acid (3 ml.). The solution gradually deposited 2.8 g. of **4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone hydrochloride** in colorless needles, m.p. 165–170°. Several crystallizations from absolute ethanol raised the m.p. to 178–179°. The hydrochloride was decomposed by addition of dilute aqueous sodium hydroxide in the presence of ether. Evaporation of the ether afforded **4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (III)** which separated from a mixture of ethanol and petroleum ether in colorless needles, m.p. 91–92°.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.67; H, 5.03.

With an equivalent quantity of picric acid in 95% ethanol, this nitro ketone formed a **picrate** which separated from ethanol in yellow needles, m.p. 134–135°.

Anal. Calcd. for $C_{22}H_{19}N_5O_{10}$: C, 51.46; H, 3.73. Found: C, 51.69; H, 3.74.

The oxime of this isomer of III formed colorless needles, m.p. 152–154°.

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.33; H, 6.14; N, 13.98.

The original reaction mixture, from which the aforementioned hydrochloride had been filtered, was evaporated and the residue was shaken with aqueous sodium hydroxide and ether. Evaporation of the ethereal extract left a residue which, together with 3.7 g. of picric acid, was dissolved in the minimum volume of boiling 95% ethanol. Upon cooling, the solution deposited 4.9 g. of the picrate of a diastereoisomeric nitro ketone III which formed yellow needles when recrystallized from 95% ethanol, m.p. 155–156°.

Anal. Calcd. for $C_{22}H_{19}N_5O_{10}$: C, 51.46; H, 3.73. Found: C, 51.74; H, 3.68.

The diastereoisomeric **4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (III)**, formed by decomposition of this picrate with 3% aqueous ethanolamine in the presence of ether, separated from a mixture of ethanol and petroleum ether in colorless needles, m.p. 82–84°.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.97; H, 5.93.

(c) **With 1-Nitropropane.**—A solution of ketone I (10.4 g.), 1-nitropropane (13.4 g.) and diethylamine (1.1 g.) in methanol (20 ml.) deposited 12.7 g. (86%) of **4-nitro-3-phenyl-1-(3-pyridyl)-1-hexanone (IV)**, melting above 142°, upon standing at room temperature. The ketone separated from methanol in colorless needles, m.p. 145–146°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08. Found: C, 68.56; H, 6.22.

The oxime of IV formed colorless needles, m.p. 143–144°.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11. Found: C, 64.95; H, 6.20.

The original Michael condensation mixture, from which IV had been filtered, was evaporated under reduced pressure to yield a residue which was recrystallized from a mixture of absolute ethanol and petroleum ether. The resulting diastereoisomeric **4-nitro-3-phenyl-1-(3-pyridyl)-1-hexanone** (1.5 g., 10%) formed colorless needles, m.p. 84–85°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08. Found: C, 68.52; H, 5.95.

The picrate of this isomer formed yellow needles, m.p. 138–139°.

Anal. Calcd. for $C_{23}H_{21}N_5O_{10}$: C, 52.37; H, 4.01. Found: C, 52.66; H, 4.17.

The oxime separated from aqueous ethanol in colorless needles, m.p. 152–153° dec.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.13; H, 6.20; N, 13.63.

(d) **With 2-Nitropropane.**—**Pure 4-methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (V)**, m.p. 141–142°, separated in colorless needles when a solution of ketone I (10.4 g.), 2-nitropropane (6.7 g.) and diethylamine (0.55 g.) in methanol (20 ml.) was allowed to stand at room temperature for 3 days; yield 14.0 g. (95%).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08. Found: C, 68.41; H, 6.52.

The picrate formed yellow leaflets, m.p. 189–190°.

Anal. Calcd. for $C_{23}H_{21}N_5O_{10}$: C, 52.37; H, 4.01. Found: C, 52.60; H, 4.33.

When 1 g. of V was warmed with 0.5 ml. of phenylhydrazine, 10 ml. of 95% ethanol and 2 drops of acetic acid, there were obtained two isomeric **phenylhydrazones**. One crystallized directly in yellow leaflets, m.p. 173–175°, when the reaction mixture was cooled; yield 600 mg. (46%).

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23. Found: C, 71.31; H, 6.38.

Concentration of the reaction yielded 300 mg. (23%) of an isomeric phenylhydrazone in colorless needles, m.p. 128–130°.

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23. Found: C, 71.42; H, 6.19.

Reaction of β-Pyridyl β-Styryl Ketone with Malonic Acid Esters.—After standing for 2 days at room temperature, a solution of ketone I (5.2 g.), dimethyl malonate (3.3 g.) and diethylamine (0.55 g.) in methanol (10 ml.) had deposited 7.8 g. of colorless needles. Concentration of the solution brought the total yield of **dimethyl 1-phenyl-3-(3-pyridyl)-3-oxopropylmalonate (VIII)** to 8.3 g. (98%), colorless needles, m.p. 95–96°.

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61. Found: C, 66.79; H, 5.46.

Ketone I reacted similarly with diethyl malonate in ethanol to give **diethyl 1-phenyl-3-(3-pyridyl)-3-oxopropylmalonate (IX)**, m.p. 76–77°, in 68% yield.

Ester VIII (5 g.) was hydrolyzed readily when it was heated at 60–70° for 5 minutes with 20% aqueous potassium hydroxide (50 ml.). The resulting cooled solution was diluted with water to 100 ml. and any unhydrolyzed ester was separated. After acidification of the solution with concentrated sulfuric acid, aqueous sodium hydroxide was added as long as **1-phenyl-3-(3-pyridyl)-3-oxopropylmalonic acid (X)** precipitated; yield 3.6 g. (78%), m.p. 147–147.5°. The acid separated from aqueous ethanol in colorless needles, m.p. 149–150°.

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82. Found: C, 65.17; H, 4.83.

(16) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202, procedure B.

The same acid was obtained when ester IX was hydrolyzed.

When 5 g. of acid X was heated to 180° until evolution of carbon dioxide ceased, there remained 4 g. (93%) of **5-oxo-3-phenyl-5-(3-pyridyl)-pentanoic acid** which separated from 95% ethanol in colorless needles, m.p. 147–148°.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.24; H, 5.68.

Reaction of β-Pyridyl β-Styryl Ketone with Fluorene Derivatives.—Ketone I (5.2 g.) was allowed to react with fluorene (8.4 g.) and 50% aqueous sodium hydroxide (5 ml.) in pyridine (50 ml.) for 12 hours at room temperature and the solvents were then removed under reduced pressure. Crystallization of the residue from benzene yielded 4.0 g. (55%) of **5-(9-fluoryl)-4-nicotinoyl-3,5-diphenyl-1-(3-pyridyl)-1-pentanone (XV)**, m.p. 258–260°.

Anal. Calcd. for $C_{41}H_{32}N_2O_2$: C, 84.22; H, 5.52. Found: C, 84.07; H, 5.72.

The mother liquor from crystallization of XV was evaporated and the residue was dissolved in hot 95% ethanol. Excess fluorene separated from the cooled solution. Addition of 3.0 g. of picric acid to the filtered ethanol solution produced 5.8 g. (representing 39% of XII) of the **picrate of 9-(2-nicotinoyl-1-phenylethyl)-fluorene** in yellow needles, m.p. 180–182°.

Anal. Calcd. for $C_{33}H_{24}N_4O_8$: C, 65.55; H, 4.00; N, 9.26. Found: C, 65.68; H, 3.87; N, 9.18.

When 2 g. of the picrate was shaken with 100 ml. of 3% aqueous ethanolamine there was obtained 1.0 g. of ketone XII, which melted at 105–106° after crystallization from ethanol.

Anal. Calcd. for $C_{27}H_{21}NO$: C, 86.37; H, 5.64. Found: C, 86.48; H, 5.74.

The yields of XV and XII were 11 and 62%, respectively, when this condensation was repeated with a 10-to-1 molar ratio of fluorene to ketone I.

A mixture of ketone I (5.2 g.), 9-carboethoxyfluorene (5.9 g.) and 95% ethanol (20 ml.) was warmed until all solids had dissolved and diethylamine (0.5 g.) was then added. After 2 days at room temperature the crystalline adduct was filtered. Concentration of the mother liquor afforded additional material making the yield of **9-carboethoxy-9-(2-nicotinoyl-1-phenylethyl)-fluorene (XIII)** essentially quantitative; m.p. 87–91°. Recrystallization from ethanol raised the m.p. to 91–92°.

Anal. Calcd. for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63. Found: C, 80.48; H, 5.82.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, THE ARMOUR LABORATORIES]

The Preparation of Methyl-substituted DL-Phenylalanines

BY ROSS R. HERR, TAKASHI ENKOJI AND JOSEPH P. DAILEY

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A number of methyl-substituted phenylalanines and the corresponding diethyl acetamidomalonate intermediates have been prepared. The amino acids were evaluated as phenylalanine antagonists in the *E. coli* assay. The substituted malonates were prepared by the reaction between sodium diethyl acetamidomalonate and the appropriate benzyl bromide, benzyl chloride or benzyltrimethylammonium iodide. A modified procedure for the condensation of a quaternary iodide with sodium diethyl acetamidomalonate was devised. Hydrolysis and decarboxylation of these condensation products resulted in 2-methyl-, 3-methyl-, 4-methyl-, 2,3-dimethyl-, 2,4-dimethyl-, 2,5-dimethyl-, 2,6-dimethyl, 3,4-dimethyl-, 3,5-dimethyl- and 2,4,6-trimethylphenylalanines. Of these, only 3-methylphenylalanine will inhibit completely the growth of *E. coli*. Each of the compounds will reverse the growth-inhibiting effect of β-2-thienylalanine.

In view of the potential usefulness of compounds which are competitively antagonistic to specific amino acids, we have prepared a series of compounds which are chemically similar to phenylalanine. Each compound possesses the basic structure of phenylalanine with one or more methyl groups in different positions on the aromatic ring.

Previous investigators have shown that some *dl*-phenylalanines substituted in the phenyl ring act as competitive antagonists in the utilization of phenylalanine by microörganisms. Some of these compounds also are capable of replacing phenylalanine in reversing the inhibitory action of other competitive antagonists such as β-2-thienylalanine.[1-3]

The effect of methyl substituents in these phenylalanines would be expected to be more steric than polar. Information pertaining to the relationship between steric and polar effects and that between utilization and competitive antagonism could possibly be obtained by means of these methyl-substituted phenylalanines. Alkyl substitution in any position on the phenyl ring would hinder the hydroxylation of that position, and this, in turn, would block some of the possible pathways through which this amino acid could be metabolized.

Dakin[4] has prepared 4-methylphenylalanine and found it to cause a 35% inhibition of DOPA decarboxylase in dogs. In later studies,[3] it was found to reverse the inhibitory action of β-2-thienylalanine in *E. coli*. Burckhalter and Stephens[1] prepared 3-methylphenylalanine, and Harper, Furst and Morris[5] found that this compound did not inhibit the growth of *Leuconostoc mesenteroides* P-60, a lactobacillus, in concentrations up to 100 γ per cc. of medium.

The compounds listed in Table I were synthesized by condensing benzyl halides or benzyltrimethylammonium iodides with sodium diethyl acetamidomalonate, and the resulting substituted malonic esters were hydrolyzed and decarboxylated by refluxing with a halogen acid.[6]

Three methods were used for the preparation of the substituted malonic esters, and the data pertaining to these products are summarized in Table II. Method A consists of condensing diethyl acetamidomalonate with the methyl-substituted ben-

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