SOME REACTIONS OF ETHYL 2-PYRIDINEACETATE 1,2-DICARBETHOXY-3-OXO-OCTAHYDROPYRROCOLINE[1]

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ABSTRACT

Ethyl α-acetoxy-2-pyridineacetate and ethyl α-bromo-2-pyridineacetate have been prepared, and the latter converted in three steps to 1,2-dicarbethoxy-3-oxo-octahydropyrrocoline. The main carbonyl band of simple saturated five membered lactams in the infrared is observed to lie close to 1700 cm^{-1}.

The methylene group of ethyl 2-pyridineacetate is of comparable activity to that of ethyl acetoacetate. For example, a useful anion can be obtained by reaction with sodium or potassium (1, 4). Further parallel between the reactivities of the two compounds has now been found in the ease of bromination and acetoxylation. Like acetoacetic ester (6), 2-pyridineacetic esters react rapidly with a molar equivalent of bromine at 5°C. in carbon disulphide solution to give α-bromo esters, and react at room temperature with lead tetraacetate in benzene to give the α-acetoxy compound. In contrast, the methylene group of malonic esters does not react at a useful rate with lead tetraacetate in benzene until the solution is heated to around 100° (6).

The synthesis of octahydropyrrocolines with reactive substituents has been achieved by Clemo and co-workers (2, 3, 4) and by Lions and Willison (10). The work of Diels and co-workers (5, and earlier papers) has led to pyrrocolines substituted with carboxyls, which presumably could be reduced to the corresponding octahydro derivatives. By reaction of ethyl α-bromo-2-pyridineacetate with the anion from ethyl malonate, reduction of the product, and cyclization, 1,2-dicarbethoxy-3-oxo-octahydropyrrocoline III has now been obtained. The malonic hydrogen and carboxyl groups in this compound are of potential value for building additional rings on the five membered ring.

The reactions used in preparing and characterizing the various products are shown in the flowsheet. The mixture obtained when the bromo compound reacted with the malonic anion contained some ethyl 1,1,2,2-ethanetetracarboxylate, probably arising from ethyl bromomalonate formed by bromine exchange. This could be partly removed by distillation under high vacuum, but the desired product I could not be distilled without considerable decomposition. By chromatography on neutral alumina, however, I could be freed from the ethanetetracarboxylic ester, unchanged malonic ester, and colored impurities.

I proved to be a very weak base (pK_A around 2.4 in 50% aqueous methanol). A somewhat low basicity (pK 3.6) has been observed for α,α-di-(2-pyridyl)-

[1]*Manuscript received May 7, 1954.*
Contribution from the Division of Pure Chemistry, National Research Council, Ottawa, Canada. Issued as N.R.C. No. 3323.
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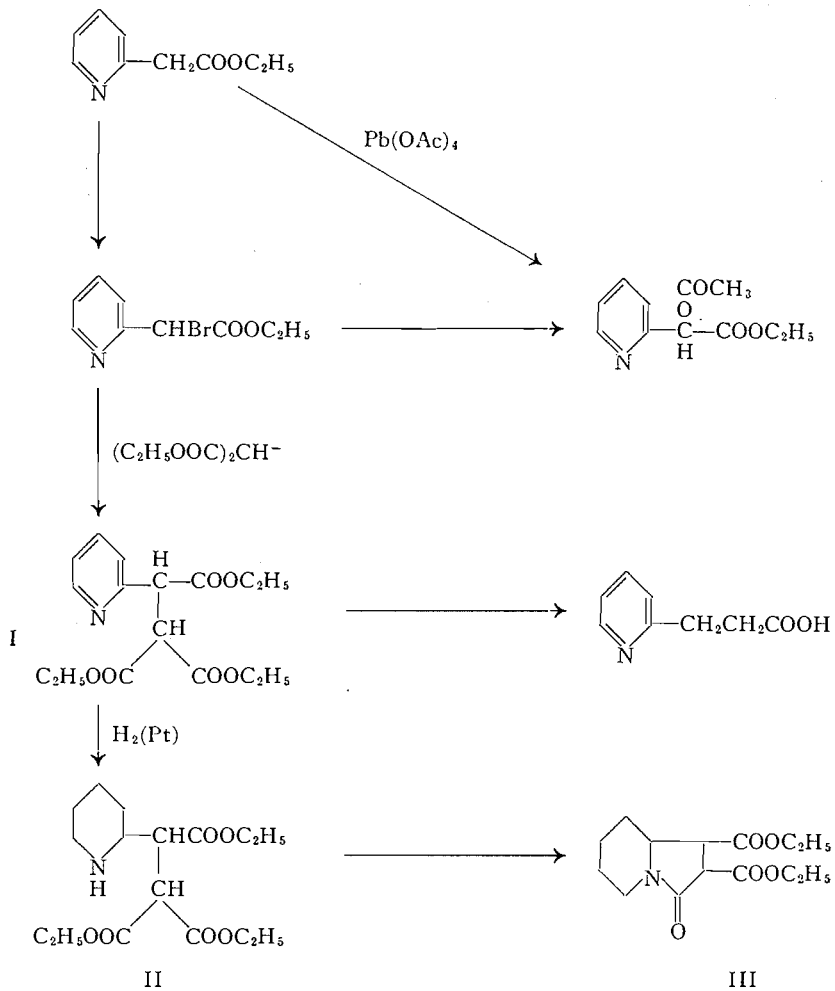
FLOWSHEET



γ,γ-dicarbethoxypropane (9). This may in part be due to interaction across space between the nitrogen and the ester carbonyls. In the case of I, however, the inductive effect of the three carbethoxy groups must be the main cause of the low basicity. The ultraviolet spectrum of I (λ_{max} 261mμ, log ε 3.54) was very similar to that of α-picoline, hence no rearrangement of the double bonds had taken place.

Attempts to prepare ethyl α–β-di(2-pyridyl)-succinate by reaction of ethyl α-bromo-2-pyridineacetate and the anion from ethyl pyridineacetate gave intractable highly colored products. Similar results were obtained in an attempt to obtain this compound by coupling two molecules of the anion using iodine.

When the crude I was hydrolyzed and decarboxylated, considerable tar was produced, but a 27% yield of β-(2-pyridyl)-propionic acid was obtained.

The piperidine triester II underwent smooth cyclization when distillation was attempted and only the lactam III was obtained. When III was hydrolyzed, the mixture of stereoisomeric acids proved reluctant to crystallize. On long standing, however, two diastereoisomers melting with decomposition near 170° were obtained in poor yield.

The C=O stretching vibration in saturated N-alkyl six membered lactams gives rise to an absorption band near 1640 cm.$^{-1}$ (8). The position of this band for four pyrrolidones is indicated in Table I. From these observations it appears

TABLE I

Compound	Wave number, cm.$^{-1}$	State
Lactam III	1705	Liquid film
	1690	Chloroform solution
N-methyl-2-pyrrolidone	1690	Liquid film
	1680	Chloroform solution
Octahydrogelsemine*	1693	Nujol mull
2-Pyrrolidone	1695	Film from melt

The authors wish to thank Dr. L. Marion for permission to use this value.

that in simple saturated systems the position of this band can be used to assign ring size to a lactam. The spectrum of the 3-oxo-octahydropyrrocolinedicarboxylic acid, however, had unusual absorption in the 6 μ region, and the bands cannot be assigned to any individual vibration.

It is interesting to note that the relatively intense band in the OH, NH stretching region (around 3450 cm.$^{-1}$) which has been observed for N-alkyl six membered lactams (8) also appears in the spectra of the N-substituted five membered lactams. In a recent paper (11) this band has been attributed to water in the samples. We consider this unlikely in our own cases in view of the high distillation temperatures (center cuts were taken), the good carbon, hydrogen analyses of the compounds, and the complete disappearance of the bands in chloroform solution. Hence, unless some very unusual spectral effect gives rise to this band, it seems likely that it is due to the presence of considerable enol in the liquid state.

EXPERIMENTAL

The infrared spectra were taken on a Perkin-Elmer model 21 double beam spectrophotometer with a sodium chloride prism. The location of the bands is given in cm.$^{-1}$ followed in brackets by the percentage absorption. The ultraviolet spectra were taken using a Beckmann D.U. spectrophotometer.

Methyl α-Bromo-2-pyridineacetate

Methyl 2-pyridineacetate (2.0 gm., b.p. 90°, 2 mm.) was dissolved in carbon disulphide in a flask surrounded by cracked ice. A solution of 2.2 gm. of bromine in 10 ml. of carbon disulphide was added slowly while the reaction mixture was

stirred. After the addition the reaction mixture was allowed to stand at room temperature for one hour. The carbon disulphide was boiled off and the residue covered with a layer of ether. Excess saturated potassium carbonate solution was added, the ether layer separated, and the aqueous layer extracted three times with ether. The yellow oil recovered from the dried ether solution was distilled over a short path at a bath temperature of 90°, 0.2 mm. Yield, 2.3 gm. Found: C, 41.78; H, 3.32; N, 5.69. Calc. for $C_8H_8O_2NBr$: C, 41.76; H, 3.51; N, 6.09.

Ethyl α-Bromo-2-pyridineacetate

Prepared as described for the methyl ester in 77% yield. Distilled over a short path at a bath temperature of 90°, 0.2 mm. Found: Br, 31.76, 31.12. Calc. for $C_9H_{10}O_2NBr$: Br, 32.74. The compound is sensitive, and develops color on heating or keeping, hence the somewhat low bromine values.

Ethyl α-(Dicarbethoxymethyl)-2-pyridineacetate (I)

To ethyl α-bromo-2-pyridineacetate (2.75 gm.) in 10 ml. of absolute ethanol was added dropwise a solution of sodio–malonic ester (from 0.265 gm. of sodium and 1.80 gm. of ethyl malonate) in 5 cc. of ethanol. After the addition the mixture was allowed to sit for 0.5 hr. at room temperature. The ethanol was then removed under reduced pressure. The residue was taken up in methylene chloride, and this solution extracted three times with 3 *N* hydrochloric acid (40 cc.). The methylene chloride solution contained 2.8 gm. of oil. The aqueous solution was made alkaline with ammonia and extracted with methylene chloride giving 0.91 gm. of base.

The neutral oil was chromatographed on 56 gm. of neutral alumina (activity 2–3, Brockmann scale). Three hundred cubic centimeters of benzene eluted 2.38 gm. of pale reddish oil. The remaining esters were eluted with chloroform and ethanol in chloroform (304 mgm.). The benzene eluates were rechromatographed on 51 gm. of neutral alumina activity 1–2. The first three groups of eluates were colorless oils. Fraction 1 contained some ethyl malonate, and

Solvent	Volume, cc.	Weight eluted, mgm.	λ_{max} in mμ	ϵ_{max}
1. 50% Petroleum ether – benzene	400	876	260.5	1690
2. Benzene	250	489	260.5	3420
3. 50% Chloroform benzene	200	276	260.5	3470
4. Chloroform and ethanol in chloroform	400	490	Not determined	

ethyl 1,1,2,2-ethanetetracarboxylate in addition to the desired product. The first two esters could be separated by distillation under high vacuum. The distillate crystallized. After recrystallization from ether petroleum ether it

melted at 76° (1,1,2,2-ethanetetracarboxylate melts at 76°). Found: C, 52.84; H, 6.93. Calc. for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97.

Fraction 3 in 0.01 *N* hydrochloric acid in ethanol had λ_{max} 262 mμ, log ϵ 3.78. It had a pK_A of 2.4 in 50% aqueous methanol.

Distillation of a sample of fraction 3 under 5×10^{-5} mm. and a bath temperature of 110° gave an orange oil, and left a tarry residue. The distillate was analyzed. Found: C, 58.00; H, 6.71. Calc. for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55.

Hydrolysis and Decarboxylation of I

Four grams of crude I was hydrolyzed with hot dilute sodium hydroxide solution. The solution was made just acid to Congo red paper with hydrochloric acid. The water was removed under reduced pressure and the residue extracted with ethanol. This was transferred to a bulb and heated under 0.2 mm. pressure. At 120° brisk decomposition took place. The product was then sublimed under 3×10^{-3} mm. pressure, giving 520 mgm. of crystalline solid. This was suspended in hot benzene and filtered. The crystals melted at 141° (β-(2-pyridyl)-propionic acid is reported to melt at 141° (7)). Found: C, 63.38; H, 5.79. Calc. for $C_8H_9O_2N$: C, 63.56; H, 6.00.

1,2-Dicarbethoxy-3-oxo-octahydropyrrocoline

A sample of I, calculated from the ultraviolet spectrum to contain 1.2 gm. of the triester, was dissolved in 15 ml. of ethanol containing 0.5 ml. of concentrated hydrochloric acid. In the presence of platinum from 0.16 gm. of platinum oxide this absorbed 260 ml. of hydrogen at 25°C. in 35 min. (2.9 moles per mole). After removal of the catalyst and ethanol, the product was dissolved in dilute acid and the neutral impurity extracted with ether. The acid solution was made basic with sodium carbonate and the base extracted with methylene chloride giving 960 mgm. of colorless oil. No crystalline picrate of this base could be obtained. On treatment with acetic anhydride at room temperature a sample of the base gave a neutral oil. When the base was distilled under 10^{-3} mm. at a bath temperature of 120°, a neutral oil resulted which analyzed correctly for the pyrrocolone. Found: C, 59.75; H, 7.56. The distillate was dissolved in methylene chloride, washed with acid and alkali, dried, and the oil redistilled. Found: C, 59.78, 59.20; H, 7.50, 7.31. Calc. for $C_{14}H_{21}O_5N$: C, 59.33; H, 7.49. Infrared spectrum (liquid film): 3450 (12), 2960 (56), 2880 (35), 1740 (93), 1705 (94), 1452 (67), 1435 (62), 1404 (49), 1375 (63), 1315 (58), 1263 (83), 1237 (79), 1215 (80), 1180 (78), 1117 (38), 1097 (40), 1030 (66), 972 (27), 949 (21), 915 (11), 885 (18), 855 (32), 700 (27).

1,2-Dicarboxy-3-oxo-octahydropyrrocoline

A solution of 0.98 gm. of base from the hydrogenation of I was saponified overnight with sodium hydroxide in aqueous ethanol. The solution was made just acid to Congo red paper with hydrochloric acid, then evaporated to dryness under reduced pressure. No amino acid could be extracted from this residue by boiling chloroform. The salts were dissolved in 6 *N* hydrochloric acid, then the solution taken to dryness. The residue was taken up in water

and again taken to dryness under reduced pressure. The solid was extracted with cold dry ethanol, giving 0.73 gm. of viscous oil. This was readily soluble in chloroform. When a concentrated chloroform–ether solution of this acid stood for several weeks a crystalline compound (40 mgm.) separated. After two recrystallizations from acetone ether this gave 10 mgm. m.p. 175° dec. neutral equivalent: 107. Calc. for $C_{10}H_{13}O_5N$, neutral equivalent 113.6. On long standing the main mother liquor deposited a second crop of crystals. After recrystallization 60 mgm. was obtained, m.p. 171° dec. When mixed with the first crop this melted at 165° dec. Found: neutral equivalent, 126; C, 53.18; H, 5.69; N, 6.38. Calc. for $C_{10}H_{13}O_5N$: C, 52.86; H, 5.77; N, 6.17, neutral equivalent, 113.6. The pK_A's of the two carboxyl groups were approximately 4.1 and 5.7 in 50% aqueous methanol.

Ethyl α-Acetoxy-2-pyridineacetate

(*a*) Ethyl α-bromo-2-pyridineacetate (1.13 gm.) was added to a solution of 4.0 gm. of sodium acetate in 20 cc. of ethanol and 1 cc. of water. The mixture was refluxed for six hours, the solvent then removed under reduced pressure, and the residue extracted with ether. The 715 mgm. of oil recovered from the ether was distilled at a bath temperature of 97° under 0.2 mm. pressure giving 490 mgm. of nearly colorless oil. Found: C, 59.20; H, 5.63. Calc. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87. Infrared spectrum (liquid film) 3480 (6), 3080 (16), 3000 (37), 1750 (93), 1600 (65), 1580 (45), 1479 (56), 1443 (65), 1376 (75), 1342 (46), 1235 (83), 1216 (91), 1187 (80), 1099 (53), 957 (27), 925 (26), 830 (18), 754 (57), 699 (29), 649 (25).

The base, probably because of its low basicity, formed a picrate which had more of the character of a molecular complex than that of a salt. It was quite soluble in ether, and it had to be crystallized from a concentrated solution in this solvent. It melted at 100°. Found: C, 45.22, 45.53; H, 3.55, 3.65. Calc. for $C_{17}H_{16}N_4O_{11}$, C, 45.14; H, 3.57.

(*b*) Ethyl 2-pyridineacetate (2.0 gm.) was added to a solution of 4 gm. of lead tetraacetate in 30 cc. of benzene. Some heat was evolved, the solution turned brown, and a crystalline precipitate settled. After one hour at room temperature the mixture was filtered and the solid washed with benzene. The benzene solution was washed with sodium bicarbonate solution, dried, and distilled. A residue of 1.6 gm. of dark liquid remained. This was distilled over a short path at a bath temperature of 85–120° under 0.3 mm. pressure. The 600 mgm. of brown distillate was redistilled, giving 450 mgm. of faintly colored oil. The infrared spectrum of this was identical to that of the product from (*a*).

1-Methyl-2-pyrrolidone[5]

This was distilled under one atmosphere pressure (b.p. 200°), a center cut being taken for the spectra. Calc. for C_5H_9ON: C, 60.58; H, 9.15. Found: C, 60.90; H, 9.24. Infrared spectrum: (*a*) Liquid film, 3480 (34), 2950 (39), 2900 (38), 1690 (92), 1508 (48), 1479 (40), 1465 (42), 1442 (45), 1432 (48), 1407 (55), 1303 (67), 1267 (45), 1230 (18), 1173 (13), 1114 (36), 1025 (10), 985 (25), 925 (11), 847 (11), 740 (13), 650 (34). (*b*) Chloroform solution 31

mgm. per ml.; 3020 (66), 2900 (33), 1680 (97), 1508 (51), 1479 (37), 1465 (36), 1446 (40), 1432 (44), 1410 (59), 1305 (67), 1266 (43), 1210 (67), 1175 (14), 1115 (33), 1025 (9), 985 (22).

2-Pyrrolidone[5]

[5]*The authors wish to thank the General Aniline and Film Corporation for generous gifts of these compounds.*

Melting point 25°. For the spectrum, a crystal was melted between rock salt plates. Infrared spectrum: 3260 (49), 2980 (29), 2910 (30), 1695 (89), 1500 (20), 1470 (31), 1445 (27), 1431 (30), 1385 (18), 1290 (50), 1272 (40), 1230 (12), 1170 (10), 1070 (21), 996 (22), 916 (7), 885 (9), 680 (32).

ACKNOWLEDGMENT

The authors wish to thank Dr. R. N. Jones and Mr. R. Lauzon for taking the infrared spectra, and Mr. J. Eagen and Mr. H. Seguin for the analyses.

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