Novel Rearrangement of an Isoxazole to a Pyrrole. *X*-Ray Molecular Structure of Diethyl 5-(Ethoxycarbonylmethyl)pyrrole-2,4-dicarboxylate

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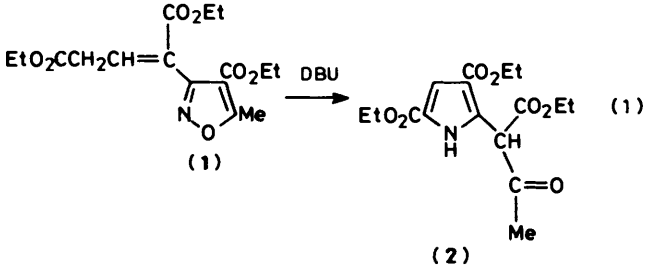
A basic and novel example of mononuclear heterocyclic rearrangement, the isoxazole–pyrrole conversion, was realized by the rearrangement of diethyl 2-(4-ethoxycarbonyl-5-methylisoxazol-3-yl)glutaconate to diethyl 5-(1-ethoxycarbonyl-2-oxopropyl)pyrrole-2,4-dicarboxylate. An ethoxy-migration was observed in the condensation reaction of 7-ethoxymethylene-6,7-dihydroxy-3-methylpyrano[4,3-*c*]isoxazole-4,6(7*H*)-dione with diethyl malonate.

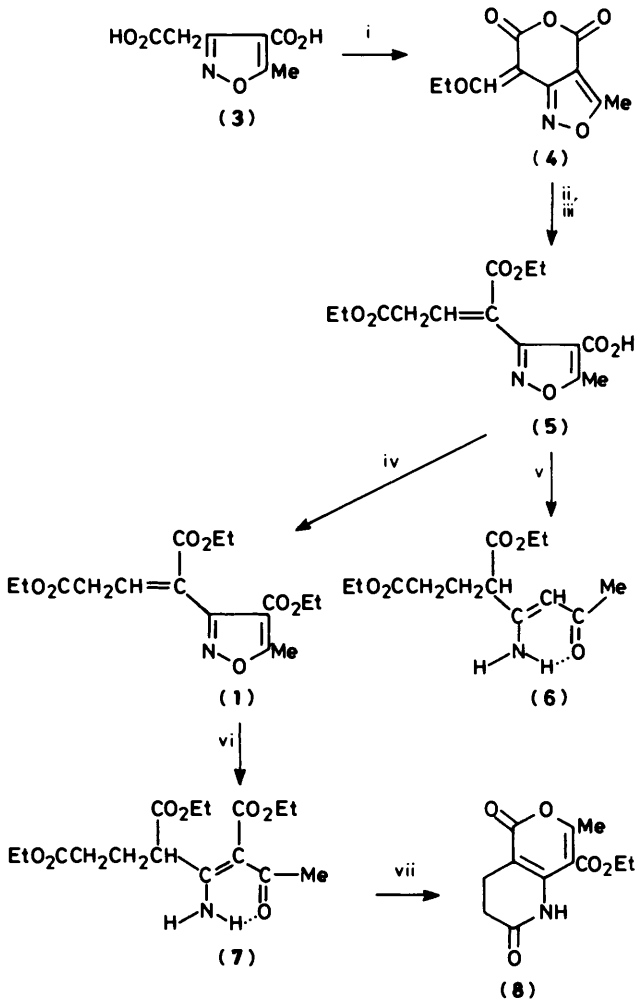
The rearrangement of several five-membered heterocyclic compounds by the following scheme is well known.[1] This scheme

includes many possible azole–azole interconversions but the known examples are limited to heterocycles containing an N–O bond (*i.e.* isoxazoles and oxadiazoles). The 'abc' side-chain is a heteroallyl moiety and the nucleophilic centre (c) is usually a heteroatom (N, O, or S). However, there are also some rearrangements reported with a carbanion as the nucleophilic centre,[2] giving imidazole as the final ring.

The present communication reports on the first synthesis of pyrroles by a mononuclear heterocyclic rearrangement—realizing the isoxazole–pyrrole conversion. This is the first and most basic example of rearrangements which involve a non-hetero allyl side-chain. This is realized by transformation (1).



The starting compound, diethyl 2-(4-ethoxycarbonyl-5-methylisoxazol-3-yl)glutaconate (**1**), was obtained as shown in (Scheme 1). By analogy with the known azlactone synthesis, a condensation reaction of the isoxazole-acetic acid (3)[3] in acetic anhydride with triethyl orthoformate produced the dione (**4**) *via* a cyclic anhydride intermediate. Compound (**4**) did not give the expected simple condensation reaction, because the triethylamine salt formed in the condensation of dione (**4**) with excess of diethyl malonate in the presence of triethylamine lost carbon dioxide on heating in acidic water and was converted into diester (**5**). The structure of compound (**5**) was proved on the one hand by its convertion on catalytic hydrogenation into compound (**6**), and on the other hand by its esterification to the triester (**1**). The structure of compound (**1**) was confirmed by the fact that the acid-catalysed thermal

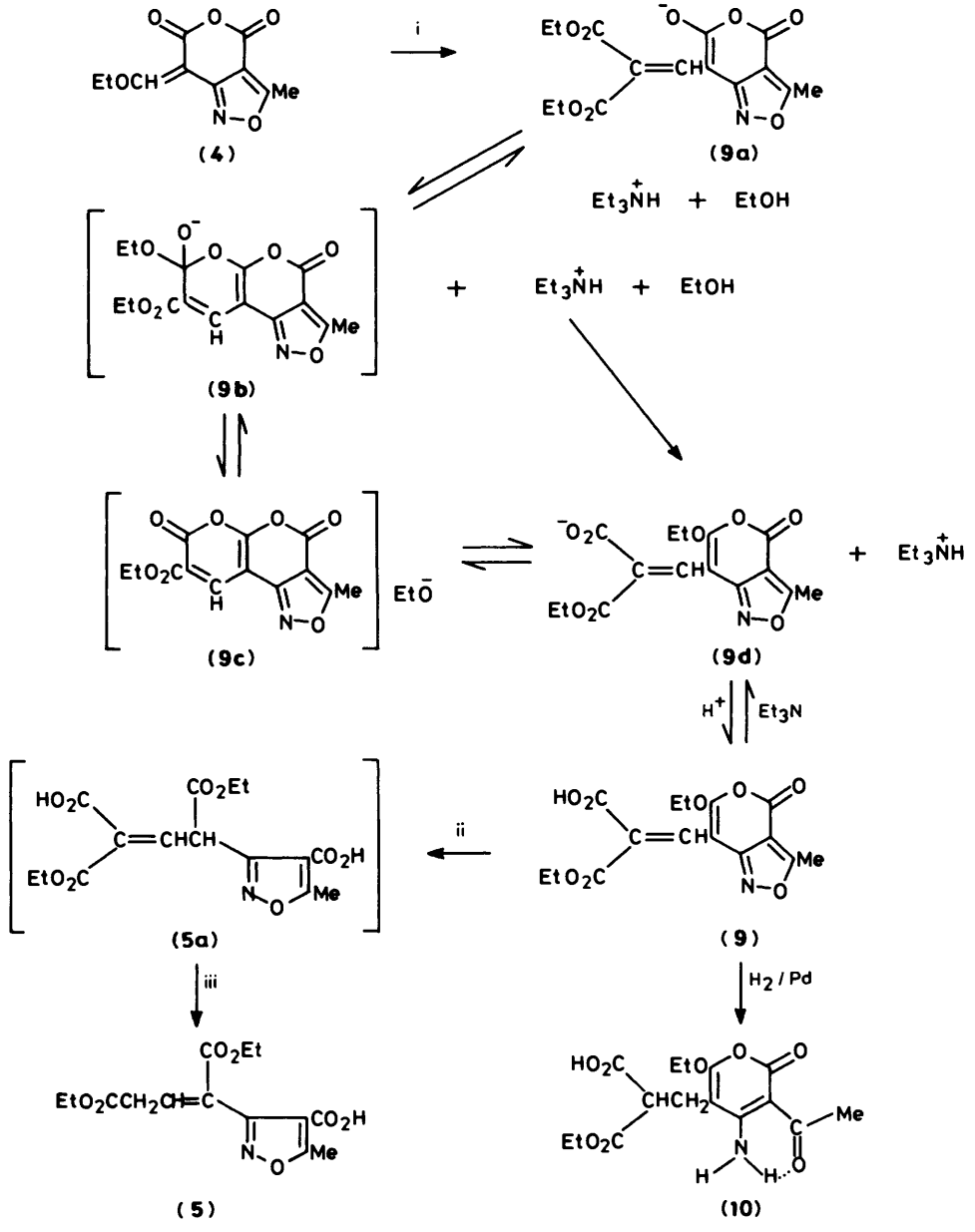


Scheme 1. *Reagents and conditions:* i, Ac_2O, $(EtO)_3CH$; ii, $(EtO_2C)_2CH_2$, E_3N; iii, H_2O^+, heat, $-CO_2$; iv, EtOH, H^+; v, H_2/Pd, CO_2; vi, H_2/Pd; vii, BF_3·Et_2O, heat, $-2EtOH$

cyclization of compound (7), formed in the catalytic hydrogenation of the isoxazole (1), yielded the bicyclic lactam (8).

As in analogous derivatives[4] a strong hydrogen bond is formed between the amino and the acetyl groups in compounds (6) and (7). In the ^{1}H n.m.r. spectrum of triester (7) the signal of 3-H is at δ_H 4.04, *i.e.* at lower field (by 0.91 p.p.m.) than the corresponding signal in compound (6). This is a consequence of the anisotropic effect of the 5-ethoxycarbonyl group. The signal of the acetyl group of triester (7) is at δ_H 2.23, *i.e.* a downfield shift of 0.24 p.p.m. in comparison with (6). Considering these data it is likely that in the predominant conformer of triester (7) the 3-H and the 5-ethoxycarbonyl group are close.

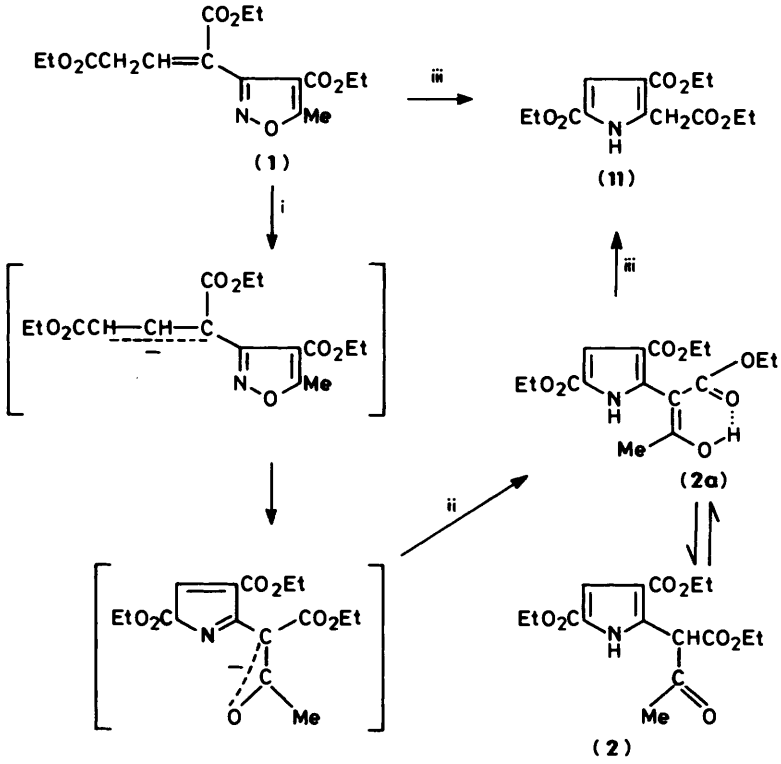
The formation of the isoxazole (5) can be rationalized by the cyclization of the triethylamine salt (9a) primarily formed in the condensation; ethanolysis of the tricyclic intermediates (9b) or (9c) yielded the acidic malonate (9) (Scheme 2). Diester (5) was formed by hydrolysis and decarboxylation from the malonate (9). Indeed, the product obtained by the careful acidification of the triethylamine salt turned out to be compound (9). The structure of compound (9) was confirmed by ^{1}H and ^{13}C n.m.r. spectra which showed the presence of two different ethyl groups' signals: O=C–O*C*H$_2$ δ_C 61.0; δ_H 4.26 (q); C=C–O*C*H$_2$ δ_C 67.6; δ_H 4.65 (q). In the catalytic hydrogenation of the isoxazole (9) cleavage of the isoxazole ring and saturation of the C–C double bond was not followed by decarboxylation. This indicated the presence of the pyrano[4,3-*c*]isoxazole ring in compound (9) and excluded the possibility of an alternative structure. However, the structure of the triethylamine salt is uncertain. Evidence in favour of formula (9d) was given by the fast formation of compound (9) on acidification. When trifluoroacetic acid was added to a solution of the triethylamine salt in deuteriochloroform, after 30 sec only the signals corresponding to compound (9) could be found in the ^{1}H n.m.r. spectrum. Addition of triethylamine and diethyl ether to a solution of compound (9) in ethyl acetate resulted in deposition



Scheme 2. *Reagents and conditions:* i, $(EtO_2C)_2CH_2$, Et_3N; ii, H_2O; iii, heat, $-CO_2$, $\sim H$

of a triethylamine salt which was identical with the primary product of the condensation. These reactions confirm structure (**9d**) by showing a simple acid–base relationship with compound (**9**). However, based on the ^1H and ^{13}C n.m.r. spectra which showed coincident ethoxy signals, structure (**9a**) is more likely [OCH_2 δ_C 60.2 and δ_H 4.18 (q)].

When an ethereal solution of the triethyl ester (**1**) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), compound (**2**) was obtained in an exothermic reaction (Scheme 3). On



Scheme 3. *Reagents and conditions:* i, DBU, $-H^+$; ii, H^+, $\sim$H; iii, KOH–EtOH, $-$AcOH

treatment with ethanolic potassium hydroxide compound (**2**) gives the pyrrolylacetic ester (**11**) by the loss of an acetyl group. The same product is also obtained directly when triester (**1**) was kept with ethanolic potassium hydroxide. Compound (**2**) was shown by n.m.r. spectra to be a 1:3 mixture of the keto and enol forms in deuteriochloroform at room temperature. The signal of the enolic hydroxy group of (**2a**) is at δ_H 13.25, in accord with strong internal hydrogen bonding. The ^{15}N chemical shifts measured for the keto and enol forms also differ in a characteristic manner: (**2a**) δ_N 218.5 p.p.m., and (**2**) δ_N 224.3 p.p.m. In the case of compounds (**2**) and (**11**) the values of the ^{15}N chemical shifts and ^1J(NH) coupling constants [(**2a**) ^1J(NH) 101 Hz and (**2**) ^1J(NH) 102 Hz], determined by the INEPT method, are in good accord with values observed for analogous pyrrole derivatives.[6]

The structure of triester (**11**) was further elucidated by *X*-ray analysis. The molecular diagram is depicted in the Figure. The lattice is built up by hydrogen-bonded dimers around the inversion centres [N(1)–(1)H $\cdots$ O(18) $2-x$, $-y$, $2-z$, H $\cdots$ O 1.990(3) Å, N–H $\cdots$ O 172.1(3)°]. No unusual structural features were observed.

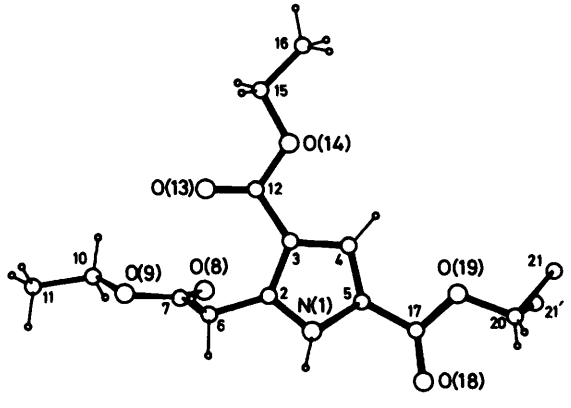


Figure. A diagram of the molecule with the atomic numbering used in the crystal structure analysis. Numbers are for carbon atoms unless indicated otherwise. Hydrogen atoms attached to the disordered C(21) and C(21') atoms are omitted for clarity

Experimental

All the m.p.s were measured on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were measured as KBr discs using a Spectromom 2000 spectrometer. The ^1H, ^{13}C, and ^{15}H n.m.r. spectra were recorded in the PFT mode (16K data point for the FID) at 99.6, 25.0, and 10.04 MHz, respectively, with internal deuterium lock at room temperature using a Jeol FX-100 multinuclear spectrometer. The ^1H and ^{13}C chemical shifts are given on the δ scale (δ_{SiMe_4} 0.0 p.p.m.). The ^{15}N chemical shifts were determined relative to the signal of external $K^{15}NO_3$ (δ_N $-$ 3.55 p.p.m.) and then converted into a scale using the fact that external neat nitromethane has δ_N 0.0 p.p.m.

7-Ethoxymethylene-6,7-dihydro-3-methylpyrano[4,3-c]*isoxazole-4,6(7H)-dione* (**4**) (*Geometry Unknown*).—(4-Carboxy-5-methylisoxazol-3-yl) acetic acid (3)[3] (35 g, 190 mmol) was treated with a mixture of acetic anhydride (70 ml) and triethyl orthoformate (70 ml) at 100 °C for 30 min. The brown solution

obtained was cooled to 0 °C, and the crystals which separated were filtered off, washed with ether, and dried to give the *title dione* (36 g, 85%), m.p. 183—184 °C (from acetic anhydride) (Found: C, 54.1; H, 4.0; N, 6.55. $C_{10}H_9NO_5$ requires C, 53.8; H, 4.1; N, 6.3%); $\nu_{max.}$ 1 780 (CO) and 1 720 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.57 (3 H, t, OCH_2CH_3), 2.80 (3 H, s, 3-Me), 4.56 (2 H, q, OCH_2CH_3), and 8.20 (1 H, s, =CH); $\delta_C(CDCl_3)$ 12.7 (3-CH_3), 15.5 (OCH_2CH_3), 75.4 (OCH_2), 94.1 (C-3a), 102.3 (C-7), 154.6 (C-7a), 161.7 (C-4 and-6), 168.9 (OCH), and 176.1 (C-3); *m/z* 223 (M^+), 195 (9.3%), 167 (43.3), 123 (18.2), 108 (9.3), 84 (5.5), 80 (6.0), 68 (5.4), 52 (12.8), and 43 (100).

Condensation Reaction of Dione (**4**) *and Diethyl Malonate.*—(*a*) Dry triethylamine was added to a stirred and cooled mixture of dione (**4**) (12 g, 54 mmol) and diethyl malonate (25 ml, 158 mmol) at 5 °C. The mixture was stirred for a further 40 min under ice-water cooling, then for 30 min without cooling. The orange crystalline substance which separated was filtered off, washed with ether, and dried in air to give a product [(**9a**) or (**9d**)] (21.7 g, 92%), m.p. 106—107 °C (from ethyl acetate) (Found: C, 57.3; H, 6.8; N, 6.3. $C_{21}H_{30}N_2O_8$ requires C, 57.5; H, 6.85; N, 6.4%); $\nu_{max.}$ 2 680br ($\overset{+}{N}H$), 1 720 (CO), 1 705 (CO), and 1 680 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.26 (6 H, t, OCH_2CH_3), 1.32 (9 H, t, NCH_2CH_3), 2.68 (3 H, s, Me), 3.22 (6 H, q, $\overset{+}{N}CH_2$), 4.18 (4 H, q, OCH_2), 8.10 (1 H, s, CH), and 8.96 (1 H, s, $\overset{+}{N}H$); $\delta_C(CDCl_3)$ 8.9 (NCH_2CH_3), 12.8 (3′-CH_3), 14.1 (OCH_2CH_3), 14.6 (OCH_2CH_3), 46.8 (NCH_2), 60.2 (OCH_2), 78.6 (C-7′), 102.5 (C-2), 159.6 (CO), 163.8 (CO), 167.4 (CO), 169.2 (CO), and 173.9 (C-3′); *m/z* 337 (6.2%) 292 (22.2), 265 (22.9), 245 (12.7), 219 (100), 191 (19.3), 86 (40.3), 43 (84.5), and 29 (93.7).

(*b*) Ether (45 ml) was added to a solution of diester (**9**) (see below) (0.7 g, 2 mmol) and triethylamine (0.4 ml, 2.85 mmol) in ethyl acetate (15 ml). The mixture was kept at 0 °C for 1 h, and the crystalline substance which precipitated was filtered off, washed with ether, and dried in air (0.3 g, 34%), and was shown to be identical with the product obtained as described in (*a*) above on the basis of m.p., mixed m.p., and its i.r. spectrum.

Ethyl Hydrogen (6-*Ethoxy*-3-*methyl*-4-*oxo*-4H-*pyrano*[4,3-c]-*isozazol*-7-*yl*)*methylenemalonate* (**9**).—The triethylamine salt (**9a** or **b**) (17.2 g, 39 mmol) was thoroughly mixed in dichloromethane (160 ml) with conc. HCl (16 ml) and water (60 ml). The dichloromethane phase was separated, washed successively with a mixture of conc. HCl (16 ml) and water (60 ml), and then with water, and evaporated to dryness to afford the *title acid ester* (**9**) (10 g, 70%), m.p. 146—148 °C (decomp.) [from ethyl acetate–n-pentane (1:2)] (Found: C, 53.5; H, 4.9; N, 4.3. $C_{15}H_{15}NO_8$ requires C, 53.4; H, 4.45; N, 4.15%); $\nu_{max.}$ 1 760br (CO) and 1 690 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.32 (3 H, t, $CO_2CH_2CH_3$), 1.52 (3 H, t, OCH_2CH_3), 2.68 (3 H, s, Me), 4.26 (2 H, q, CO_2CH_2), 4.65 (2 H, q, OCH_2), and 8.22 (1 H, s, CH); $\delta_C(CDCl_3)$ 13.5 (3-CH_3), 14.2 (OCH_2CH_3), 14.4 ($COCH_2CH_3$), 61.0 (OCH_2), 67.6 (OCH_2), 91.4 (C-7), 104.2 (CCO_2H), 108.9 (C-3a), 148.9 (C=CH), 157.6 (C-7a), 162.6 (CO), 166.0 (CO), 166.3 (CO), and 176.7 (C-3); *m/z* 337 (M^+, 4.8%), 293 (10.4), 292 (12.8), 291 (16.4), 247 (7.2), 219 (87.1), 191 (18.8), 175 (8.8), 43 (71.8), and 29 (100).

Diethyl 2-(4-*Carboxy*-5′-*methylisoxazol*-3-*yl*)*glutaconate* (**5**) (*Geometry Unknown*).—The acid ester (**9**) (5.2 g, 15.4 mmol) was stirred in water (50 ml) on a water-bath at 100 °C for 10 min. When carbon dioxide evolution ceased, the mixture was cooled, and extracted with dichloromethane, and the extract was evaporated to dryness to give the *diester* (**5**) (3.6 g, 75%), m.p. 98—99 °C [from ethyl acetate–n-pentane (1:2)] (Found: C, 54.1; H, 5.55; N, 4.7. $C_{14}H_{17}NO_7$ requires C, 54.0; H, 5.5; N, 4.5%); $\nu_{max.}$ 1 710 (1 730sh) (CO) and 1 670 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.24 (6 H, t, OCH_2CH_3), 2.74 (3 H, s, Me), 3.30 (2 H, d, *J* 7.3 Hz, 4-H_2), 4.19 (2 H, q, OCH_2), 4.22 (2 H, q, OCH_2), 7.40 (1 H, q, 3-H), and 10.15 (1 H, s, CO_2H); $\delta_C(CDCl_3)$ 13.4 (5′-CH_3), 14.1 (OCH_2CH_3), 35.1 (C-4), 61.3 (OCH_2), 61.4 (OCH_2), 109.1 (C-4′), 124.9 (C-2), 140.5 (C-3), 157.5 (C-3′), 164.4 (CO), 166.7 (CO), 169.6 (CO), and 176.7 (C-5′); *m/z* 311 (M^+, 6.8%) 283 (21.1), 265 (25.2), 237 (22.5), 224 (62.7), 220 (40.2), 219 (45.7), 193 (18.4), 43 (100), and 29 (84.6).

Diethyl 2-(4′-*Ethoxycarbonyl*-5′-*methylisozazol*-3′-*yl*)*glutaconate* (**1**) (*Geometry Unknown*).—The acid ester (**5**) (11.3 g, 36 mmol) was refluxed with a mixture of ethanol (50 ml) and conc. H_2SO_4 (10 ml) for 8 h. The greenish-yellowish solution obtained was poured into ice–water (200 g), and extracted with ether. The extract was washed successively with water, aqueous sodium hydrogen carbonate, and water, dried over $CaCl_2$, decolorized with carbon, and evaporated to dryness. Chromatography on silica gel with benzene–ethanol (7:1) as eluant yielded the *triester* (**1**) (9 g, 71%) as a yellow oil (Found: C, 56.8; H, 6.0; N, 4.4. $C_{16}H_{21}NO_7$ requires C, 56.65; H, 6.2; N, 4.1%); $\nu_{max.}$ 1 710 (1 730sh) (CO) and 1 640 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.24 (6 H, t, OCH_2CH_3), 1.28 (3 H, t, OCH_2CH_3), 2.71 (3 H, s, Me), 3.29 (2 H, d, *J* 7.3 Hz, 4-H_2), 4.10 (2 H, q, OCH_2), 4.15 (4 H, q, OCH_2CH_3), and 7.38 (1 H, t, 3-H); $\delta_C(CDCl_3)$ 12.4 (5′-CH_3), 13.6 (OCH_2CH_3), 34.4 (C-4), 60.3 (OCH_2), 60.6 (OCH_2), 60.7 (OCH_2), 109.4 (C-4′), 125.1 (C-2), 139.7 (C-3), 156.9 (C-3′), 160.9 (CO), 163.4 (CO), 169.0 (CO), and 174.8 (C-5′); *m/z* 339 (M^+, 20.4%), 293 (100), 278 (12.8), 247 (29.8), 219 (68.7), 191 (12.2), 174 (19.5), 150 (15.4), 149 (13.1), and 106 (13.7).

Diethyl 2-[1′-*Amino*-3′-*oxobut*-1′(Z)-*enyl*]*glutarate* (**6**).—Compound (**5**) (2 g, 6.4 mmol) was hydrogenated at room temperature in ethanol (200 ml) in the presence of 5% palladium–carbon catalyst (1 g). After hydrogen uptake the catalyst was filtered off, washed with ethanol, and the filtrate was evaporated to dryness. Chromatography of the residue on silica gel with benzene–ethanol (7:1) as eluant yielded the *amino diester* (**6**) (1.3 g, 75%) as a yellow oil (Found: C, 57.5; H, 7.55; N, 5.3. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.8; N, 5.2%); $\nu_{max.}$ 3 420—3 200 (NH) and 1 740br cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.23 (6 H, t, OCH_2CH_3), 1.99 (3 H, s, Me_3), 2.0—2.5 (4 H, m, CH_2CH_2), 3.13 (1 H, t, 2-H), 5.05 (1 H, s, 2′-H), 6.60 (1 H, br s, NH), and 9.62 (1 H, br s, NH); $\delta_C(CDCl_3)$ 13.0 (OCH_2CH_3), 13.1 (OCH_2CH_3), 26.5 (C-3), 28.2 (C-4′), 30.4 (C-4), 49.5 (C-2), 59.4 (OCH_2), 60.5 (OCH_2), 93.7 (C-2′), 159.8 (C-1′), 170.2 (CO), 171.4 (CO), and 195.8 (C-3′); *m/z* 271 (M^+, 100%), 225 (26), 183 (93.1), 170 (54.1), 167 (15.3), 141 (35.9), 137 (24.4), 110 (25.0), 96 (15.1), and 43 (20.1).

Triethyl 4-*Amino*-6-*oxohept*-4(E)-*ene*-1,3,5-*tricarboxylate* (**7**).—The isoxazole (**1**) (12.0 g, 34.4 mmol) was hydrogenated at 50 °C in ethanol (200 ml) in the presence of 5% palladium–carbon catalyst (2 g). After uptake of 2 equiv. of hydrogen the catalyst was filtered off, washed with ethanol, and the filtrate was evaporated to dryness. The yellow oil obtained was kept at 0 °C overnight. The crystalline substance which had formed was then treated with n-pentane (25 ml), the suspension was filtered, and the solid was dried in air to give the *amino triester* (**7**) (7 g, 59%), m.p. 70—71 °C (from ether) (Found: C, 55.7; H, 7.1; N, 4.4. $C_{16}H_{25}NO_7$ requires C, 55.95; H, 7.35; N, 4.1%); $\nu_{max.}$ 3 300 (NH), 3 150 (NH), and 1 725br cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.23 (3 H, t, OCH_2CH_3), 1.28 (3 H, *t*, OCH_2CH_3), 1.34 (3 H, t, OCH_2CH_3), 2.0—2.5 (4 H, m, CH_2CH_2), 2.23 (3 H, s, Me), 4.04 (1 H, s, 3-H), 4.12 (2 H, q, OCH_2), 4.17 (2 H, q, OCH_2), 4.26 (2 H, q, OCH_2), 6.74 (1 H, brs, NH), and 11.11 (1 H, brs, NH); $\delta_C(CDCl_3)$ 14.2 (OCH_2CH_3) 28.1 (C-2), 30.2 (C-7), 31.6 (C-1), 46.5 (C-3), 60.6 (OCH_2), 61.9 (OCH_2), 103.9 (C-5), 164.2 (C-4), 169.2 (CO), 172.2 (CO), and 197.2 (C-6).

Ethyl 1,3,4,5-*Tetrahydro*-7-*methyl*-2,5-*dioxo*-2H-*pyrano*[4,3-b]*pyridine*-8-*carboxylate* (**8**).—The triester (**7**) (3.4 g, 9.9 mmol) was stirred in decalin (20 ml) for 15 min at 200 °C, then the solution obtained was cooled, boron trifluoride-diethyl ether (0.3 ml, 2.3 mmol) was added, and the mixture was stirred for a further 20 min at 200 °C. The warm solution was decanted from the tarry residue and cooled. The yellow precipitate which formed was filtered off and triturated with ether; the suspension was filtered, and the solid was washed with n-pentane and dried in air to give the *ester lactam* (**8**) (1.4 g, 56%), m.p. 135—136 °C (from ethyl acetate) (Found: C, 57.5; H, 5.0; N, 5.45. $C_{12}H_{13}NO_5$ requires C, 57.4; H, 5.2; N, 5.6%); $\nu_{max.}$ 3 280 (NH), 1 720 (CO), 1 700 (CO), and 1 670 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.40 (3 H, t, OCH_2CH_3), 2.45—2.95 (4 H, m, CH_2CH_2), 2.71 (3 H, s, Me), 4.39 (2 H, q, OCH_2), and 9.82 (1 H, brs, NH); $\delta_C(CDCl_3)$ 14.1 (OCH_2CH_3), 18.6 (4-C), 22.4 (7 CH_3), 29.2 (C-3), 62.4 (OCH_2), 97.8 (C-4a), 132.2 (C-8), 139.2 (C-7), 147.8 (C-8a), 165.5 (CO), 169.9 (CO), and 170.0 (CO); *m/z* 251 (M^+, 30.2%), 250 (13.9), 223 (18.6), 176 (13.9), 55 (18.6), 43 (100), 39 (20.9), 29 (34.8), 28 (34.8), and 27 (37.8).

Ethyl Hydrogen (5-*Acetyl*-4-*amino*-2-*ethoxy*-6-*oxo*-6'H-*pyran*-3-*yl*)*methylmalonate* (**10**).—Compound (**9**) (3 g, 8.9 mmol) was hydrogenated in the presence of 5% palladium–carbon catalyst (1 g) at room temperature. After hydrogen uptake the catalyst was filtered off, and washed with ethyl acetate. The filtrate was evaporated to dryness. The remaining yellow oil crystallized at 0 °C to give the *title compound* (1.7 g, 56%), m.p. 144—145 °C (decomp.) (from Pr^iOH) (Found: C, 52.8; H, 5.5; N, 4.2. $C_{15}H_{19}NO_8$ requires C, 52.8; H, 5.6; N, 4.1%); $\nu_{max.}$ 3 390 (NH), 3 140 (NH), 2 500br (OH), 1 740 (CO), 1 710 (CO), and 1 670 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.24 (6 H, t, OCH_2CH_3), 2.55 (2 H, m, 3-CH_2), 2.58 (3 H, s, Me), 3.50 (1 H, s, NH), 3.78 (1 H, t, CH), 4.18 (4 H, q, OCH_2CH_3), 7.49 (1 H, br s NH), and 11.10 (1 H, br s, OH; $\delta_H(C_5D_5N)$ 1.08 (6 H, t, OCH_2CH_3), 2.94 (3 H, s, Me), 3.50 (2 H, d, 3-CH_2), 4.13 (4 H, q, OCH_2CH_3), 4.43 (1 H, t, OH), and 10.49 (1 H, br s, NH); δ_C (C_5D_5N) 13.7 (OCH_2CH_3), 24.3 (3-CH_2), 32.7 (Me), 51.1 (CH), 60.9 (OCH_2), 80.5 (C-3), 107.9 (C-5), 164.2 (C-4), 169.9 (CO), 170.4 (CO), and 197.2 [C(O)Me].

Diethyl 5-(1'-*Ethoxycarbonyl*-2'-*oxopropyl*)*pyrrole*-2,4-*dicarboxylate* (**2**).—A solution of DBU (6.6 g, 43 mmol) in ether (50 ml) was added dropwise to a stirred, ice-cooled solution of the isoxazole (**1**) (14.5 g, 43 mmol) in ether (50 ml) during 10 min, and the mixture was kept overnight at room temperature. The mixture was then stirred with a mixture of conc. HCl (20 ml) and water (80 ml); the ethereal phase was separated, washed successively with a mixture of conc. HCl (10 ml) and water (50 ml), then with water, dried ($MgSO_4$), decolourized with carbon, and evaporated to dryness to afford the *pyrrolyl triester* (**2**), (6.2 g, 42%), m.p. 95—96 °C [from ether–n-pentane (1:2)] (Found: C, 56.6; H, 5.8; N, 4.3. $C_{16}H_{21}NO_7$ requires C, 56.6; H, 6.2; N, 4.1%); $\nu_{max.}$ 3 180 (NH), 1 700 (CO), and 1 670 cm^{-1} (CO); $\delta_H(CDCl_3)$ [mixture of (**2**) and (**2a**)] 1.12 (3 H, t, OCH_2CH_3), 1.29 (3 H, t, OCH_2CH_3), 1.37 (3 H, t, OCH_2CH_3), 1.90 [0.75 × 3 H, s, $C(OH)CH_3$], 2.37 [0.25 × 3 H, s, $C(O)CH_3$], 3.9—4.45 (6 H, m, 3 × OCH_2), 6.04 (0.25 × 1 H, s, 1'-H), 7.28 (0.25 × 1 H, d, *J* 2.5 Hz, 3-H), 7.37 (0.75 × 1 H, d, *J* 2.5 Hz, 3-H), 10.35 (0.25 × 1 H, d, NH), 10.80 (0.75 × 1 H, d, NH), and 13.25 (0.75 × 1 H, s, OH); $\delta_C(CDCl_3)$ [(**2**) minor] 14.1 (OCH_2CH_3), 29.5 (C-3'), 56.0 (C-1'), 60.0 (OCH_2), 60.8 (OCH_2), 62.6 (OCH_2), 114.8 (C-4), 116.2 (C-3), 122.8 (C-2), 131.9 (C-5), 160.2 (CO_2Et), 163.9 (CO_2Et), 166.9 (CO_2Et), and 199.1 (C-2'); [(**2a**) major] 13.7 (OCH_2CH_3), 19.7 (C-3'), 59.6 (OCH_2), 60.6 (OCH_2), 94.8 (C-1'), 116.2 (C-4), 117.1 (C-3), 121.7 (C-2), 134.5 (C-5), 161.6 (CO), 164.1 (CO), 171.5 (CO), and 176.6 (C-2'); *m/z* 339 (M^+, 19.7%), 297 (55.4), 294 (26.0), 293 (46.5), 251 (100), 237 (14.0), 223 (66.4), 205 (11.0), 177 (32.1), and 43 (28.5).

Diethyl 5-(*Ethoxycarbonylmethyl*)*pyrrole*-2,4-*dicarboxylate* (**11**).—(*a*) A solution of compound (**2**) (2 g, 5.8 mmol) and sodium ethoxide (0.75 g, 11 mmol) or potassium hydroxide (0.6 g, 11 mmol) in ethanol (15 ml) was stirred at 50 °C for 30 min. A precipitate separated. After the mixture had cooled, water (10 ml) was added, followed by conc. HCl (2 ml). The solution obtained was extracted with ether; the extract was washed successively with water, aqueous sodium hydrogen carbonate, and water again, dried ($MgSO_4$), and evaporated to dryness to give the *title triester* (1 g, 50%), m.p. 79—80 °C [from ether–n-pentane (1:1)] (Found: C, 56.55; H, 6.4; N, 5.0. $C_{14}H_{19}NO_6$ requires C, 56.6; H, 6.3; N, 4.7%); $\nu_{max.}$ 3 280 (NH), 1 710 (1 730sh) (CO) and 1 690 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.24 (3 H, t, OCH_2CH_3), 1.35 (3 H, t, OCH_2CH_3), 1.36 (3 H, t, OCH_2CH_3), 4.10 (12 H, s, CH_2), 4.13 (2 H, q, OCH_2), 4.25 (2 H, q, OCH_2), 4.30 (2 H, q, OCH_2), 7.25 (1 H, d, *J* 2.5 Hz, 3-H), and 10.83 (1 H, d, NH); $\delta_C(CDCl_3)$ 13.9 (OCH_2CH_3), 14.1 (OCH_2CH_3), 37.2 (CH_2CO_2Et), 59.8 (OCH_2), 61.0 (OCH_2), 61.6 (OCH_2), 114.7 (C-4), 116.9 (C-3), 121.5 (C-2), 135.2 (C-5), 164.1 (CO), 164.2 (CO), and 169.8 (CO); *m/z* 271 (100%), 226 (26.0), 184 (93.1), 171 (54.1), 156 (13.7), 142 (35.9), 138 (24.4), 110 (25.0), 96 (15.1), and 43 (20.3).

(*b*) A solution of the isoxazole (**1**) (10.6 g, 30.3 mmol) and sodium ethoxide (4.4 g, 65 mmol) or potassium hydroxide (3.65 g, 65 mmol) in ethanol (80 ml) was kept at room temperature for 1 h. Initially the solution became warm and its colour darkened. Water (50 ml) and conc. HCl (8 ml) were added, and the mixture was extracted with ether. The extract was washed successively with water, aqueous sodium hydrogen carbonate, then with water again, and evaporated to dryness. The yellow oil obtained was recrystallized from ether–n-pentane (1:2) to give the title triester (6.2 g, 63%), identical with the product obtained as described in (*a*) on the basis of m.p., mixed m.p., and i.r. spectral data.

Crystal Data of Triester (**11**).—$C_{14}H_{19}NO_6$, M = 297.3. Triclinic, a = 8.241(2), b = 9.105(2), c = 11.249(3) Å, α = 81.46(2), β = 71.50(2), γ = 75.30(2)°, V = 771.8(4) Å^3 (by

Table. Final positional parameters (× 10^4) for the non-hydrogen atoms with their e.s.d.s in parentheses

Atom	*x*	*y*	*z*
O(8)	7 091(3)	1 332(2)	13 616(2)
O(9)	5 302(2)	2 707(2)	15 197(1)
O(13)	3 028(2)	2 622(2)	13 190(2)
O(14)	3 037(2)	2 003(2)	11 339(1)
O(18)	10 079(2)	4 481(2)	8 500(2)
O(19)	8 562(2)	3 407(2)	7 686(1)
N(1)	7 577(2)	4 108(2)	10 904(2)
C(2)	6 238(4)	3 750(3)	11 858(3)
C(3)	5 273(3)	3 093(3)	11 350(3)
C(4)	6 094(3)	3 077(3)	10 056(3)
C(5)	7 510(4)	3 703(3)	9 794(3)
C(6)	5 979(4)	3 989(3)	13 189(3)
C(7)	6 189(4)	2 516(3)	13 998(3)
C(10)	5 366(5)	1 353(4)	16 060(3)
C(11)	4 701(6)	1 798(5)	17 347(3)
C(12)	3 696(4)	2 567(3)	12 075(3)
C(15)	1 414(4)	1 516(4)	11 935(4)
C(16)	988(5)	867(4)	10 965(4)
C(17)	8 844(4)	3 925(4)	8 622(3)
C(20)	9 792(5)	3 556(5)	6 451(4)
C(21)	9 481(8)	2 669(8)	5 627(5)
C(21')	10 360(20)	2 420(20)	6 220(20)

least-squares refinement on diffractometer angles of 25 carefully centred reflections, Mo-K_α radiation, $\lambda = 0.7107$ Å), space group $P\bar{1}$ (from structure refinement), $D_c = 1.27$ g cm^{-3} (by flotation), $Z = 2$, $D_x = 1.279$ g cm^{-3}. The crystal used was in the form of transparent plates, and had dimensions 0.03 × 0.25 × 0.30 mm, $\mu = 0.94$ cm^{-1}.

Data Collection and Processing.—CAD4 diffractometer, $\omega/2\theta$ mode, with ω scan width = 0.40 + 0.35 tanθ, max. scan speed 1° min^{-1}, graphite-monochromated Mo-K_α radiation, 2 397 non-zero reflexions measured ($1.5 \leqslant \theta \leqslant 25.0$), giving 2 024 with $I > 3\sigma(I)$.

Structure Analysis and Refinement.—Direct methods, with full-matrix least-squares refinement of non-hydrogen atoms, were employed. Empirical absorption correction [7] was applied at the end of the isotropic refinement (R dropped from 0.15 to 0.12; maximum and minimum absorption corrections: 0.620 and 1.564, mean 1.019; the large correction affected only a few low-order reflexions). All hydrogen atomic positions were generated from assumed geometries except for 1-H which was located in a difference map. The C-21 methyl group was found to be disordered, the occupancies of the two statistically filled positions refining to 0.74 and 0.26 (primed atoms). Non-hydrogen atoms were refined by anisotropic least-squares but they were included in structure factor calculations. The weighting scheme applied was $w = 1/[\sigma^2(F_o) + 0.01F_o^2]$ with $\sigma(F_o)$ from counting statistics. Anomalous dispersion corrections were applied to O, N, and C atoms. Final R and R_w values are 0.056 and 0.060. Final positional parameters for non-hydrogen atoms are given in the Table. Programs and the computer used, and sources of scattering factor data, are given in ref. 8.*

* *Supplementary data available* (No. SUP 56516, 5 pp.); Anisotropic temperature factors and thermal parameters, bond lengths, and bond angles for compound (**11**). See Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1. Structure factors are available from the editorial office on request.

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