Tetrahedron. Vol. 29, pp. 213 to 220. Pergamon Press 1973. Printed in Great Britain

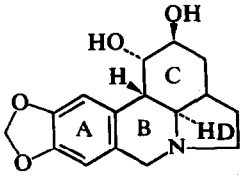
LYCORINE: STUDIES IN SYNTHESIS

S. F. DYKE, M. SAINSBURY and J. R. EVANS
School of Chemistry and Chemical Engineering, University of Bath, Bath, Somerset, England.

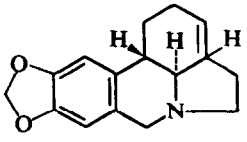
(*Received in the UK* 14 *August* 1972; *Accepted for publication* 5 *September* 1972)

Abstract—Several unsuccessful attempts are described at the synthesis of the carbon-nitrogen skeleton of lycorine, utilising 1,2-dihydroisoquinoline intermediates.

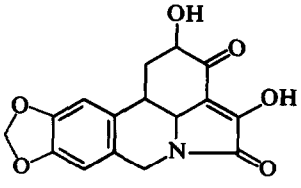
All attempts that have been made so far to synthesise Amaryllidaceae alkaloids of the lycorine (1) type have failed, although compounds containing the pyrrolo[1,2,3-de]phenanthridine nucleus have been prepared. Compounds with ring C aromatic have usually been produced[1-4] by using the Pschorr ring-closure, whereas partially reduced derivatives, such as β-lycorane[5] (2) and (3),[6] have been obtained in sequences utilising a Diels-Alder reaction as the key step.



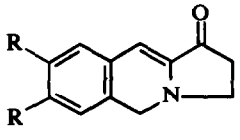
1



2

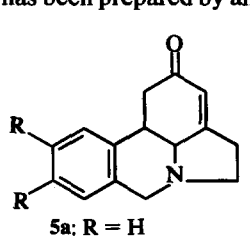


3

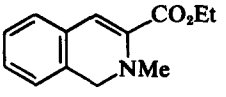


4a: R = H
4b: 2R = CH_2O_2

It has been established[7] that 1,2-dihydroisoquinolines may undergo electrophilic attack (e.g. by aldehydes) at C_4 and, in the derived imminium ion, nucleophilic attack at C_3. The approach to the synthesis of lycorine to be described here involved the preparation of the enamine (**4b**) followed by the introduction of a 3-carbon unit at C_4 capable of cyclisation with the CO function. It was envisaged that pyruvic aldehyde might provide such a fragment and that the tetracyclic compound (**5b**) may result. Since it is known[8] that ring C of lycorine is aromatised by light, oxygen or heat, a synthetic scheme that leaves the formation of ring C to a late stage seemed to possess considerable advantages. Since the completion of our work,[9] the enone (**5b**) has been prepared by an alternative method.[10]

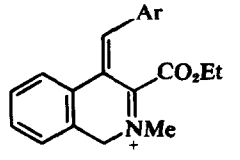


5a: R = H
5b: 2R = CH_2O_2

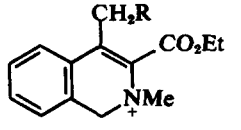


6

1,2-Dihydroisoquinolines that possess an electron-attracting group attached to the enamine system have not been investigated previously, so as a preliminary to our main aim, we studied some properties of the enamine (**6**). The methiodide of the readily available[11,12] methyl isoquinoline-3-carboxylate was reduced easily to **6** with sodium borohydride; even in aqueous ethanol solution, reduction did not proceed any further. The enamine (**6**) reacted normally with piperonal, veratraldehyde, glyoxylic acid and pyruvic aldehyde to give the 1,4-dihydro-4-benzylideneisoquinolines (**7**) or the aromatic quaternary salts (**8**). The 1,2-dihydroisoquinoline (**6**) failed, however, to react with the ethyl acetoacetate under the conditions of the Michael reaction.

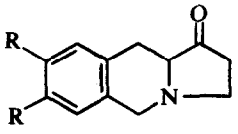


7a: Ar = 3,4-$CH_2O_2C_6H_3$
7b: Ar = 3,4-$(OMe)_2C_6H_3$

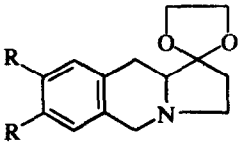


8a: R = 3,4-$CH_2O_2C_6H_3$
8b: R = 3,4-$(OMe)_2C_6H_3$
8c: R = CO_2H
8d: R = $COCH_3$

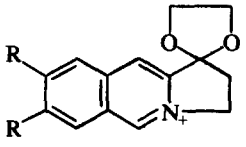
Encouraged by this result, attempts were made to prepare the model compound (**4a**). The known[13] amino ketone (**9a**) gave only black, polymeric material when attempts were made to dehydrogenate it with iodine, but the ethylene ketal (**10a**) when treated with iodine and sodium acetate gave a very small amount of a yellow solid, the spectral characteristics of which are in agreement with those expected for the required salt (**11a**). Insufficient material precluded any further investigation of **11**, in particular its reduction with LAH.



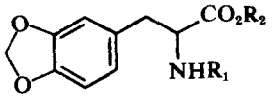
9a: R = H
9b: 2R = CH_2O_2



10a: R = H
10b: 2R = CH_2O_2



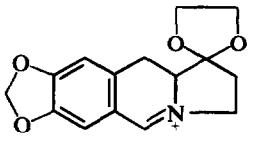
11a: R = H
11b: 2R = CH_2O_2



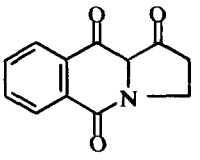
12a: $R_1 = R_2 = H$
12b: $R_1 = CH_2CH_2CN$; $R_2 = H$
12c: $R_1 = CH_2CH_2CO_2Et$; $R_2 = Et$

The tricyclic ketone (**9b**) was prepared in acceptable yield from **12a**, the product obtained from the azlactone of piperonal. Alkylation with 3-bromopropiononitrile gave **12b**, which with sulphuric acid and ethanol yielded the diester **12c**. A Pictet-Spengler reaction on the latter, followed by a Dieckmann ring-closure of the resultant 1,2,3,4-tetrahydroisoquinoline-3-ester produced **9b**, an unstable oil. Oxidation of the derived ketal (**10b**) with iodine as before gave a mixture of **13** and the required **11b**. The former was converted into the latter by a more extended reaction time. Once again the overall yield of **11b** was very small, so an alternative approach was investigated.

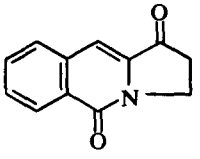
Whilst the above work was in progress, the preparations of **14** and **15** were reported[14] in a lengthy series of reactions. In repeating this work we have introduced some minor modifications (Experimental) involving glycine, rather than β-alanine, as starting material. Our spectral data for **14** indicated that the compound exists entirely in the enol form (**16**) and all efforts to ketalise, acetylate or benzoylate



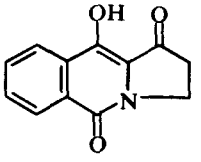
13



14



15

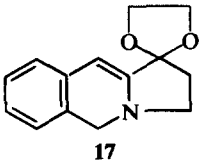


16

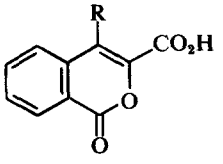
it, or to reduce it with LAH failed. However, ketalisation of **15** followed by reduction with LAH gave the required 1,2-dihydroisoquinoline (**17**). The yield was 2% in a thirteen stage sequence from glycine.

A shorter route has been developed from ethyl isocoumarin-3-carboxylic acid (**18a**),[15] which, with ethyl β-aminoproprionate afforded the isocarbostyril (**19a**). The derived ester (**19b**) was successfully cyclised to **15**, and shown to be identical with the material obtained by Shamma and Novak.[14]

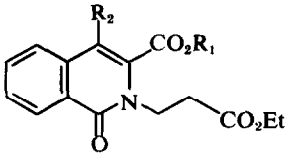
The reaction of the enamine **17** with pyruvic aldehyde was then subjected to an intensive study, but none of the hoped-for condensation product could be isolated from the complex reaction mixtures.



17

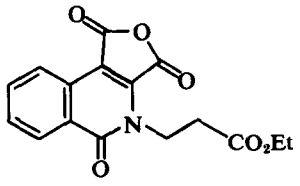


18a: R = H
18b: R = CO_2Et

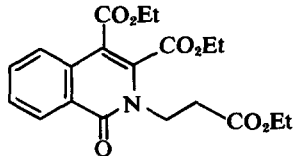


19a: $R_1 = R_2 = H$
19b: $R_1 = Et$, $R_2 = H$
19c: $R_1 = H$ $R_2 = CO_2Et$

In a final attempt to prepare the required C–N skeleton of lycorine, the acid-ester[15] (**18b**) was reacted with ethyl β-aminoproprionate, but the expected product (**19c**) was not obtained: the anhydride **20** was formed instead. Prolonged heating with ethanolic sulphuric acid yielded the tri

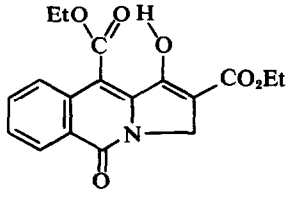


20



21

ester (21), which, with sodium ethoxide yielded a substance the spectral characteristics of which are in accord with the structure 22. However, in view of the many difficulties and poor yields of products, even in the model series, this type of approach to the synthesis of lycorine has been abandoned.



22

EXPERIMENTAL

All m.ps are uncorrected. UV spectra are reported for solns in EtOH (95%) and IR data refer to nujol mulls. NMR spectra were recorded at 60 MH_Z using TMS as internal reference.

2-Methyl-3-carbethoxyisoquinolinium iodide. To a soln of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10 g) in tetralin (300 ml), was added Pd-C (2 g; 10%), and the resulting suspension was heated under reflux for 6 hr, under N_2. After cooling, the charcoal was removed by filtration, the soln extracted with 2N HCl (3 × 100 ml) and the extracts combined and washed with ether. On basification with Na_2CO_3, the aqueous soln was re-extracted with ether (3 × 50 ml). After drying and evaporation, the combined ethereal extracts gave 2-methyl-3-carbethoxyisoquinoline as a pale yellow oil (8·85 g). Without further purification, the base was dissolved in acetone (20 ml) and MeI (10 ml) added. After standing overnight, pale yellow needles were obtained m.p. 162–163° (8·5 g; 72%) ν_{max} cm^{-1}, 1735 (C=O); $\lambda_{max}(\epsilon)$ nm, 241 (56,300) 277 (3,320) 341 (7,400); NMR (CD_3SOCD_3) ppm, 10·44 singlet [1] (C_1—*H*) 9·28 singlet [1] (C_4—*H*) 8·1–8·7 complex [4] (aromatics) 4·70 singlet [3] (N^+—CH_3) 4·56 quartet [2] $J = 7$ Hz (—OCH_2CH_3) 1·48 triplet [3] $J = 7$ Hz (—OCH_2CH_3). (Found: C, 45·45; H, 4·0; N, 4·25; I, 36·6. $C_{13}H_{14}NO_2I$ requires: C, 45·5; H, 4·1; N, 4·1; I, 37·0%.)

Condensation of aldehydes with ethyl 2-methyl-1,2-dihydroisoquinoline-3-carboxylate. To a soln of the crude 1,2-dihydroisoquinoline (ex borohydride reduction of the above methiodide (1·0 g)) in EtOH (20 ml) was added an equimolecular amount of the aldehyde. The resulting soln was heated with stirring in a N_2 atmosphere, and conc HCl (5 ml) was added dropwise. After 2 hr heating, the soln was left to cool overnight. The mixture was reduced to low bulk *in vacuo*, water (10 ml) added and the soln washed with ether (3 × 20 ml). The aqueous phase was again evaporated, and the residue dissolved in EtOH (5 ml). After adding a few drops of perchloric acid, the appropriate 4-substituted isoquinolinium salt slowly deposited (Tables 1 and 2).

The ketal (**10a**). A soln of **9a**[13] (0·90 g), *p*-toluenesulphonic acid (0·9 g) and ethylene glycol (2·0 ml) in dry benzene (50 ml) was heated under a Dean and Stark trap until no more water was liberated (about 4 hr). On cooling, the soln was washed with sat $NaHCO_3$aq and water, and then dried. Evaporation of the solvent yielded a pale yellow oil which slowly crystallised to give nearly colourless plates. Recrystallisation from light petroleum (60–80°)

Table 1. Physical data of products from the alkylation of **6**

	% Yield*	m.p.	Molecular Formula	Analysis Required C	H	N	Cl	Found C	H	N	Cl
R=C_6H_5	62	177–179°	$C_{20}H_{20}NO_6Cl$	59·2	5·0	3·45	8·7	59·5	5·3	3·6	8·4
R=3,4-$C_6H_3(OCH_3)$	56	159–161°	$C_{22}H_{24}NO_8Cl$	56·7	5·2	3·0	7·6	56·5	5·4	3·3	7·9
R=3,4-$C_6H_3(O_2CH_2)$	56	248–250°	$C_{21}H_{20}NO_8Cl$	56·0	4·7	3·1	7·9	56·4	4·2	3·4	7·6
R=$CO_2C_2H_5$	26	141–143°	$C_{17}H_{18}NO_8Cl$	50·8	5·0	3·5	8·8	50·5	4·5	4·1	9·2
R=$COCH_3$	47	155–157°	$C_{16}H_{18}NO_7Cl$	51·7	4·9	3·8	9·5	52·0	4·7	4·0	9·85

*Based on methiodide of ethyl isoquinoline-3-carboxylate

Table 2. Spectral data of products from the alkylation of **6**

	NMR–ppm						IR	UV
	C_1—H	CH_2 s	CH_3 Ns	CH_2 q	CH_3 t	Misc.	ν_{max} cm^{-1}	λ_{max} nm
R=C_6H_5	9·68	4·72	4·66	4·68	1·42		1785 (C=O) 1735 1635 (C=N$^+$)	237 (62,000) 282 (7,150) 342 (8,250)
R=3,4-$C_6H_3(OCH_3)_2$	9·74	4·66	4·66	4·68	1·48	3·94s (OCH_3)	1745 (aroms) 1635 (C=N$^+$)	237 (41,800) 344 (7,200)
R=3,4-$C_6H_3(O_2CH_2)$	9·70	4·74	4·68	4·70	1·50	5·96s (OCH_2O)	1780 (C=O) 1735 1630 (C=N$^+$)	238 (51,200) 344 (7,900)
R=$COOC_2H_5$	9·24	4·94	4·68	4·42	1·34	4·82q (CH_2) 1·60t (CH_3)	1740 (C=O) 1635 (C=N$^+$)	240 (61,300) 280 (4,150) 343 (10,000)
R=$COCH_3$	9·72	4·74	4·66	4·68	1·56	2·60 ($COCH_3$)	1730 (C=O) 1635 (C=N$^+$)	242 (45,300) 345 (8,600)

s = singlet; t = triplet; q = quartet; m = multiplet.

gave the required **10a** (0·92 g; 83%) m.p. 87°; NMR ($CDCl_3$) ppm, 7·1 complex [4] (aromatics) 3·9 complex [4] (—OCH_2CH_2O—) 4·2–2·0 complex [9] (aliphatics). (Found: C, 72·8; H, 7·6; N, 6·2. $C_{14}H_{17}NO_2$ requires: C, 72·7; H, 7·4; N, 6·1%.)

Dehydrogenation of ketal (**10a**). A soln of the ketal (500 mg) and anhyd NaOAc (200 mg) in EtOH (20 ml) was heated on a steam-bath, while I_2 (1·0 g), as a soln in EtOH, was slowly added. On cooling, the soln was saturated with SO_2 to remove excess I_2, and then concentrated to low bulk. Water (100 ml) was added, and the mixture was extracted with chloroform (3 × 20 ml). After drying and evaporation of the solvent, the combined extracts gave a yellow solid (220 mg) which was recrystallised from EtOH m.p. 205–210°; ν_{max} cm^{-1} 1640 (C=N$^+$) 1615 (C=C); λ_{max} nm 235, 342.

N-(*β-Cyanoethyl*)-3,4-*methylenedioxyphenylalanine*. 3,4-Methylenedioxyphenylalanine (3·65 g) was suspended in water (15 ml) and NaOH (0·70 g) added; the mixture was then vigorously stirred until complete soln was attained. Acrylonitrile (1·15 ml) was introduced, maintaining the temp below 20°. The soln was left stirring overnight at room temp, and then heated on a steam-bath for 2 hr. After cooling, the soln was neutralised to pH 7 with 2N HCl. The resultant solid was collected and recrystallised from water, giving the nitrile as white needles (3·76 g; 82%) m.p. 233–234°; ν_{max} cm^{-1} 3200–2400 (NH_2^+) 2250 (C≡N) 1585 (CO_2^-); NMR (CF_3COOH) ppm, 6·9 complex [3] (aromatics) 6·00 singlet [2] (—OCH_2O—) 4·05 multiplet [1] (—CH_2CH—) 2·8–3·9 complex [6] (3x—CH_2—). (Found: C, 59·75; H, 5·5; N, 10·7. $C_{13}H_{14}N_2O_4$ requires: C, 59·5; H, 5·4; N, 10·7%.)

N-(*β-Carbethoxyethyl*)-3,4-*methylenedioxyphenylalanine, ethyl ester*. N-(β-cyanoethyl)-3,4-methylenedioxyphenylalanine (2·94 g), dissolved in EtOH (120 ml) and conc H_2SO_4 (10 ml), was heated under reflux for 40 hr. After concentration *in vacuo* to approx 30 ml, ice-water was added and the soln was made alkaline with ammonia. The mixture was extracted with ether (3 × 25 ml) and the extracts dried. Evaporation of the solvent gave a pale-yellow oil (3·11 g; 82%); ν_{max} cm^{-1} 3360 (N—H) 1730 (C=O); NMR ($CDCl_3$) ppm, 6·7 complex [3] (aromatics) 5·90 singlet [2] (—OCH_2O—) 4·12 quartet [4] J = 7 Hz (2x—OCH_2CH_3) 3·4 multiplet [1] (—CH_2CHCO—) 2·1–3·0 complex [6] (3x—CH_2—) 1·96 singlet [1] (—N*H*—, disappears on deuteration) 1·22/1·18 two triplets [6] J = 7 Hz (2x—OCH_2CH_3).

Ethyl 2-(*β-carbethoxyethyl*)-6,7-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline*-3-*carboxylate*. The previously described diester (3·1 g) was suspended in water (20 ml) and conc HCl (1·0 ml) was added. Complete soln was obtained by vigorous shaking, and the pH was then adjusted to 4 with NaOHaq. After addition of formalin (9·0 ml; 37%), the soln was left at 32° for 72 hr. Then a further portion of conc HCl (0·70 ml) was added, and the mixture was heated on a steam-bath for ½ hr. After cooling, the aqueous soln was extracted with ether, and then made basic with ammonia. Extraction with ether and evaporation gave a yellow oil (2·28 g; 71%); ν_{max} cm^{-1} 1735 (C=O); λ_{max} nm 293; NMR ($CDCl_3$) ppm, 6·52/6·48 two singlets [2] (C_5—*H*, C_8—*H*) 5·86 singlet [2] (—OCH_2O—) 4·12 quartet [4] J = 7 Hz (2x—OCH_2CH_3) 3·6–3·9 complex [3] (ArCH_2N<, —CH_2CH<) 3·0 complex [4] (ArCH_2CH—, —CH_2CH_2CO—) 2·56 triplet [2] J = 7 Hz (>NCH_2CH_2—) 1·22/1·20 two triplets [6] J = 7 Hz (2x—OCH_2CH_3).

1,2,3,4,5,10,10a-*Hexahydro*-7,8-*methylenedioxypyrrolo*-[1,2-b]*isoquinoline*-1-*one* (**9b**). Na (80 mg) was added to "super-dry" EtOH (20 ml). When the reaction had ceased, dry benzene (100 ml) was introduced and the mixture heated on a steam-bath. After removal of the solvents, the ester (6 g) (from the previous reaction) in dry benzene (50 ml) was added and the mixture evaporated to dryness over a period of 3 hr. HCl (20% 150 ml) was then introduced and the soln heated to 100° for a further 3 hr. After cooling and extraction with ether, the soln was basified with Na_2CO_3. Re-extraction with CH_2Cl_2 and evaporation of the dried extracts afforded a pale yellow

solid (3·65 g, 92%); m.p. 176–178° (MeOH); ν_{max} cm^{-1}, 1750 (C=O); λ_{max} 294 nm; NMR ($CDCl_3$) ppm, 6·64, 6·56 two singlets [2] (aromatics) 5·9 singlet [2] (—OCH_2O—) 4·0 multiplet [1] (—CH_2CHCO—), 4·5 multiplet [2] (Ar.CH_2N) 2·2–3·0 complex [6] (3x CH_2—). This material rapidly darkened on standing and was characterized *via* its derivatives:

The ketone (1·09 g) was dissolved in aqueous EtOH (20 ml) and $NaBH_4$ (1·0 g) added in portions over 3 hr. Extraction with chloroform (3 × 25 ml) gave, after removal of the solvent, a colourless residue (0·91 g) which crystallized from EtOH to produce needles of **9b** m.p. 189–190°; λ_{max} cm^{-1}, 3200 (OH); λ_{max} (ε) nm, 292 (4,300). (Found: C, 66·95; H, 6·45; N, 6·1. $C_{13}H_{15}NO_3$ requires: C, 66·9; H, 6·5; N, 6·0%.)

Ketalisation of **9b**. The ketone (7·6 g) was dissolved in dry benzene (250 ml), together with ethylene glycol (10 ml) and *p*-toluenesulphonic acid (7·6 g). The mixture was then heated under a Dean and Stark trap, until free from water. After cooling, the soln was washed firstly with Na_2CO_3aq and then with water. The benzene soln was then dried and evaporated to give a pale yellow oil (2·08 g).

The crude ketal (0·2 g) was purified by eluting through a column of alumina (30 g) with 1:3 chloroform-benzene as solvent. The resultant oil then slowly crystallised to give buff-coloured plates m.p. 97–98°; λ_{max} (ε) nm, 293 (5,200); NMR ($CDCl_3$) ppm, 6·60/6·52 two singlets [2] (aromatics) 5·88 singlet [2] (—OCH_2O—) 3·9 complex [4] (—OCH_2-CH_2O—) 1·8–3·5 complex [9] (aliphatics). (Found: C, 64·5; H, 6·0; N, 4·95. $C_{15}H_{17}NO_4$ requires: C, 65·4; H, 6·2; N, 5·1%.)

The methiodide of the above ketal (**10b**) was prepared as buff-coloured blades (EtOH), m.p. 262–263°; λ_{max} (ε) nm, 293 (5,150). (Found: C, 46·3; H, 5·0; N, 3·3; I, 30·8. $C_{16}H_{20}NO_4I$ requires: C, 46·1; H, 4·8; N, 3·4; I, 30·4%.)

Dehydrogenation of the ketal (**10b**). The ketal (1·8 g) was dehydrogenated as previously described for **9a** to yield brown prisms (1·37 g; 32%) which recrystallised from EtOH to give **11b** as dark brown needles m.p. 212–213° (dec); ν_{max} cm^{-1} 1620 (C=N^+); λ_{max} (ε) nm 260 (99,000); NMR (DMSO) ppm, 9·8 singlet [1] (C_1—*H*), 8·3 singlet [1] (C_4—H), 7·85, 7·76 two singlets [2 × 1] (C_5—*H*, C_8—*H*), 6·4 singlet [2] (OCH_2O), 5·0 triplet J = $4H_z$ [2] ($^+NCH_2$) 4·2 complex [4] (OCH_2CH_2O), 2·8 triplet $J = 4H_z$ [2] (CH_2C). (Found: C, 28·1; H, 2·3; N, 2·3; I, 58·0. $C_{15}H_{14}NO_4I_3$ requires: C, 27·8; H, 2·2; N, 2·15; I, 58·2%.)

On repetition of the above experiment using smaller amounts of I_2 and shorter reaction times (3 hr), a further periodide salt was isolated in similar yields (15–25%) which proved to be **13** as brown needles m.p. 170–171° (dec) (EtOH/acetone); ν_{max} cm^{-1} 1650 (C=N^+); λ_{max} (ε) nm 255 (19,900) 295 (21,700) 370 (20,300). (Found: C, 27·7; H, 2·6; N, 2·0; I, 58·4. $C_{15}H_{16}NO_4I_3$ requires: C, 27·5; H, 2·5; N, 2·1; I, 58·2%.)

Ethyl N-*carbethoxymethyl*-β-*aminopropionate*. N-β-cyanoethylglycine (82·4 g) was heated under reflux for 36 hr with a mixture of conc H_2SO_4 (100 ml) and EtOH (1 l). The soln was concentrated *in vacuo* to 200 ml and ice-water added. After basification with ammonia, the mixture was extracted with ether (3 × 50 ml). After being washed with water and dried, the combined etheral extracts gave a colourless oil (90·4 g; 68%); ν_{max} cm^{-1} 3380 (N—H) 1735 (C=O); NMR (CCl_4) ppm, 4·24/4·18 two quartets [4] $J = 7$ Hz (2x—OCH_2CH_3) 3·32 singlet [2] (—$NHCH_2CO$) 2·3–3·1 complex [4] ($NHCH_2CH_2$—) 2·08 singlet [1] (—N*H*, disappears on deuteration) 1·34 triplet [6] $J = 7$ Hz (—OCH_2CH_3).

Ethyl N-*carbethoxy*-N-*carbethoxymethyl*-β-*aminopropionate*. The diester (90·4 g) described in the previous experiment was cooled to 10° and ethyl chloroformate (60·0 g) slowly added. The mixture was allowed to warm to room temp and left for 1 hr. $NaCO_3$ (25·0 g) in water (90 ml) was then added, and the mixture heated on a steam-bath for ½ hr. On cooling, ether (200 ml) was added and the etheral layer washed with 2N HCl (2 × 200 ml), and then water. On drying and evaporation a colourless oil was obtained (106·8 g; 88%); ν_{max} cm^{-1} 1740 (C=O) 1700 (NC=O).

1,4-*Dicarbethoxypyrrolidin*-3-*one*. The triester (106·8 g) described above, in benzene (100 ml) was slowly added to a heated soln of NaOEt (from Na 18·0 g) in benzene (300 ml), while the solvent was allowed to distil slowly from the reaction vessel. After all the triester had been added (about 3 hr) the heating was continued for a further 3 hr, until liberation of the EtOH produced in the reaction was complete. On cooling, AcOH (100 ml) was added and the organic phase washed with water. The benzene layer gave a yellow oil (80·2 g; 90%); ν_{max} cm^{-1} 1770, 1700 (C=O) after evaporation.

1-*Carbethoxypyrrolidin*-3-*one*. The β-ketoester (80·2 g) from the previous reaction was heated under reflux for 8 hr with AcOH (75·6 g) in water (600 ml). On cooling, the soln was made basic with 2N NaOH, and extracted with CH_2Cl_2 (5 × 50 ml). Evaporation of the organic extracts gave 1-carbethoxypyrrolidin-3-one as a pale yellow oil (48·9 g; 89%); ν_{max} cm^{-1} 1760 (C=O) 1700 (NC=O); NMR (CCl_4) ppm, 4·14 quartet [2] $J = 7$ Hz (—OCH_2-CH_3) 3·80 triplet [2] $J = 7$ Hz (—CH_2CH_2CO—) 3·70 singlet [2] (—$NHCH_2CO$) 2·56 triplet [2] $J = 7$ Hz (—CH_2CH_2NH—) 1·26 triplet [3] $J = 7$ Hz (—OCH_2-CH_3).

7-*Carbethoxy*-1,4-*dioxa*-7-*azaspiro*[4,4]*nonane*. 7-Carbethoxy-pyrrolidin-3-one (48·9 g), *p*-toluenesulphonyl chloride (1·0 g) and ethylene glycol (20 ml) were heated together under reflux in benzene (300 ml) for 6 hr, with a Dean-Stark adaptor fitted to trap the water produced. The soln was then washed with Na_2CO_3aq, and water. On drying and evaporating the benzene, a pale yellow oil (47·5 g; 76%); ν_{max} cm^{-1} 1700 (C=O); NMR (CCl_4) ppm, 4·24 quartet [2] $J = 7$ Hz (—OCH_2CH_3) 3·80 triplet [2] $J = 8$ Hz (—COH_2CH_2) 3·70 singlet [2] (—NCH_2CO—) 2·56 triplet [2] $J = 8$ Hz (—NCH_2CH_2—) 1·26 triplet [3] $J = 7$ Hz (—OCH_2CH_3), was formed, which was used for the next stage without further purification.

1,4-*Dioxa*-7-*azaspiro* [4,4] *nonane*. The amide (47·5 g) was heated overnight under reflux with KOH (37·5 g) in water (180 ml). After cooling, the mixture was extracted with CH_2Cl_2 (4 × 40 ml), and, after drying and evaporation of the solvent, the combined extracts gave a pale yellow oil. Vacuum distillation afforded a colourless oil (23·2 g; 76%) b.p.$_{12}$ 90–95° (Lit. [14]b.p.$_{0.4}$ 53°); ν_{max} cm^{-1} 3350 (N—H); NMR (CCl_4) ppm, 3·84 singlet [4] (—OCH_2CH_2-O—) 2·94 triplet [2] $J = 7$ Hz (—$NHCH_2CH_2$—) 2·74 singlet [2] (—CCH_2NH—) 1·88 singlet [1] (—N*H*, disappears on deuteration) 1·82 triplet [2] $J = 7$ Hz (—CCH_2CH_2—).

7-(*o*-*Carbomethoxybenzoyl*)-1,4-*dioxa*-7-*azaspiro* [4,4]-*nonane*. 1,4-Dioxa-7-azaspiro [4,4] nonane (23·2 g) and K_2CO_3 (13·5 g) were stored at 0° in water (300 ml) while methyl *o*-chloroformylbenzoate (36·0 g) in acetone (120 ml) was added dropwise over a period of 5 min. The soln was left overnight at room temp, and then extracted with

ether (3 × 50 ml). The combined ether extracts were washed with 2N HCl, and water. After drying, the solvent was evaporated to yield a pale yellow oil (42·9 g; 82%); ν_{max} cm^{-1} 1720 (C=O) 1635 (>NC=O).

N-(o-*Carbomethoxybenzoyl*)*pyrrolidin*-3-*one*. The preceeding ketal (14·5 g) and oxalic acid (12·6 g) were heated overnight under reflux in EtOH (100 ml) and water (200 ml). The soln was extracted with chloroform (3 × 50 ml), and the combined organic layers were washed with $NaHCO_3$aq and then water. On drying and evaporation, a colourless oil (8·72 g; 71%) remained which slowly crystallised on standing to give the required ketone m.p. 95–97° (lit.[14] m.p. 97–98°).

2,3-*Dihydro*-10-*hydroxypyrrolo*[1,2-b]*isoquinolin*-1,5-*dione*. The previously obtained ester (3·0 g) was heated under reflux in diphenylether (50 ml) for 20 min. On cooling, the soln was extracted with dilute NaOHaq (3 × 20 ml), and the combined aqueous layers were acidified.

The resultant green solid was collected, and recrystallised from EtOH to give **14** (1·96 g; 79%) m.p. 172–173° (Lit.[14] m.p. 175–176°) ν_{max} cm^{-1} 3600–3200 (O—H) 1695 (C=O) 1625 (>NC=O); λ_{max} (ϵ) nm 217 (28,200) 260 (6,100) 356 (6,800); NMR ($CDCl_3$) ppm, 8·6–7·5 complex [4] (aromatics) 4·38 triplet [2] J = 8 Hz (—COCH_2CH$_2$—) 2·92 triplet [2] J = 8 Hz (—CH$_2$CH_2N<). (Found: C, 66·4; H, 4·4; N, 6·3. Calc. for $C_{12}H_9NO_3$: C, 67·0; H, 4·2; N, 6·5%.)

Attempted reactions of 2,3-*dihydro*-10-*hydroxypyrrolo*-[1,2-b]*isoquinolin*-1,5-*dione*.

(i) The ketone (1·0 g) and *p*-toluenesulphonic acid (20 mg) was heated under reflux in benzene (50 ml) for 6 hr with ethylene glycol (5 ml). The mixture was cooled, and extracted with 2N NaOH (2 × 20 ml). Acidification of the combined aqueous layers gave unchanged starting material (0·94 g).

(ii) The ketone (1·0 g) was heated on a steam-bath for 6 hr with Ac_2O (or benzoyl chloride) (10 ml). On cooling, water (100 ml) was carefully added and the resultant solid collected, and recrystallised from EtOH to yield starting material (0·82 g).

(iii) The ketone (1·0 g) was heated on a steam-bath with acetyl chloride (2 ml) in pyridine (10 ml) for 6 hr. The mixture was poured into water, and acidified with 2N HCl to give starting material (0·98 g).

(iv) The ketone (1·0 g) was heated under reflux with LAH (1·0 g) for 6 hr in THF (50 ml). On cooling, saturated sodium potassium tartrate soln (20 ml) was carefully added, and the resultant clear soln decanted. The THF was removed *in vacuo*, benzene (30 ml) added, and the soln was extracted with 2N NaOH (2 × 20 ml). Acidification with HCl gave starting material (0·92 g).

7-(o-*Hydroxymethylbenzoyl*)-1,4-*dioxa*-7-*azaspiro*[4,4]-*nonane*. A mixture of the ester (5·0 g) and $NaBH_4$ (5·0 g) were stirred overnight at room temp in EtOH (150 ml). Water (500 ml) was added and the soln extracted with chloroform (3 × 50 ml). After drying and evaporation of the solvent, a colourless oil (2·80 g; 62%) was obtained, which was used in the next stage without further purification; ν_{max} cm^{-1} 3420 (O—H) 1615 (C=O).

7-(o-*Formylbenzoyl*)-1,4-*dioxa*-7-*azaspiro*[4,4]*nonane*. A mixture of the crude alcohol (2·80 g) and freshly prepared MnO_2 (15·0 g) in EtOH-free chloroform (150 g) was stirred overnight at room temp. The MnO_2 was removed by filtration and the solvent evaporated from the filtrate to yield a colourless oil (1·88 g; 68%); ν_{max} cm^{-1} 1705 (CH=O) 1620 (>NC=O).

2,3-*Dihydropyrrolo*[1,2-b]*isoquinolin*-1,5-*dione* (**15**). The above aldehyde (1·88 g) was dissolved in conc H_2SO_4 (20 ml), and the soln left overnight. The mixture was then poured onto ice-water, and the aqueous phase was extracted with chloroform (3 × 20 ml). On drying and evaporation of the solvent, a yellow solid (0·80 g; 56%) remained which recrystallised from EtOH to give pale-yellow plates m.p. 189–191° (lit.[14] m.p. 191–192°); ν_{max} cm^{-1} 1730 (C=O) 1650 (>NC=O); λ_{max} (ϵ) nm 250 (9,600) 335 (14,400); NMR ($CDCl_3$) ppm, 8·4 multiplet [1] (C$_6$—*H*)7·7 complex [3] (aromatics) 7·12 singlet [1] (C$_{10}$—H) 4·32 triplet [2] J = 6 Hz (—COCH_2CH$_2$—) 2·88 triplet [2] J = 7 Hz (—CH$_2$CH_2—N<). (Found: C, 72·4; H, 4·7; N, 7·2. Calc. for $C_{12}H_9NO_2$: C, 72·35; H, 4·55; N, 7·0%.)

Ketalisation of 2,3-*dihydropyrrolo*[1,2-b]*isoquinolin*-1,5-*dione*. A soln of the ketone (0·20 g), *p*-toluenesulphonic acid (0·10 g) and ethylene glycol (5·0 ml) were heated under reflux in dry benzene (100 ml) under a Dean and Stark trap. When no more water could be removed, the mixture was cooled, and washed with sat Na_2CO_3aq and water. Evaporation of the benzene yielded a pale-yellow oil, which was eluted through a column of alumina (30 g) with 1:1 benzene-chloroform mixture. This gave the ketal as a pale yellow oil (0·21 g; 86%) which slowly recrystallised to buff-coloured platelets m.p. 35–38°; ν_{max} cm^{-1} 1660, 1630, 1600 (>NC=O); λ_{max} (ϵ) nm, 226 (17,800) 249 (7,300) 291 (9,500) 325 (4,800) 338sh (3,500); NMR ($CDCl_3$) ppm, 8·5 multiplet [2] (C$_6$—*H*) 7·6 complex [3] (aromatics) 6·62 singlet [1] (C$_{10}$—*H*) 4·2 complex [6] (—OCH_2CH_2O—, —NCH_2CH$_2$—) 2·38 triplet [2] J = 7 Hz (—CCH_2CH$_2$). (Found: C, 69·1; H, 5·2; N, 5·7. $C_{14}H_{13}NO_3$ requires: C, 69·1; H, 5·4; N, 5·8%.)

Reduction of the above ketal. The ketal (250 mg) was dissolved in THF (150 ml) and LAH (0·50 g) was added. The suspension was heated for 2 hr and, after cooling, the excess LAH was destroyed with sat sodium potassium tartrate soln. The THF soln was decanted off and evaporated to low bulk *in vacuo*. The residue was dissolved in water (50 ml) and extracted with CH_2Cl_2 (3 × 25 ml). After drying and evaporation, the combined extracts yielded the amine **17** as an off-white solid (186 mg; 79%), which recrystallised from EtOH as white needles m.p. 112–116°; ν_{max} cm^{-1} 1645 (C=C); λ_{max} (ϵ) nm, 238 (6,300) 334 (6,900); (Found: C, 73·2; H, 6·7; N, 6·1. $C_{14}H_{15}NO_2$ requires: C, 73·4; H, 6·6; N, 6·1%.)

N-(*β-Carbethoxyethyl*)*isocarbostyril*-3-*carboxylic acid* (**19a**).

(a) Isocoumarin-3-carboxylic acid (0·2 g) was heated under reflux in EtOH (50 ml) for 6 hr, during which time ethyl *β*-aminopropionate (5 ml) was slowly added. The heating was continued for a further 10 hr, and the soln then concentrated to low bulk. Benzene (50 ml) was added and the soln extracted with sat Na_2CO_3aq (3 × 30 ml). After washing with benzene, the combined aqueous extracts were made acid with HCl and extracted with chloroform (3 × 30 ml). After drying and evaporation, the chloroform soln gave a white ppt (0·21 g; 69%). Recrystallisation from benzene gave the isocarbostyril as white needles m.p. 112–113°; ν_{max} cm^{-1} 3300–2500 (O—H) 1725 (C=O) 1630 (CON<); λ_{max} (ϵ) nm, 225 sh (14,800) 301 (7,800)

325 sh (6,000); (Found: C, 62·2; H, 5·2; N, 4·9. $C_{15}H_{15}NO_5$ requires: C, 62·3; H, 5·2; N, 4·8%.)

(b) Isocoumarin-3-carboxylic acid (7·75 g) in EtOH (100 ml) was stood for 7 days at room temp with ethyl β-aminopropionate (25 g). The EtOH was removed *in vacuo*, benzene (100 ml) added and the soln extracted with sat Na_2CO_3aq (3 × 50 ml). The combined aqueous extracts were washed with benzene and then acidified with dilute HCl. Extraction with chloroform (3 × 50 ml) and evaporation of the solvent gave 2-β-carbethoxyethylisocarbostyril-3-carboxylic acid (10·7 g; 91%.)

Ethyl N-(*β-carbethoxyethyl*) *isocarbostyril-3-carboxylate* (**19b**). The acid (2·46 g) was heated under reflux for 18 hr with conc HCl acid (30 ml) in EtOH (250 ml). The soln was reduced to 50 ml *in vacuo* and ice-water added. After basification with ammonia, the soln was extracted with CH_2Cl_2 (3 × 30 ml). The extracts were dried and evaporated to a yellow oil (2·25 g; 83%); ν_{max} cm^{-1} 1725 (CO_2Et) 1660 (CON<); NMR ($CDCl_3$) ppm, 8·4 multiplet [1] (C_8—*H*) 7·4–7·8 complex [3] (aromatics) 7·22 singlet [1] (C_4—*H*) 4·0–4·7 complex [6] (2x—OCH_2CH_3, —CH_2CH_2CO—) 2·94 triplet [2] $J = 7$ Hz (>NCH_2-CH_2—) 1·42/1·22 two triplets [6] $J = 7$ Hz (2x—OCH_2-CH_3).

Ethyl 1,5-*dioxa*-2,3-*dihydropyrrolo*[1,2-b]*isoquinoline*-2-*carboxylate*. A soln of NaOEt, made *in situ* from Na (0·4 g), was heated under reflux in benzene (250 ml) and EtOH (20 ml), while a benzene soln of ethyl N-(β-carbethoxyethyl)isocarbostyril-3-carboxylate (2·8 g) was added dropwise. The azeotropic benzene-ethanol mixture was allowed to distill slowly from the mixture. When all the EtOH had been removed, the soln was cooled and extracted with 2N NaOH (3 × 30 ml). After washing with benzene the aqueous extracts were acidified with HCl and the resulting ppt extracted with CH_2Cl_2. On drying and evaporation, a brown solid (1·85 g; 77%) resulted which afforded the β-ketoester on recrystallisation from EtOH as pale brown plates m.p. 166–169°; ν_{max} cm^{-1} 1730, 1710 (C=O) 1660 (CON<); λ_{max} (ε) nm, 249 (11,500) 254 (12,700) 261 sh (10,100) 329 (19,200) 345 (20,300) 355 (17,000). (Found: C, 67·4; H, 4·8; N, 5·5. $C_{15}H_{13}NO_4$ requires: C, 66·4; H, 4·8; N, 5·2%.)

2,3-*Dihydropyrrolo* [1.2-b] *isoquinolin*-1,5-*dione* (**15**). A soln of the β-ketoester (1·85 g) in EtOH (100 ml) was heated under reflux with 6N HCl (100 ml) for 3 hr. The EtOH was evaporated *in vacuo*, and the aqueous soln was extracted with chloroform (3 × 50 ml). After drying and evaporation of the combined extracts, the residue was recrystallised from EtOH to give the required ketone as pale-yellow plates (1·26 g; 93%) m.p. 189–191° (Lit.[14] m.p. 191–192°). This material was identical in all respects (m.p. mixed m.p., IR, UV, NMR) with authentic 2,3-dihydropyrrolo[1,2-b]isoquinolin-1,5-dione as prepared by the previous method.

Attempted reaction of amine (**17**) The amine (1·0 g), stirring under N_2, was heated under reflux with pyruvic aldehyde (10 ml) in EtOH (50 ml) while 6N HCl (10 ml) was added dropwise. The heating was then continued for 3 hr. The EtOH was removed *in vacuo*, and the aqueous soln was washed with ether (3 × 20 ml). The aqueous phase was then evaporated to dryness *in vacuo*, until all excess HCl had been removed. The residue was taken up in EtOH (10 ml), and perchloric acid (1·0 ml) added. The resultant solid was collected and recrystallised to give the quaternary salt (11a) as buff coloured needles (540 mg; 38%) m.p. 222–224°; ν_{max} cm^{-1} 1635 (C=N^+); NMR (CD_3SOCD_3) ppm, 10·00 singlet [1] (C_5—*H*) 8·74 singlet [1] (C_{10}—*H*) 8·6–8·0 complex [4] (aromatics) 5·06 triplet [2] $J = 7$ Hz (—CH_2CH_2—N^+) 4·3 complex [4] (—OCH_2-CH_2O—) 2·80 triplet [2] $J = 7$ Hz (—CCH_2CH_2—). (Found: C, 51·6; H, 4·5; N, 4·3; Cl, 11·0. $C_{14}H_{14}NO_6Cl$ requires: C, 51·3; H, 4·3; N, 4·3; Cl, 10·8%.)

Anhydride (**20**). 4-Carbethoxyisocoumarin-3-carboxylic acid (0·50 g) was heated under reflux with EtOH (20 ml) for 18 hr, ethyl β-aminopropionate (5 ml) being added very slowly over the first 6 hr. The EtOH was removed *in vacuo*, benzene (50 ml) added and the soln was extracted with sat Na_2CO_3aq (3 × 20 ml). After being washed with benzene, the combined aqueous extracts were acidified with dil HCl and then extracted with chloroform (3 × 30 ml). Drying and evaporation of the chloroform gave a pale-yellow oil. The product was heated with a small volume of benzene, whereupon the yellow colour intensified, and upon cooling the anhydride was deposited as yellow needles (0·30 g; 50%) m.p. 151–153°; ν_{max} cm^{-1} 1860, 1800, 1735, 1670 (C=O); λ_{max} (ε) nm, 214 (36,700) 299 (11,200). (Found: C, 60·7; H, 4·1; N, 4·6. $C_{16}H_{13}NO_6$ requires: C, 60·95; H, 4·3; N, 4·4%.)

Diethyl 2-(*β-carbethoxyethyl*) *isocarbostyril*-3,4-*dicarboxylate* (**21**). The anhydride (1·5 g) was dissolved in EtOH (250 ml) and the soln heated under reflux with conc H_2SO_4 (30 ml) for 72 hr. The soln was concentrated to low bulk, the residue dissolved in benzene, and the soln washed with sat Na_2CO_3aq and water. Evaporation of the benzene solution gave a pale-yellow oil (1·54 g; 84%) which was used in the next stage without further purification.

Diethyl 1,5-*dioxo*-2,3-*dihydropyrrolo* [1,2-b] *isoquinoline*-2,10-*dicarboxylate* (**22**). A soln of **21** (1·33 g) and NaOEt (from 0·16 g Na) in dry benzene (200 ml) were heated under reflux for 6 hr during which the azeotropic mixture of benzene and EtOH was slowly distilled. On cooling, the mixture was extracted with 2N NaOH (3 × 50 ml), washed with benzene, and the aqueous extracts rendered acid with 2N HCl. After chloroform extraction and drying, a white semi-solid (0·37 g; 32%) resulted on evaporation. Recrystallisation from EtOH gave the β-ketoester as white platelets m.p. 196–198°; ν_{max} cm^{-1} 3260 (O—H) 1735, 1720 (C=O) 1665 (CON<); λ_{max} (ε) nm, 214 (25,600) 256 sh (8,500) 332 sh (14,900) 347 (16,600) 356 (14,000); NMR ($CDCl_3$) ppm, 9·2 broad absorption [1] (—O*H*, disappears on deuteration) 8·4 multiplet [1] (C_8—*H*) 7·8–7·4 complex [3] (aromatics) 4·68 singlet [2] (—C—CH_2—N<) 4·46/4·34 two quartets [4] $J = 7$ Hz (—OCH_2CH_3) 1·46/1·38 two triplets [6] $J = 7$ Hz (—OCH_2CH_3). (Found: C, 63·0; H, 5·1; N, 3·95. $C_{18}H_{17}NO_6$ requires: C, 63·0; H, 5·0; N, 4·1%.)

REFERENCES

[1] J. W. Cook, J. D. Loudon and P. McCloskey, *J. Chem. Soc.* 4176 (1954).

[2] L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima and N. Yanaihara, *Ibid.* 4622 (1954).

[3] H. M. Fales, E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.* **77**, 5885 (1955).

[4] F. Benington and R. D. Morin, *J. Org. Chem.* **27**, 142 (1962).

[5] R. K. Hill, J. A. Joule and L. J. Loeffler, *J. Am. Chem. Soc.* **84**, 4951 (1962).

[6]J. B. Hendrickson, R. W. Alder, D. R. Dalton and D. G. Hey, *J. Org. Chem.* **34**, 2667 (1969).
[7]S. F. Dyke in *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky and A. J. Boulton) Vol. 14, p. 279, Academic Press (1972).
[8]W. C. Wildman in *The Alkaloids* (Edited by R. H. F. Manske) Vol. 6, p. 363, Academic Press (1960).
[9]J. R. Evans, Ph.D. thesis, University of Bath (1971).
[10]B. Ganem, *Tetrahedron Letters* 4105 (1971).
[11]C. E. Teague and A. Roe, *J. Am. Chem. Soc.* **73**, 688 (1951).
[12]H. E. Baumgarten and J. E. Dirks, *J. Org. Chem.* **23**, 900 (1958).
[13]N. J. Leonard, S. Swan and G. Fuller, *J. Am. Chem. Soc.* **76**, 3193 (1954).
[14]M. Shamma and L. Novak, *Tetrahedron* **25**, 2275 (1969).
[15]N. N. Vorozhtsov and A. T. Petushkova, *J. Gen. Chem. USSR* **27**, 2342 (1957).