New Heterocyclic Systems. Benzo[4,5]cyclohepta[1,2-*b*]pyrrole and Benzo[5,6]cyclohepta[1,2-*f*]pyrrolizidine Derivatives (1)

J. Ackrell (2), F. Franco, R. Greenhouse A. Guzmàn, and J. M. Muchowski (2)

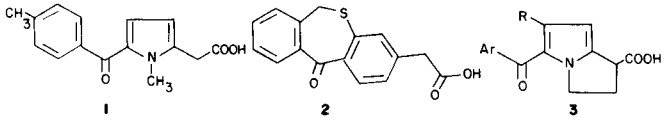
Research Laboratories, Syntex, S.A., Apartado Postal 10-820, Mexico 10, D.F., Mexico

Received March 17, 1980

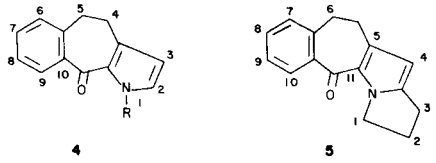
The synthesis of the polycyclic pyrrole acetic acids **9e**, **13e** and **13g** by multistep processes from 1-bromo-4-phenylbutan-2-one (**6c**) is reported. An instance of the use of the 2-chloroethyl moiety as a pyrrole nitrogen protecting group is described. The α-methylaminoketone (**6e**) was synthesised by a novel two step process from **6c** and methyl *N*-methylformimidate (**12**).

J. Heterocyclic Chem., **17**, 1081 (1980).

In connection with studies in progress concerning the synthesis of potential antiinflammatory agents incorporating structural features of tolmetin (**1**) (3), tiopinac (**2**) (4), and 5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids (**3**) (5), it became of interest to prepare acetic acid derivatives of the previously unknown tri- and tetracyclic systems **4** and **5**. This paper describes the synthesis of members of each of these heterocyclic systems.



1 **2** **3**



4 **5**

The synthetic embarkation point for the precursors of the polycyclic pyrrole derivatives described herein was 1-bromo-4-phenylbutan-2-one (**6c**) which was obtained from hydrocinnamoyl chloride (**6a**) *via* the diazoketone (**6b**).

The synthesis of compounds of the tetracyclic series commenced with the alcoholic diester (**7a**) which was prepared by means of a Hantzsch synthesis (6) from the bromoketone (**6c**), ethanolamine, and dimethyl acetonedicarboxylate. The methanesulfonate (**7b**), derived from the alcohol (**7a**), was converted into the tetrasubstituted 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole derivative (**8a**) with sodium hydride in dimethylformamide (DMF). Acylation of the bicyclic ester with phosgene provided the acid chloride (**8b**) which underwent cyclization to the tetracyclic ketodiester (**9a**) in polyphosphoric acid at 70° (7). Saponification of the diester, followed by preferential Fischer esterification of the least hindered carboxyl group with isopropanol, and thermal decarboxylation of the monoacid (**9c**), obtained thereby, gave the ester (**9d**) which was hydrolysed, under alkaline conditions to the carboxylic acid (**9e**).

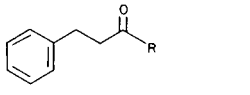
An attempt to utilize the Hantzsch synthesis to prepare the precursor (**7f**) of the *N*-unsubstituted tricyclic acetic acid (**13e**) failed because of the formation of the isomeric 2,3,5-trisubstituted pyrrole (**10**) (8). The required diester could, however, be obtained by a five step reaction sequence from the methanesulfonate (**7b**). Thus, displacement of methyl sulfonate from ester (**7b**), with lithium chloride in DMF, gave the chloride (**7c**), which upon dehydrohalogenation with methanolic potash and subsequent esterification with diazomethane produced the *N*-vinyl compound (**7d**). This compound was transformed into the carbinolamine (**7e**), with aqueous hydrochloric acid in acetonitrile, and the nitrogen substituent was removed therefrom with silver benzoate in wet acetonitrile. The conditions for the removal of the 1-hydroxyethyl group from compound (**7e**) are similar to those which have been reported by Anderson and Groves (10) for the cleavage of 1-hydroxymethylpyrroles. The diester (**7f**) [51%, based on the sulfonate (**7b**)] was then converted into the tricyclic compound (**13a**) and thence into the carboxylic acid (**13a**) by a reaction sequence identical to that described above for the synthesis of the tetracyclic analog (**9e**).

The *N*-methylated tricyclic acetic acid **13g** was synthesised by a process which differed in several aspects from those described above. For example, the diester (**7g**), though obtainable in principle by the Hantzsch method, was instead prepared by a Knorr synthesis (see references 6a and 6b, pp. 51-57 and 210-220, respectively) from 1-methylamino-4-phenylbutan-2-one (**6e**) and dimethyl acetone-dicarboxylate. The α-methylaminoketone hydrochloride (**6e**) was synthesised by alkylation of methyl *N*-methylformimidate (**12**) (11) with the bromoketone (**6c**), followed by hydrolysis of the resulting formamide (**6d**) with methanolic hydrogen chloride solution. This synthesis of α-alkylaminoketones has apparently not previously been reported in the literature (12). The dicarboxylic acid (**7h**) corresponding to (**7g**), when subjected to Fischer esterification conditions in hot 2-propanol, gave a (1:2)

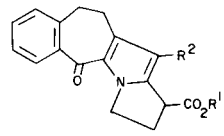
0022-152X/80/051081-05$02.25

mixture of the expected acidic monoester (**7i**) and the decarboxylation product (**11b**) thereof. Consequently, the latter substance was converted into the acid chloride (**11c**), which after cyclization and subsequent saponification provided the carboxylic acid (**13g**).

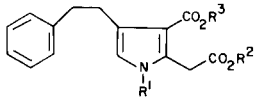
Neither the antiinflammatory nor the analgesic activities of the acetic acids **9e**, **13e** and **13g** were sufficient to merit further synthetic studies in this area (13).



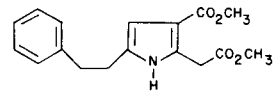
6a, R = Cl
6b, R = CHN_2
6c, R = CH_2Br
6d, R = CH_2NCH_3CHO
6e, R = CH_2NHCH_3 · HCl



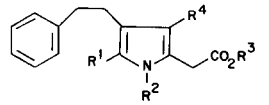
9a, R^1 = CH_3, R^2 = CO_2CH_3
9b, R^1 = H, R^2 = CO_2H
9c, R^1 = $CH(CH_3)_2$, R^2 = CO_2H
9d, R^1 = $CH(CH_3)_2$, R^2 = H
9e, R^1 = R^2 = H



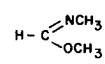
7a, R^1 = CH_2CH_2OH; R^2, R^3 = CH_3
7b, R^1 = $CH_2CH_2OSO_2CH_3$; R^2, R^3 = CH_3
7c, R^1 = CH_2CH_2Cl; R^2, R^3 = CH_3
7d, R^1 = $CH=CH_2$; R^2, R^3 = CH_3
7e, R^1 = $CHOHCH_3$; R^2, R^3 = CH_3
7f, R^1 = H; R^2, R^3 = CH_3
7g, R^1, R^2, R^3 = CH_3
7h, R^1 = CH_3; R^2, R^3 = H
7i, R^1 = CH_3, R^2 = $CH(CH_3)_2$, R^3 = H



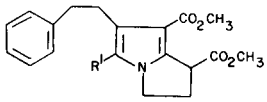
10



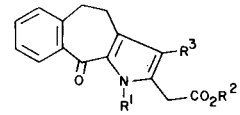
11a, R^1 = $COCl$, R^2 = H, R^3 = CH_3, R^4 = CO_2CH_3
11b, R^1, R^4 = H; R^2 = CH_3, R^3 = $CH(CH_3)_2$
11c, R^1 = $COCl$, R^2 = CH_3, R^3 = $CH(CH_3)_2$ R^4 = H



12



8a, R = H
8b, R = COCl



13a, R^1 = H, R^2 = CH_3, R^3 = CO_2CH_3
13b, R^1 = R^2 = H; R^3 = CO_2H
13c, R^1 = H, R^2 = $CH(CH_3)_2$, R^3 = CO_2H
13d, R^1, R^3 = H; R^2 = $CH(CH_3)_2$
13e, R^1, R^2, R^3 = H
13f, R^1 = CH_3, R^2 = $CH(CH_3)_2$, R^3 = H
13g, R^1 = CH_3; R^2, R^3 = H

EXPERIMENTAL

The melting points were determined in a Mel-Temp apparatus and are corrected. The infrared spectra were measured in chloroform solution, unless specified otherwise, and were recorded with a Perkin-Elmer model 237 grating infrared spectrophotometer. The ultraviolet spectra were recorded with a Perkin-Elmer model 402 ultraviolet visible spectrophotometer in methanol solution. The nmr spectra were taken in deuteriochloroform solution, unless specified otherwise, with a Varian T-60 spectrometer. The chemical shifts are expessed as ppm (δ) from internal tetramethylsilane.

1-Diazo-4-phenylbutan-2-one (**6b**).

A mixture of phenylpropionic acid (15.0 g., 100 mmoles) and thionyl chloride (40 ml.) was heated at reflux temperature for 4 hours. The excess thionyl chloride was removed *in vacuo* and the residue was added to an excess of ethereal diazomethane at 0°. When gas evolution had terminated, the solvent was removed *in vacuo* and the residual oil was percolated through a column of neutral alumina (800 g., Fluka, Acta. I) using hexane-ethyl acetate as the percolating solvent. The oil (15.6 g., 90%) which remained after removal of the solvent was used as such in the next step; uv: 210.5 (7410), 249 (10,000), 268 (8910) nm; ir: 2070, 1640 cm^{-1}; nmr: 2.41-3.07 (m, 4H), 5.10 (s, 1H), 7.15 (s, 5H).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.12; H, 5.96; N, 16.27.

1-Bromo-4-phenylbutan-2-one (**6c**).

A saturated etheral solution of hydrogen bromide was added slowly to a stirred solution of the diazoketone (15.0 g., 86 mmoles) in ether until tlc analysis [silica gel, ethyl acetate-hexane (2:3)] showed that the reaction was complete. The solvent was evaporated *in vacuo* to give a solid (16.5 g., 85%) which on crystallization from ethyl acetate-hexane had m.p. 36-37°; uv: 212 (6030) nm; ir: 1723, 1605 cm^{-1}; nmr: 2.93 (s, 4H), 3.78 (s, 2H), 7.17 (s, 5H).

Anal. Calcd. for $C_{10}H_{11}BrO$: C, 52.93; H, 4.88. Found: C, 53.05; H, 4.84.

N-Methyl-*N*-(4-phenylbutan-2-one-1-yl)formamide (**6d**).

A solution of the bromoketone (**6c**, 11.3 g., 50 mmoles) in benzene (100 ml.), containing methyl *N*-methylformimidate (**12**, 4.0 g., 55 mmoles), was heated at reflux temperature for 24 hours. The solvent was removed *in vacuo* and the residue was subjected to column chromatography on silica gel (1 kg.) using ethyl acetate-hexane-2-propanol (2:8:1) as the eluting solvent. The oil (5.1 g., 50%) obtained after removal of the solvent was used as such in the next step; uv: 218 (4790) nm: ir (liquid film): 1740, 1675 cm^{-1}; nmr: 2.50-3.04 (m, 4H), 2.86 (s, 3H), 3.82, 4.00 (singlets, total 2H, 14), 7.12 (s, 5H), 7.73, 7.79 (singlets, total 1H, 14).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.11; H, 7.39; N, 6.58.

1-Methylamino-4-phenylbutan-2-one Hydrochloride (**6e**).

A solution of the above formamide (7.0 g., 34 mmoles) in methanol (150 ml.) which was 3*N* in hydrogen chloride, was heated at gentle reflux for 12 hours. The solvent was removed *in vacuo*, the residue was washed with dry acetone, and dried under vacuum. This material (6.3 g., 87%) had m.p. 163-164° after crystallization from ethyl acetate-hexane; uv: 217 (2950) nm; ir (potassium bromide): 2780, 2680, 2490, 2410, 1732 cm^{-1}; nmr (deuterium oxide): 2.78 (s, 3H), 2.99 (s, 4H), 4.12 (s, 2H), 7.13 (s, 5H).

Anal. Calcd. for $C_{11}H_{15}NO \cdot HCl$: C, 61.82; H, 7.54; N, 6.55. Found: C, 62.10; H, 7.63; N, 6.50.

Methyl 1-(2-Hydroxyethyl)-3-methoxycarbonyl-4-(2-phenylethyl)pyrrole-2-acetate (**7a**).

Ethanolamine (13.4 g., 220 mmoles), dimethyl acetonedicarboxylate (3.5 g., 19 mmoles) and water (2 ml.) were mixed (exothermic reaction) and the resultant was cooled 0-5°. The bromoketone (**6c**, 4.5 g., 20 mmoles) was added slowly in portions with stirring so that the reaction temperature did not exceed 10°. The mixture was then stirred for 1 hour at room temperature, the reaction mixture was made acidic with 4*N* hydrochloric acid, and the resultant was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel (300 g.) the product being eluted with ethyl acetate-hexane (1:1). Crystallization of the product thus obtained from ethyl acetate-hexane gave a solid (2.1 g., 32%) m.p. 55°; uv: 216.5 (13,800), 241.5 (8910), 261 (6170) nm: ir: 3500, 1740, 1695 cm^{-1}; nmr: 2.85 (s, 4H), 3.50-3.90 (m, 4H), 3.65 (s, 3H), 3.72 (s, 3H), 3.97 (s, 2H), 6.24 (s, 1H), 7.12 (s, 5H).

Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 60.07; H, 6.71; N, 4.06. Found: C, 66.06; H, 6.69; N, 3.86.

Methyl 1-(2-Methanesulfonyloxyethyl)-3-methoxycarbonyl-4-(2-phenylethyl)pyrrole-2-acetate (**7b**).

Trimethylamine (0.45 g., 4.5 mmoles) was added slowly, at 0°, to a stirred solution of the alcohol (**7a**, 1.18 g., 3.4 mmoles) in anhydrous dichloromethane (15 ml.) containing methanesulfonyl chloride (0.45 g., 4.2 mmoles). The reaction was stirred for 0.5 hour at this temperature, the solution was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residual solid (1.38 g., 97%) on crystallization from ethyl acetate-hexane had m.p. 108-109°; uv: 215.5 (14,500), 238.5 (10,000), 260 (6610) nm; ir: 1745, 1700, 1360, 1145 cm^{-1}; nmr: 2.77 (s, 3H), 2.89 (s, 4H), 3.69 (s, 3H), 3.77 (s, 3H), 4.07 (t, 2H, J = 4.3 Hz), 4.32 (t, 2H, J = 4.3 Hz), 6.37 (s, 1H), 7.17 (s, 5H).

Anal. Calcd. for $C_{20}H_{25}NO_7S$: C, 56.74; H, 5.95; N, 3.30. Found: C, 56.74; H, 5.90; N, 3.38.

Methyl 1-(2-Chloroethyl)-3-methoxycarbonyl-4-(2-phenylethyl)pyrrole-2-acetate (**7c**).

A solution of the methanesulfonate (**7b**, 12.7 g., 30 mmoles) in anhydrous DMF (100 ml.) containing lithium chloride (5.1 g., 120 mmoles) was heated at 70-80° for 1 hour. Water was added to the solution at room temperature and the product was extracted into ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The solid which remained (10.0 g., 91%) had m.p. 76° after crystallization from ether-hexane; uv: 214.5 (17,800), 238.5 (10,200), 260 (6460) nm; ir: 1743, 1698 cm^{-1}; nmr: 2.88 (s, 4H), 3.62-4.17 (m, 4H), 3.68 (s, 3H), 3.76 (s, 3H), 4.04 (s, 2H), 6.27 (s, 1H), 7.13 (s, 5H).

Anal. Calcd. for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.10; N, 3.85. Found: C, 62.51; H, 6.13; N, 3.82.

Methyl 1-Vinyl-3-Methoxycarbonyl-4-(2-phenylethyl)pyrrole-2-acetate (**7d**).

A solution of the chloride (**7c**, 3.93 g., 10.8 mmoles) in methanol (60 ml.) and 2-propanol (20 ml.) containing potassium hydroxide (1.79 g., 86%, 27.5 mmoles) was heated at reflux temperature for 8 hours. The solvent was removed *in vacuo*, the residue was made acidic with 10% hydrochloric acid, and the products were extracted into ethyl acetate. The extract was evaporated *in vacuo* and ethereal diazomethane was added to the residue. The solvent was removed and the residue was subjected to chromatography on silica gel (320 g.) using ethyl acetate-hexane (1:4) as the eluting solvent. The desired vinyl compound was eluted first followed by *ca.* 10% of the hydroxy compound (**7a**). The vinyl compound (2.7 g., 77%) had m.p. 66-67° after crystallization from ether-hexane; uv: 220 (18,600), 231 (20,000), 263 (14,800) nm; ir: 1742, 1698, 1648 cm^{-1}; nmr: 2.90 (s, 4H), 3.66 (s, 3H), 3.78 (s, 3H), 4.83 (d, 1H, J = 9.8 Hz), 5.12 (d, 1H, J = 15.8 Hz), 6.65 (s, 1H), 6.82 (q, 1H, J = 9.8, 15.8 Hz), 7.18 (s, 5H).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.57; H, 6.56; N, 4.25.

Methyl 1-(1-Hydroxyethyl)-3-methoxycarbonyl-4-(2-phenylethyl)pyrrole-2-acetate (**7e**).

A solution of the vinyl compound (5.0 g., 15.3 mmoles) in acetonitrile (50 ml.) containing water (2 ml.) and concentrated hydrochloric acid (3 ml.) was left at room temperature the reaction being carefully monitored by tlc [ethyl acetate-hexane (1:3)]. As soon as the starting material had disappeared (0.75 hour) saturated sodium chloride solution (100 ml.) was added the organic phase was separated and washed again with saturated sodium chloride solution (50 ml.). The organic phase was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (290 g.) using ethyl acetate-hexane (1:3) as the eluting solvent. The product (4.0 g., 76%) had m.p. 93° after crystallization from ether-hexane; uv: 212.5 (15,100), 238.5 (8910), 260 (6030) nm; ir: 3460, 1722, 1698 cm^{-1}; nmr: 1.62 (d, 3H, J = 5.9 Hz), 2.87 (s, 4H), 3.73 (s, 3H), 3.76 (d, 1H, J = 17.2 Hz), 3.79 (s, 3H), 4.52 (d, 1H, J = 17.2 Hz), 5.73 (q, 1H, J = 5.9 Hz), 6.64 (s, 1H), 7.19 (s, 5H).

Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.05. Found: C, 65.82; H, 6.70; N, 3.88.

Methyl 3-Methoxycarbonyl-4-(2-phenylethyl)pyrrole-2-acetate (**7f**).

A solution of the hydroxy compound (**7e**, 3.54 g., 10.3 mmoles) in acetonitrile (40 ml.) containing water (2 ml.) was mixed with silver benzoate (2.83 g., 12 mmoles) and the mixture was heated at reflux temperature for 5 minutes. Saturated sodium chloride solution was added to the cooled mixture, the organic phase was separated, washed with saturated salt solution and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (240 g.) using ethyl acetate-hexane (3:7) as the developing solvent. There was obtained a solid (2.68 g., 87%) which had m.p. 81° after crystallization from ether-hexane; uv: 212.5 (12,600), 232.5 (7940), 260 (5500), nm; ir: 3740, 3440, 1733, 1700 cm^{-1}; nmr: 2.93 (s, 4H), 3.73 (s, 3H), 3.77 (s, 3H), 4.06 (s, 2H), 6.41 (d, 1H, J = 2.0 Hz), 7.20 (s, 5H), 9.44 (m, 1H, W_H = 15 Hz).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.75; H, 6.17; N, 4.58.

Methyl 1-Methyl-3-methoxylcarbonyl-4-(2-phenylethyl)pyrrole-2-acetate (**7g**).

A solution of the aminoketone hydrochloride (**6e**, 5.21 g., 24 mmoles) in water (40 ml.) was added rapidly to a mixture of pyrrolidine (1.43 g., 20 mmoles) and dimethyl acetonedicarboxylate (5.27 g., 29 mmoles) in dimethoxyethane (40 ml.). The mixture was heated at reflux temperature for 24 hours, the dimethoxyethane was removed *in vacuo*, and the aqueous phase was extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (600 g.) using hexane-ethyl acetate (4:1) as the eluting solvent. In this way, a mixture of the product and dimethyl acetonedicarboxylate was obtained. The latter was removed by distillation *in vacuo* (70°/0.5 mm.) and the residue was crystallized from ethyl acetate-hexane to give the product (4.60 g., 61%), m.p. 70-71°, in two crops; uv: 242 (8510), 256.5 (6030) nm: ir: 1745, 1700 cm^{-1}; nmr: 2.87 (s, 4H), 3.43 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 4.00 (s, 2H), 6.18 (s, 1H), 7.13 (s, 5H).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.52; H, 6.64; N, 4.34.

1-Methyl-3-carboxy-4-(2-phenylethyl)pyrrole-2-acetic Acid (**7h**).

The pyrrole diester (**7g**, 3.15 g., 10 mmoles) in methanol (20 ml.) and water (10 ml.) containing sodium hydroxide (2.0 g., 50 mmoles) was heated at reflux temperature for 12 hours. The solvent was removed *in vacuo*, water (5 ml.) was added to the residue and the solution was made acidic with 50% hydrochloric acid. The precipitated solid was collected by filtration, washed with cold water and dried. Crystallization of this solid (2.80 g., 86%) from methanol gave a material which decomposed at 250-300°. The elemental analysis of this substance corresponded to that expected for the mono potassium salt of the expected dicarboxylic acid.

Anal. Calcd. for $C_{16}H_{16}\cdot KNO_4$: C, 59.03; H, 4.95; N, 4.30. Found: C, 59.08; H, 5.02; N, 4.39.

The above salt was mixed with water and concentrated hydrochloric acid and the resultant was extracted with ethyl acetate. Removal of the solvent *in vacuo* and crystallization of the residue from methanol gave the desired dicarboxylic acid, m.p. 191-192° uv: 243 (6610), 262 (5890) nm; ir: (potassium bromide): 2640, 2560, 1715, 1655 cm^{-1}; nmr (perdeuteriomethanol): 2.68 (s, 4H), 3.41 (s, 3H), 3.93 (s, 2H), 6.34 (s, 1H), 7.15 (s, 5H).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.71; H, 5.52; N, 4.76.

Isopropyl 1-Methyl-3-carboxy-4-(2-(phenylethyl)pyrrole-2-acetate (**7i**) and Isopropyl 1-Methyl-4-(2-phenylethyl)pyrrole-2-acetate (**11b**).

A saturated solution of hydrogen chloride in 2-propanol (20 ml.) was added to a solution of the dicarboxylic acid (3.35 g., 12 mmoles) in 2-propanol (250 ml.) and the resultant was heated at reflux temperature for 9 hours. The solvent was removed *in vacuo* and the residue was subjected to column chromatography on silica gel (200 g.) using ethyl acetate-hexane (3:7) as the eluting solvent. The mono ester (**11b**, 1.20 g., 35%) was eluted first followed by the mono acid mono ester (**7i**, 0.30 g.,

8%). This latter material was the exclusive product if the esterification was conducted at 0° in 2-propanol which was 2*N* in hydrogen chloride. After crystallization from ethyl acetate-hexane it had m.p. 150°; uv: 243 (7590), 260 (5420) nm; ir (potassium bromide): 2635, 1734, 1662 cm^{-1}; nmr: 1.21 (d, 6H, J = 6.1 Hz), 2.91 (s, 4H), 3.42 (s, 3H), 3.98 (s, 2H), 4.95 (septet, 1H, J = 6.1 Hz), 6.19 (s, 1H), 7.12 (s, 5H).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.08; H, 6.83; N, 3.96.

The mono ester (**11b**) had m.p. 48-49° after crystallization from ethyl acetate-hexane; uv: 217 (11,500) nm; ir: 1738 cm^{-1}; nmr: 1.22 (d, 6H, J = 6.2 Hz), 2.74 (s, 4H), 3.45 (s, 3H), 3.48 (s, 2H), 4.94 (septet, 1H, J = 6.2 Hz), 5.82 (d, 1H, J = 2.0 Hz), 6.26 (d, 1H, J = 2.0 Hz), 7.11 (s, 5H).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.53; H, 8.81; N, 4.68.

Methyl 6-(2-Phenylethyl)-7-carbomethoxy-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate (**8a**).

A solution of the methanesulfonate (**7b**, 4.2 g., 10 mmoles) in dry DMF (18 ml.) was added to a stirred suspension of sodium hydride (0.28 g., 12 mmoles) in the same solvent (70 ml.) maintained in a nitrogen atmosphere. After 0.5 hour, the solution was diluted with water and the product was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residual solid (2.94 g., 90%) had m.p. 97-98° after crystallization from ethyl acetate-hexane; uv: 215 (14,500), 239.5 (8710), 260 (6310), nm; ir: 1740, 1705 cm^{-1}; nmr: 2.45-3.12 (m, 2H), 2.91 (s, 4H), 3.68 (s, 3H), 3.72 (s, 3H), 3.75-4.42 (m, 3H), 6.30 (s, 1H), 7.17 (s, 5H).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.46; N, 4.27. Found: C, 69.86; H, 6.54; N, 4.42.

Dimethyl 1,2,3,5,6,11-Hexahydrobenzo[5,6]cyclohepta[1,2-*f*]pyrrolizidin-11-one-3,4-dicarboxylate (**9a**).

A solution of the bicyclic ester (**8a**, 6.72 g., 20 mmoles) in benzene (60 ml.) was mixed with a saturated solution of phosgene in benzene (60 ml.) and the resultant was heated at reflux temperature for 2 hours. The solvent was removed *in vacuo* leaving a solid, m.p. 116-117°, which was added to polyphosphoric acid (45 g.). The mixture was heated at 70° for 1 hour, water (150 ml.) was added, and the product was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The solid (5.0 g., 71%) which remained had m.p. 137-138° after crystallization from ethyl acetate-hexane; uv: 216 (15,100), 232 (16,600), 242 (16,200), 264 (6610), 319.5 (15,100) nm; ir: 1745, 1718, 1622 cm^{-1}; nmr: 2.53-3.43 (m, 6H), 3.72 (s, 3H), 3.76 (s, 3H), 4.18 (q, 1H, J_{AX} = 5.9 Hz, J_{BX} = 8.1 Hz), 4.56 (t, 2H, J = 7.2 Hz), 7.10-7.45 (m, 3H), 7.83-8.07 (m, 1H).

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.01; H, 5.21; N, 4.03.

1,2,3,5,6,11-Hexahydrobenzo[5,6]cyclohepta[1,2-*f*]pyrrolizidin-11-one-3,4-dicarboxylic Acid (**9b**).

A solution of the diester (**9a**, 3.53 g., 10 mmoles) in methanol (20 ml.) and water (5 ml.) containing 85% potassium hydroxide (3.92 g., 60 mmoles) was heated at reflux temperature for 16 hours. The methanol was removed *in vacuo*, water (10 ml.) was added to the residue and the solution was made acidic with 50% hydrochloric acid. The solid which separated was collected by filtration, washed well with water and dried *in vacuo*. Crystallization of this material (2.93 g., 90%) from methanol gave a solid with m.p. 260-265° dec.; uv: 218 (13,800), 233 (15,500), 243 (15,100), 265 (6030), 323 (1480) nm; ir (potassium bromide): 2600, 1695, 1623, 1595 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 2.41-3.50 (m, 6H), 4.13 (q, 1H, J_{AX} = 5.2 Hz, J_{BX} = 8.8 Hz), 4.47 (t, 2H, J = 6.7 Hz), 7.12-7.45 (m, 3H), 7.75-8.02 (m, 1H).

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.45; H, 4.65; N, 4.31. Found: C, 66.37; H, 4.65; N, 4.21.

Isopropyl 4-Carboxy-1,2,3,5,6,11-hexahydrobenzo[5,6]cyclohepta[1,2-*f*]pyrrolizidin-11-on-3-acetate (**9c**).

A solution of the diacid (**9b**, 2.0 g., 62 mmoles) in 2-propanol (50 ml.) saturated with hydrogen chloride was left at room temperature for 12 hours. The solvent was removed *in vacuo* and the solid (2.0 g., 88%) thus obtained was crystallized from ethyl acetate-hexane to give the product, m.p. 189-190°; uv: 217 (14,500), 232 (15,500), 243 (14,500), 264 (5890), 323.5 (15,100) nm: ir: 2600, 1735, 1680, 1620 cm^{-1}; nmr: 1.25 (d, 2H, J = 6.1 Hz), 2.53-2.86 (q, 2H), 2.97-3.39 (m, 4H), 4.18 (q, 1H, J_{AX} = 5.8 Hz, J_{BX} = 8.6 Hz), 4.57 (t, 2H, J = 7.4 Hz); 5.04 (septet, 1H, J = 6.1 Hz), 7.12-7.55 (m, 3H), 7.96 (m, 1H), 11.22 (m, 1H, W_H = 14 Hz).

Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.66; H, 5.71; N, 3.63.

Isopropyl 1,2,3,5,6,11-Hexahydrobenzo[5,6]cyclohepta[1,2-*f*]pyrrolizidine-11-one-3-carboxylate (**9d**).

The carboxylic acid (**9c**, 1.00 g., 2.7 mmoles) was heated at 180°/1 mm. As the decarboxylation proceeded a distillate was collected. This distillate contained the product as well as starting material. The mixture was separated by column chromatography on silica gel (100 g.) using ethyl acetate-hexane (3:7) as the eluting solvent. About 15% of the starting acid was recovered. The product (0.62 g., 70%) was an oil which was used as such in the next step uv: 215 (8510), 222 (8320), 257 (6920), 331 (18,200) nm; ir: 1735, 1612, 1590 cm^{-1}; nmr: 1.25 (d, 6H, J = 6.1 Hz), 2.53-3.33 (m, 6H), 3.82-4.05 (m, 1H), 4.30-4.74 (m, 2H), 5.04 (septet, 1H, J = 6.1 Hz), 5.92 (s, 1H), 7.07-7.53 (m, 3H), 7.87-8.17 (m, 1H).

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.53; H, 6.57; N, 4.35.

1,2,3,5,6,11-Hexahydrobenzo[5,6]cyclohepta[1,2-*f*]pyrrolizidin-11-one-3-carboxylic Acid (**9e**).

A solution of the isopropyl ester (**9d**, 0.500 g., 1.55 mmoles in methanol (20 ml.) and water (5 ml.) containing potassium carbonate (0.312 g., 2.26 mmoles) was heated at reflux temperature for 3 hours. The solvent was removed *in vacuo*, the residue was made acidic with 50% hydrochloric acid and the product was extracted into ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. A white solid (0.411 g., 94%) was obtained which had m.p. 180° after crystallization from ethyl acetate-hexane; uv: 219 (8130), 258 (6760), 337 (17,800) nm; ir (potassium bromide): 2600, 1665, 1615 cm^{-1}; nmr: (deuteriochloroform-DMSO-d_6): 2.57-3.17 (m, 6H), 3.83-4.08 (m, 1H), 4.23-4.72 (m, 2H), 5.98 (s, 1H), 7.09-7.50 (m, 3H), 7.87-8.28 (m, 1H).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.50; H, 5.41; N, 4.90.

Methyl 3-Methoxycarbonyl-4,5-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]pyrrol-10-one-2-acetate (**13a**).

A solution of the diester (**7f**, 2.12 g., 7 mmoles) in toluene (120 ml.), which was 20% by weight in phosgene, was heated at reflux temperature for 6 hours. The solvent was removed *in vacuo* and the crude acid chloride (**11a**) was mixed with polyphosphoric acid (32 g.). The stirred mixture was heated at 80-85° for 0.75 hour, water was added to the mixture at room temperature and the product was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was purified by column chromatography on silica gel (80 g.) using ethyl acetate-hexane (1:4) as the eluting solvent. The product (1.12 g., 49%) had m.p. 173° after crystallization from dichloromethane-hexane; uv: 211 (21,900), 228 (17,800), 241 (15,500), 260 (7760), 323 (15,500) nm; ir: 3430, 3260, 1745, 1705, 1615, 1590 cm^{-1}; nmr: 3.00-3.39 (m, 4H), 3.67 (s, 3H), 3.83 (s, 3H), 4.18 (s, 2H), 7.16-7.56 (m, 3H), 7.84-8.07 (m, 1H), 11.42 (m, 1H, W_H = 14 Hz).

Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.04; H, 5.24; N, 4.28. Found: C, 65.88; H, 5.28; N, 4.26.

3-Carboxy-4,5-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]pyrrol-10-one-2-acetic Acid (**13b**).

A solution of the ester (**13a**, 1.50 g., 4.6 mmoles) in methanol (50 ml.) and water (10 ml.) containing 85% potassium hyroxide (1.21 g., 18 mmoles) was heated at reflux temperature for 24 hours. The reaction was worked up in the manner described for compound (**7h**) except that 10% hydrochloric acid was used. After crystallization from methanol, the pro-

duct (1.26 g., 92%) decomposed at 248-300°; uv: 211.5 (17,800), 227 (13,800), 242 (13,200), 260 (21,400), 330 (14,500) nm; ir (potassium bromide): 3250, 2600, 1705, 1668, 1605, 1587, 1550 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 2.94-3.43 (m, 4H), 4.05 (s, 2H), 7.00-7.57 (m, 3H), 7.86-8.07 (m, 1H).

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.14; H, 4.44; N, 4.63.

Isopropyl 3-Carboxy-4,5-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]pyrrol-10-one-2-acetate (**13c**).

A saturated solution of hydrogen chloride in 2-propanol (10 ml.) was added to a solution of the diacid (**13b**, 1.00 g., 3.3 mmoles) in 2-propanol (80 ml.) and the resultant was heated at reflux temperature for 35 minutes. Water (250 ml.) was added to the solution at room temperature, the product was collected by filtration, washed with water and dried. This solid (1.00 g., 88%) had m.p. 243-244° after crystallization from aqueous DMF; uv: 211.5 (20,900), 225 (16,200), 240 (13,800), 260 (6760), 328 (15,500) nm; ir (potassium bromide): 3275, 3250, 2600, 2550, 1749, 1670, 1611, 1585, 1551 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 1.28 (d, 3H, J = 6.4 Hz), 2.95-3.44 (m, 4H), 4.05 (s, 2H), 5.00 (septet, 1H, J = 6.4 Hz), 7.13-7.58 (m, 3H), 7.87-8.05 (m, 1H).

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.78; H, 5.63; N, 4.08.

Isopropyl 4,5-Dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]pyrrol-10-one-2-acetate (**13d**).

The ester (**13c**, 0.60 g., 1.8 mmoles) was heated at 240-250°/90 mm for 1.5 hours. The material which resulted was subjected to column chromatography on silica gel (60 g.) using ethyl acetate-hexane (1:4) as the eluting solvent. The product (0.30 g., 57%) had m.p. 123-124° after crystallization from ethyl acetate-hexane; uv: 210.5 (10,500), 225 (7590), 256.5 (7240), 333 (16,600) nm; ir: 3450, 3275, 1737, 1613, 1593, 1565 cm^{-1}; nmr: 1.23 (d, 6H, J = 6.3 Hz), 2.82-3.22 (m, 4H), 3.73 (s, 2H), 5.14 (septet, 1H, J = 6.3 Hz), 6.00 (d, 1H, J = 2.2 Hz), 7.10-7.58 (m, 3H), 7.94-8.17 (m, 1H), 10.37 (m, 1H, W_H = 16 Hz).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.39; N, 4.71. Found: C, 72.53; H, 6.44; N, 4.64.

4,5-Dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]pyrrol-10-one-2-acetic Acid (**13e**).

A solution of the ester (**13d**, 0.50 g., 1.7 mmoles) in methanol (20 ml.) and water (5 ml.) containing 85% potassium hyroxide (0.28 g., 4.2 mmoles) was heated at reflux temperature for 4 hours. The reaction was worked up in the manner described for the hydrolysis of compound (**9d**) except that 10% hydrochloric acid was used. Crystallization of the crude product from acetone-benzene gave a solid (0.37 g., 85%) m.p. 170-171°; uv: 212.5 (11,800), 224 (10,200), 228 (10,200), 240 (9120), 260 (4370), 327.5 (10,000) nm; ir (potassium bromide): 3320, 2675, 2550, 2475, 1718, 1604, 1536 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 2.72-3.22 (m, 4H), 3.34 (s, 2H), 6.00 (s, 1H), 7.20-7.53 (m, 3H), 7.83-8.22 (m, 1H), 11.08 (m, 1H, W_H = 15 Hz).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.13; N, 5.48. Found: C, 70.60; H, 5.12; N, 5.49.

Isopropyl 1-Methyl-4,5-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]pyrrol-10-one-2-acetate (**13f**).

A solution of the ester (**11b**, 1.20 g., 4.21 mmoles) in benzene (20 ml.) which was 12% by weight in phosgene was heated at reflux temperature for 1 hour. The excess phosgene was removed by passing a stream of dry nitrogen through the solution. This caused the precipitation of the solid acid chloride (**11e**), m.p. 68°, which was used directly in the next step. Thus, the acid chloride was mixed with polyphosphoric acid (25 ml.) and the mixture was heated with stirring at 60° for 0.75 hour. After the usual workup, the crude product was subjected to column chromatography on silica gel using ethyl acetate-hexane (1:4) as the eluting solvent. The product (0.400 g., 31%) which was an oil, was eluted first followed by the starting material (*i.e.* **11b**, 0.32 g.). The crude product was used directly in the next step; uv: 226 (6310), 256 (4900), 328 (13,200) nm; ir: 1740, 1700, 1618, 1600 cm^{-1}; nmr: 1.22 (d, 6H, J = 6.1 Hz), 2.68-3.10 (m, 4H), 3.55 (s, 2H), 3.89 (s, 3H), 4.96 (septet, 1H, J = 6.1 Hz), 5.87 (s, 1H), 6.97-7.37 (m, 3H), 7.72-7.92 (m, 1H).

1-Methyl 4,5-Dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]pyrrol-10-one-2-acetic Acid (**13g**).

A solution of the isopropyl ester (0.44 g., 1.3 mmoles) in methanol (10 ml.) and water (5 ml.) was heated at reflux temperature for 1 hour. The reaction was worked up as described for compound (**9d**), except that 20% hydrochloric acid was used. After crystallization from ethyl acetate-hexane the product (0.29 g., 83%) had m.p. 164-165°; uv: 230 (4900), 256 (3550), 334 (11,200) nm; ir: 1730, 1620 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 2.75-3.08 (m, 4H), 3.59 (s, 2H), 3.93 (s, 3H), 5.92 (s, 1H), 7.01-7.34 (m, 3H), 7.74-7.88 (m, 1H).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.30; H, 5.73; N, 5.11.

REFERENCES AND NOTES

(1) Contribution No. 547 from the Syntex Institute of Organic Chemistry.

(2) Present address: Syntex Research, Institute of Organic Chemistry, 3401 Hillview Ave., Palo Alto, Ca. 94304.

(3) J. R. Carson, D. N. McKinstry and S. Wong, *J. Med. Chem.*, **14**, 646 (1971); J. R. Carson and S. Wong, *ibid.*, **16**, 172 (1973).

(4) J. Ackrell, Y. Antonio, F. Franco, R. Landeros, A. Leon, J. M. Muchowski, M. L. Maddox, P. H. Nelson, W. H. Rooks, A. P. Roszkowski and M. B. Wallach, *ibid.*, **21**, 1035 (1978).

(5) J. M. Muchowski and A. F. Kluge, U. S. Patents 4,087,539 (1978); 4,089,969 (1978); 4,097,579 (1978).

(6a) R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, London, 1977, pp. 57-62; (b) A. Gossauer, "Die Chemie per Pyrrole", Springer-Verlag, 1974, pp. 224-225.

(7) A. Bhati and N. Kale, *Angew. Chem., Int. Ed. Engl.*, **6**, 1086 (1967).

(8) The structural nature of this compound was established by sequential saponification, Fischer esterification of the acetic acid carboxyl group, and thermal decarboxylation to a compound which had nmr spectral absorptions with a coupling constant (J = 4 Hz) typical [6b (pp. 82-85), 9] of 2,5-disubstituted pyrroles.

(9) R. A. Jones, in "Advances in Heterocyclic Chemistry", A. R, Katritzky and A. J. Boulton, Eds., Vol. 11, Academic Press, New York, N. Y. 1970, pp. 464-472.

(10) H. J. Anderson and J. K. Groves, *Tetrahedron Letters*, 3165 (1971).

(11) H. Bredereck, F. Effenberger and E. Henseleit, *Chem. Ber.*, **98**, 2754 (1965).

(12) This synthesis has considerable generality. Full details will be published elsewhere (A. Guzmán and N. Tun Naal, unpublished data).

(13) As determined by assays in rats, compound **13e** was considerably less active than phenylbutazone, while acids **9e** and **13g** were essentially equiactive with phenylbutazone, as antiinflammatory agents. The analgetic potency, in mice, was 7, 0.4 and 3 times aspirin for compounds **9e**, **13e** and **13g**, respectively. The animal assays were conducted in the manner described in reference 4. We thank Dr. N. Ackerman for this data.

(14) These absorptions show doubling because of restricted rotation associated with the formamide residue. The ratio of the high to the lower field resonances in each case was about 3:7.