Synthesis of some 3-Hydroxy-5-pyridylpyrrole Derivatives

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Ethyl sarcosinate adds to 2, -3- and 4-pyridylmethylidenemalonates to produce the Michael adducts, which can be conveniently cyclized to oxopyrrolidine diesters under Dieckmann conditions. Mild oxidation converted the crude adducts to the isomeric 1-methyl-3-hydroxy-5-pyridylpyrrole-2,4-dicarboxylates. Addition of ethyl glycinate to ethyl picolinoylacetate or ethyl nicotinoylacetate produced the corresponding enaminoesters, but these azadiesters were not cyclized under the usual Dieckmann conditions.

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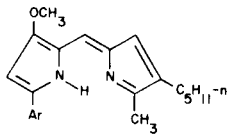
Recently we reported the synthesis of several analogs of the antibiotic bacterial pigment, prodigiosin **1** (Ar = 2-pyrryl), in which Ar was phenyl or 2-thienyl (3). In an effort to extend this work to prepare synthetic



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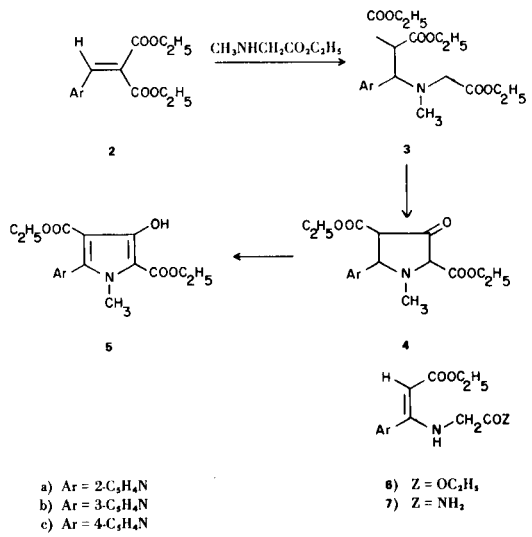
derivatives of **1** in which Ar = pyridyl, we have investigated the Michael addition of sarcosinates and glycinates to pyridinylidenemalonates, and the Dieckmann cyclization of these adducts. We have also attempted the Dieckmann cyclization of enamines derived from the addition of ethyl glycinate to pyridoylacetates.

The reactions are outlined in Scheme I. The various pyridylmethylidenemalonates (**2a, b, c**) were readily available by condensation of commercially available aldehydes with diethyl malonate, as previously described (4). The addition of ethyl sarcosinate to **2** proceeded well under nitrogen in the cold (5) to produce the adducts **3** in satisfactory yield. These can be purified, but the crude concentrates may be conveniently cyclized to the oxopyrrolidine diesters **4**, which were obtained only as impure oils which could not be crystallized, but were readily oxidized by bubbling air through a benzene solution, or by the use of *N*-bromosuccinimide (5). In this way the three isomeric diethyl 1-methyl-3-hydroxy-5-pyridylpyrrole-2,4-dicarboxylates **5** were made and characterized.

Attempts to substitute ethyl glycinate for ethyl sarcosinate in this synthesis were unsuccessful, although this approach has previously been shown to be effective (3) with other ylidenemalonates. Apparently the basic

Scheme 1



a) Ar = 2-C_5H_4N
b) Ar = 3-C_5H_4N
c) Ar = 4-C_5H_4N

6) Z = OC_2H_5
7) Z = NH_2

pyridine ring interferes with the addition of the weaker base, glycinate.

Recently Hromatka, Binder and Stanetty (6) reported the synthesis of 5-phenyl-3-hydroxypyrrole-2-carboxamide by the Dieckmann cyclization of the corresponding amide **7**. We therefore synthesized the corresponding enamine diesters **6a,b**, by addition of ethyl glycinate to ethyl picolinoylacetate and ethyl nicotinoylacetate. The latter β-ketoesters have been reported by Gilman and Broadbent (7). A number of attempts to cyclize these two diesters (**6a,b**), using Dieckmann conditions as described by Hromatka, *et al.* (6) and duplicating our previously successful conditions (5) produced only intractable tars.

EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting

point apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were obtained on a Perkin Elmer model 137 Infracord and were run neat for liquids and as potassium bromide pellets for solids. Nmr spectra were obtained on a Varian Associates' Anaspect EM-360 spectrometer or an HA-100 instrument operating in the frequency sweep mode and using tetramethylsilane as internal reference. Magnesium sulfate was used as drying agent. Microanalysis was done through the courtesy of Midwest MicroLabs, Indianapolis, Indiana. Mass spectra were determined on a Varian MAT CH-7 spectrometer at 70 eV.

Diethyl 2-Pyridylmethylidenemalonate (**2a**).

Pyridine-2-carboxaldehyde (Aldrich, 107 g., 1.0 mole), diethyl malonate (180 g., 1.1 moles), piperidine (8 g.), and benzoic acid (6.6 g.) were mixed in 1 l. of benzene, and refluxed for 2.5 hours with azeotropic distillation of the water produced during the reaction. At the end of this time the reaction mixture was cooled to room temperature, diluted with 1 l. of diethyl ether, washed with 50 ml. of 5% sodium bicarbonate solution, then with 50 ml. of water, dried, concentrated, and distilled under reduced pressure to give 147 g. of the desired **2a** (59%), b.p. 147-149°/0.6 mm) (Lit. (4a) b.p. 157°/0.5 mm).

Diethyl 3-Pyridylmethylidenemalonate (**2b**).

As above, pyridine-3-carboxaldehyde (Aldrich, 107 g., 1.0 mole) yielded 145 g. (58%) of an oil, b.p. 145-150°/0.2 mm; previously reported (4b) to boil at 130-136°/0.25 mm.

Diethyl 4-Pyridylmethylidenemalonate (**2c**).

As previously described, pyridine-4-carboxaldehyde (Aldrich, 107 g., 1.0 mole) condensed with diethyl malonate to yield 150 g. (60%) of an oil, b.p. 138-144°/0.1 mm. It was previously reported (4c) to boil at 162-164°/5 mm.

Diethyl 3-Methyl-4-(3-pyridyl)-5-carbethoxy-3-azaadipate (**3b**).

Malonate **2b** (10.0 g., 0.04 mole) was mixed with ethyl sarcosinate (9.4 g., 0.08 mole), prepared as previously reported (5) and then nitrogen gas was bubbled through the solution for 15 minutes. At the end of this time the reaction was sealed and placed in the cold room. After stirring overnight 11.85 g. (81%) of a white solid had formed in the flask. A small amount of the solid (**3b**) was dried and recrystallized from cyclohexane to melt at 62-63°; ir: 5.80 μ (C=O, broad, ester); nmr (deuteriochloroform): δ 0.89-1.55 (m, 9H, $CO_2CH_2CH_3$); 2.39 (s, 3H, N-CH_3); 3.22 (d, 2H, N-CH_2CO_2Et); 3.75-4.83 (m, 8H, $CO_2CH_2CH_3$ and -CHCH-); 7.2-7.8 (m, 2H, aromatic); 8.6 (m, 2H, aromatic).

Anal. Calcd. for $C_{18}H_{26}N_2O_6$: C, 59.01; H, 7.10; N, 7.65; m.w. 366. Found: C, 58.98; H, 7.28; N, 7.69; m/e 366.

Diethyl 3-Methyl-4-(4-pyridyl)-5-carbethoxy-3-azaadipate (**3c**).

Malonate **2c** (10.0 g., 0.04 mole) was mixed with ethyl sarcosinate (9.45 g., 0.08 mole) under nitrogen, and the mixture stirred in the cold room overnight. The solid which had formed in the flask was recrystallized from diethyl ether, with cooling and scratching, to give 9.2 g. (63%) of the desired Michael adduct, **3c**, melting at 55-56°; ir: 5.80 μ (C=O, broad, ester); nmr (deuteriochloroform): δ 1.10-1.60 (m, 9H, $CO_2CH_2CH_3$); 2.3 (s, 3H, N-CH_3); 3.15 (d, 2H, N-CH_2CO_2Et); 3.60-4.70 (m, 8H, $CO_2CH_2CH_3$ and -CHCH-); 7.2 (m, 2H, aromatic); 9.65 (m, 2H, aromatic).

Anal. Calcd. for $C_{18}H_{26}N_2O_6$: C, 59.01; H, 7.10; N, 7.65; m.w. 366. Found: C, 58.90; H, 7.24; N, 7.56; m/e 366.

Diethyl 1-Methyl-3-hydroxy-5-(2-pyridyl)pyrrole-2,4-dicarboxylate (**5a**).

Ethyl sarcosinate (23.4 g., 0.2 mole) and ethyl 2-pyridylmethylidenemalonate **2a** (24.8 g., 0.1 mole) were mixed in a 100 ml. 3-neck flask under a nitrogen atmosphere. The flask was sealed and stored in the cold room overnight. The cold solution, without purification, was added dropwise under a nitrogen atmosphere to a solution of 2.3 g. of sodium metal in 100 ml. of absolute ethanol at room temperature, then warmed to 40° and stirring continued overnight. After 16 hours the homogeneous reaction mixture was poured into 150 ml. of benzene containing 0.5 g. of glacial acetic acid. This benzene solution was extracted with five 50 ml. portions of 0.1 *N* sodium hydroxide solution. The aqueous extracts were combined, acidified with concentrated hydrochloric acid to *p*H 5.0-5.5 and extracted with five 50 ml. portions of chloroform. The organic extracts were combined, dried, and concentrated under reduced pressure to give 24.2 g. (75%) of a brown oil (**4a**) with the following characteristics: ir: ν max (AgCl) 5.65 (C=O, shoulder, 5-membered ring), 5.80 μ (C=O, broad, ester); m.w. calcd. for $C_{16}H_{20}N_2O_5$: 320. Found: m/e 320.

The oil (5.75 g., 0.018 mole) was dissolved in 50 ml. of 15% aqueous dioxane, sodium bicarbonate (1.81 g., 0.021 mole) was added, and the mixture was cooled in an ice bath. *N*-Bromosuccinimide (39 g., 0.018 mole) was added in small portions to the cooled reaction mixture which was stirred for an additional 15 minutes. Fifty ml. of chloroform was added, and the solution was transferred to a separatory funnel. The flask was rinsed with 25 ml. of water which was poured into the separatory funnel, the organic layer separated and the water layer washed again with chloroform and the organic layers combined and dried. The organic solvents were removed under reduced pressure, and the oil which was isolated was dried under vacuum for one hour. Upon titurating the oil solidified and was recrystallized from methanol to give 2.92 g. (51%) of white crystals of **5a** melting at 89-91°; ir: 5.95 μ (C=O, broad, ester); nmr (deuteriochloroform): δ 1.02 (t, 3H, J = 6 Hz, 4-$CO_2CH_2CH_3$); 1.38 (t, 3H, J = 6 Hz, 2-$CO_2CH_2CH_3$); 3.63 (s, 3H, N-CH_3); 4.06 (q, 2H, J = 6 Hz, 4-$CO_2CH_2CH_3$); 4.34 (q, 2H, J = 6 Hz, 2-$CO_2CH_2CH_3$); 7.20-7.34 (m, 2H, H-3′ and H-5′); 7.60-7.79 (m, 1H, H-4′); 8.64 (d, broad, 1H, H-6′); 9.10 (s, 1H, exchanges with deuterium oxide, OH).

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80; m.w. 318. Found: C, 60.53; H, 5.72; N, 8.72; m/e 318.

Diethyl 1-Methyl-3-hydroxy-5-(3-pyridyl)pyrrole-2,4-dicarboxylate (**5b**).

Sodium metal (0.76 g., 0.033 g.-atom) was dissolved in 60 ml. of absolute ethanol under a nitrogen atmosphere. When the metal had all dissolved, Michael adduct **3b** (11.7 g., 0.032 mole) was added to the solution in small portions, and then the reaction was heated at 45° overnight. Two ml. (0.032 mole) of glacial acetic acid was mixed with 500 ml. of benzene. The cooled reaction mixture was poured into the benzene solution. The benzene was extracted with three 150 ml. portions of 0.1 *N* sodium hydroxide solution, and the *p*H of the combined aqueous phases was adjusted to 6. The acidified solution was extracted with four 100 ml. portions of chloroform, the chloroform layers were combined, dried, and evaporated under reduced pressure to give 5.8 g. (56%) of a red oil, (**4b**, with m/e 320) (m.w. Calcd. for $C_{16}H_{20}N_2O_5$: 320).

This oil was oxidized with *N*-bromosuccimide, as described

above to give 2.38 g. (41%) of the desired pyrrole **5b** (18.5% based on ylidenemalonate) m.p. 124-125°; ir: 5.95 (C=O, broad, ester); nmr (deuteriochloroform): δ 0.58-1.62 (m, 6H, $CO_2CH_2CH_3$); 3.68 (s, 3H, N-CH_3; 3.91-4.69 (m, 4H, $CO_2CH_2CH_3$); 7.28-7.90 (m, 2H, H-4′ and H-5′); 8.58-8.88 (m, 2H, H-2′ and H-6′); 9.35 (s, 1H, exchanges with deuterium oxide, O*H*).

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80; m.w. 318. Found: C, 60.43; H, 5.83; N, 8.62; m/e 318.

Diethyl 1-Methyl-3-hydroxy-5-(4-pyridyl)pyrrole-2,4-dicarboxylate (**5c**).

Sodium metal (1.48 g., 0.64 mole) was dissolved in 100 ml. of absolute ethanol under a nitrogen atmosphere, and when all the metal had dissolved the Michael adduct **3c** (23.61 g., 0.064 mole) was added in small portions to the ethanol which was then heated at 50° overnight. After 16 hours, 3.9 ml. of glacial acetic acid was pipetted into the cooled reaction mixture. Compressed air was bubbled through the reaction mixture for one hour, after which the solution was poured into 250 ml. of chloroform, and the chloroform was washed with two 100 ml. portions of water to remove the sodium acetate. The organic layer was dried and concentrated to yield a brown oil which crystallized from 2-propanol to give 5.07 g. (25%) of the desired pyrrole, **5c**, melting at 127-129°; ir: 5.90 μ (C=O, broad, ester); nmr (deuteriochloroform): δ 0.9-1.5 (m, 6H, $CO_2CH_2CH_3$); 3.6 (s, 3H, N-CH_3); 3.9-4.55 (m, 4H, $CO_2CH_2CH_3$); 7.25 (m, 2H, H-3′ and H-5′); 9.35 (s, 1H, exchanges with deuterium oxide, O*H*); 9.70 (m, 2H, H-2′ and H-6′).

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.69; N, 8.78; m.w. 318. Found: C, 60.49; H, 5.72; N, 9.00; m/e 318.

Diethyl 3-(2-Pyridyl)-4-aza-2-hexene-1,6-dicarboxylate (**6a**).

Ethyl picolinoylacetate (29.2 g., 0.15 mole) prepared as previously reported (7), was dissolved in 50 ml. of ethanol and freshly distilled ethyl glycinate (27.0 g., 0.26 mole) (8) was added, the solution was heated at 50° overnight, after which the ethanol was removed under reduced pressure. The residual oil was chromatographed on 300 g. of silica gel using 10% tetrahydrofuran in benzene as solvent to give 25 g. (70%) of the desired adduct, **6a**, isolated as an orange oil which decomposed on attempted distillation; ir: 5.7 (C=O), 3.05 (N-H), 6.0, 6.2, 6.4, 6.65, 6.85 μ (C=C); nmr (deuteriochloroform): δ 1.1-1.5 (m, 6H, $CO_2CH_2CH_3$); 3.9-4.4 (m, 6H, $CO_2CH_2CH_3$ and N-CH_2-CO_2Et); 4.9 (s, 1H, C=C-*H*); 7.3-8.0 (m, 2H, aromatic); 8.4-9.0 (m, 2H, aromatic).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06; m.w. 278. Found: C, 60.67; H, 6.47; N, 9.90; m/e 278.

Diethyl 3-(3-Pyridyl)-4-aza-2-hexene-1,6-dicarboxylate (**6b**).

Ethyl nicotinoylacetate (2.73 g., 14.1 mmoles) (7) and ethyl glycinate (11.8 g., 17.5 mmoles) were mixed in 20 ml. of ethanol and heated at reflux overnight. The ethanol was removed under reduced pressure to give after chromatography on 50 g. of silica gel, using 10% tetrahydrofuran in benzene as solvent, 3.04 g. (79%) of the desired adduct, **6b**, ir: 5.7 (C=O), 3.05 (N-H), 6.0, 6.2, 6.3, and 6.8 μ (C=C); nmr δ (deuteriochloroform): δ 1.1-1.6 (m, 6H, $CO_2CH_2CH_3$); 3.5-3.8 (m, 2H, N-CH_2-CO_2Et); 3.9-4.4 (m, 5H, $CO_2CH_2CH_3$ and N*H*); 4.7 (s, 1H, C=C-*H*); 8.1-8.4 (m, 1H, aromatic); 8.5-8.7 (m, 1H, aromatic); 9.5 (m, 2H, aromatic).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 6.52; m.w. 278. Found: C, 60.67; H, 6.47; N, 9.90; m/e 278.

REFERENCES AND NOTES

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(2) Taken in part from a Thesis submitted to Indiana University, August 1976, by J. P. in partial fulfillment of the degree Master of Science.

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