Pyrrole Chemistry. XV. The Chemistry of Some 3,4-Disubstituted Pyrroles[1]

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The syntheses of a variety of 3,4-disubstituted pyrroles including the antimitotic agent Verrucarin E are described. 3,4-Pyrroledicarboxylic esters were prepared through a Diels–Alder reaction. Partial hydrolysis of the diesters gave the 4-ester-3-acids which were modified to achieve the synthesis of a variety of unsymmetrically 3,4-disubstituted pyrroles. Raney nickel reduction of a thiolester gave hydroxymethyl under conditions which left acyl or carbalkoxy substituents unaffected. Pyrrole reactions involving carbanionic reagents are complicated by 1-proton abstraction. Therefore, when necessary, the nitrogen was protected by an *N*-benzyloxymethyl substituent which can be cleaved to the *N*-hydroxymethyl derivative by aluminum chloride or by hydrogenolysis. Subsequent treatment with benzyltrimethylammonium hydroxide gave back the pyrrole.

On a réalisé la synthèse de divers derivés bifonctionnels du pyrrole, y compris celle de l'agent antimitotique 'Verrucarin E', à partir des esters de l'acide pyrroledicarboxylique-3,4 qui furent préparés d'une réaction du type "Diels–Alder". L'hydrolyse partielle des esters a donné les ester-4-acides-3 qui furent alors transformés en de différents composés bifonctionnels et non-symmétriques. La réduction d'un thiolester en présence de nickel de Raney conduit à l'hydroxymethyl correspondant sous des conditions qui n'ont pas touché un groupe acyle ou carboalcoxy. Les réactions de pyrrole avec des réactifs carbanioniques sont compliquées par l'arrachement du proton-1. Alors, selon le besoin, l'azote fut protégé par un substituant benzyloxymethyl-*N* qui peut être scié par traitement avec le chlorure d'aluminium ou par l'hydrogenolyse pour amener a l'hydroxymethyl correspondant. Un traitement ultérieur par l'hydroxide de benzyltrimethylammonium ramène au pyrrole.

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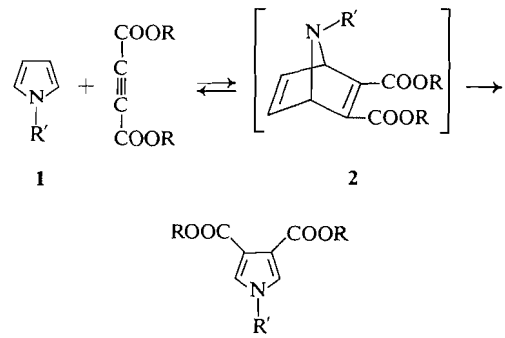
We have recently reported new syntheses of some 3-substituted pyrroles (1, 2) and in continuation of our efforts to devise viable routes to the less accessible pyrroles we have developed syntheses of a variety of 3,4-disubstituted pyrroles. These were of particular interest in view of the recent reassignment of the structure of the antimitotic agent Verrucarin E; originally thought to be 2-hydroxymethyl-4-acetylpyrrole (3), but later revised to 3-acetyl-4-hydroxymethylpyrrole (4). A synthesis of Verrucarin E starting from 2-carbethoxy-3-acetylpyrrole has been described (4), but the yield was very low and the method lacked flexibility.

The introduction of substituents into the two β-positions of the pyrrole nucleus may be accomplished by reaction with acetylenic dienophiles (5–8). Addition across the pyrrole "diene" system **1** gives 7-azanorbornadienes (**2**) which may undergo a retrodiene reaction to either reactants or the substituted pyrrole **3** (see Scheme 1). Although pyrrole itself is known to undergo cycloaddition reactions (9) the formation of 3,4-substituted pyrroles in reasonable yield requires the presence of an electron-withdrawing *N*-substituent. This is said to increase the diene character of the pyrrole system (*cf.* ref. 10) and inhibits attachment of a second molecule of dienophile (11, 12).



1 **2** **3**

SCHEME 1

Pyrrole *N*-esters have been converted to the triester **3** (R = Me or Et, R′ = COOMe or COOEt) and then selectively hydrolyzed to dialkyl 3,4-pyrroledicarboxylate (**4**, R = Me or Et) (6, 7). *N*-Benzoylpyrrole was found to give higher yields of the 3,4-diesters **3** (R = Me or

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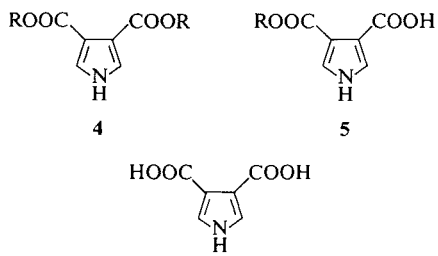
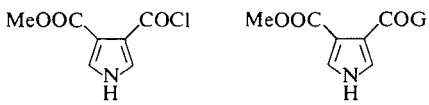
Et, R′ = COPh) with dimethyl and diethyl acetylenedicarboxylate than did the *N*-esters. Hydrolysis of the trisubstituted pyrroles may be controlled to afford either the diester **4** (R = Me or Et), the monoester **5** (R = Me or Et), or the diacid **6** in very high yield.



4 **5**

6

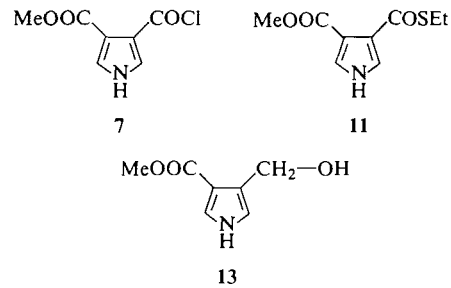
The monoester **5** is a potential starting material for the synthesis of 3,4-disubstituted pyrroles. The carboxylic acid group of the monoester **5** (R = Me) was readily converted into an aroyl ketone **8** by a Friedel–Crafts reaction of the acid chloride **7** with benzene or anisole. The anilide **9** and the mixed esters **10** and **11** were obtained by reaction of **7** with aniline, ethanol, and ethanethiol respectively. The conversion of



7 **8** G = Ph or anisyl
9 NHPh
10 OEt
11 SEt
14 Et
15 $CH(COO\text{-}t\text{-}Bu)_2$
16 CH_3

an acid derivative to a ketone generally requires a nucleophilic reagent and will be discussed later. 3,4-Pyrroledicarbonyl chloride was found to behave normally with ethanethiol, but Friedel-Crafts acylation using aluminum chloride in benzene was found to give 3,4-dibenzoylpyrrole. This contrasts with 1-*n*-butyl-2,5-dimethyl-3,4-pyrroledicarbonyl chloride which is reported to give an analog of **12** (13) (see Scheme 2).

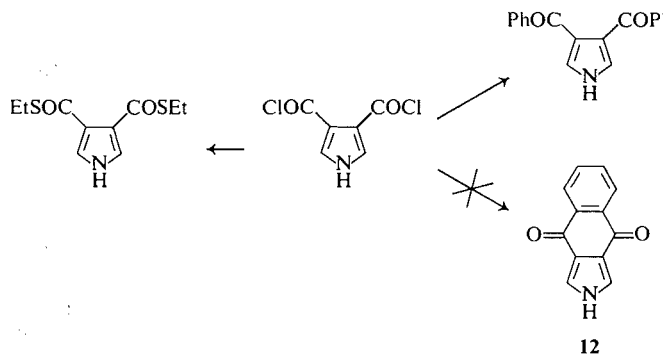
The reduction of an *N*-unsubstituted carboxylic acid derivative of pyrrole to the corresponding hydroxymethyl compound is often difficult since abstraction of the 1-proton initiates further reduction of the intermediate alcohol to the corresponding alkyl group (14) (Scheme 3). In the case of 3,4-disubstituted pyrroles the problem of reduction is further complicated by the presence of a second reducible group, either ketone or ester. Raney nickel was found to reduce selectively the corresponding ester thiolester **11** to the hydroxymethylpyrrole **13**.



7 **11**

13

The synthesis of Verrucarin E requires the conversion of one of the β-carboxylate substituents into a methyl ketone. Reaction of the acid chloride **7** with excess methylmagnesium bromide or with dimethylcadmium gave only hydrolyzed starting material, while diethylcadmium gave a low yield of the corresponding ethyl ketone **14**. The use of the less basic methylmercuric iodide alone, or catalyzed with aluminum chloride, failed to effect any reaction. Condensation of **7** with sodium di-*tert*-butyl malonate gave only low yields of the ketomalo-



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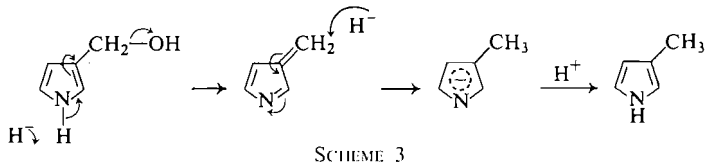
SCHEME 2



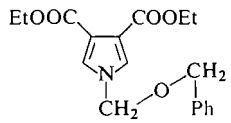
SCHEME 3

nate **15** although subsequent acid-catalyzed conversion to the ketone **16** was successful. Reaction of **7** with diazomethane resulted in *N*-methylation.

Abstraction of the acidic 1-proton by the carbanionic reagent and conjugative transfer of the resulting negative charge to the carbonyl substituents is probably the major factor accounting for the low reactivity of the chlorocarbonyl group in the above reactions.

At this point it was necessary to reconsider the synthetic approach to Verrucarin E. One problem was the very low solubility of pyrroles possessing electron-withdrawing groups in both 3- and 4-positions. This interfered with many of the reactions. For example, a potential ketone synthesis failed when it proved impossible to convert the 3,4-diacid to its cyclic anhydride because of the extreme insolubility of the diacid. The use of the di- and monoethyl esters rather than the methyl ones produced a considerable increase in solubilities and all further reactions involved these compounds.

The second major obstacle was the acidity of the *N*-hydrogen on these compounds as discussed above. This required that a base-stable, removable blocking group be found. Remers and co-workers (15) have examined 1-acetyl, 1-benzyol, 1-benzenesulfonyl, and 1-benzyl substituents for their suitability as protecting groups for the pyrrole nitrogen. Only the 1-benzyl substituent was found to be base-stable and since this is subsequently cleaved by sodium in liquid ammonia, its utility is restricted to compounds compatible with such vigorous reductive cleavage. Catalytic hydrogenolysis of the 1-benzyl substituent has previously been shown to be difficult for compounds in which the pyrrole nucleus bears electron-withdrawing substituents (16). After trials with several other reagents, diethyl 1-benzyloxymethyl-3,4-pyrroledicarboxylate (**17**) was prepared by reaction of the sodium salt of the diester **10** with benzyl chloromethyl ether. This provided an *N*-substituent stable to both acid and base but which could be cleaved by hydrogenolysis (17) or by aluminum chloride to the *N*-hydroxymethyl derivative **18**. On subsequent treatment of **18** with benzyltrimethylammonium hydroxide it rapidly lost formaldehyde to give back the pyrrole. As might be expected, it also increased the generally low solubility of the 3,4-disubstituted compounds.



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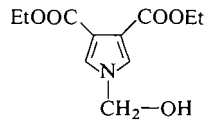
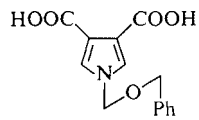


18

Basic hydrolysis of the protected diester **17** gave the corresponding 3,4-diacid **19**. On treatment with dicyclohexylcarbodiimide at 30° the diacid **19** gave an anhydride which was difficult to purify[2] and exhibited only a low reactivity towards dimethylcadmium, methylmagnesium iodide, and methyllithium.

A more satisfactory route to the ketone involves controlled hydrolysis of the diester **17** to the monoester **20**. Subsequent reaction of the corresponding acid chloride **21** with dimethylcadmium afforded the *N*-protected ketone **22** in fair yield, together with some unreacted **21**.



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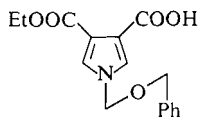

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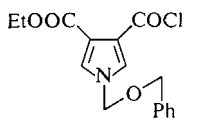

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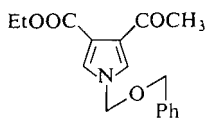
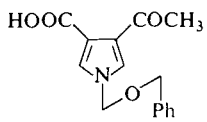


22

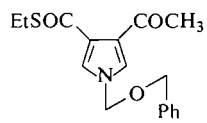
Conversion of **22** to Verrucarin E requires the removal of the *N*-protecting group and reduction of the remaining carboxylate substituent into hydroxymethyl via the thiolester. Although selective hydrogenolysis of a benzyl ether in the presence of an aromatic (including pyrrolic) ketone is usually possible (18–20) hydrogenation of **22** under various conditions resulted in either

[2]Physical properties suggested a mixture of monomeric and polymeric species.

no reaction or in preferential reduction of the ketone. Whilst cleavage of the benzyl ether occurred subsequent to reduction of the ketone, the p.m.r. of the product showed that concurrent hydrogenolysis of the hydroxyethyl group had occurred. It was then found that the benzyl ether in compound **22** could be readily cleaved to the corresponding 1-hydroxymethyl derivative with aluminum chloride. However, as the *N*-protecting group increased solubilities it was decided to retain it as long as possible. Conversion of the 3-carboxylate substituent to the 3-hydroxymethyl group is the other operation required to complete the synthesis. Hydrolysis of **22** to the acid **23** followed by conversion to the acid chloride and treatment with sodium ethanethioxide, gave an excellent yield of the corresponding thiolcarboxylate **24**. The benzyl ether in compound **24** was cleaved with aluminum chloride to the corresponding *N*-hydroxymethyl derivative **25** which on subsequent treatment with benzyltrimethylammonium hydroxide lost formaldehyde affording ethyl 3-acetyl-4-pyrrolethiolcarboxylate (**26**). The Raney nickel reduction of the thiolester group in compound **26** gave the hydroxymethyl derivative, Verrucarin E (**27**). The m.p. and i.r., u.v., and p.m.r. spectra of the synthetic compound were identical with those of natural Verrucarin E. The R_f values of the synthetic product were in agreement with those of the natural compound in various solvent systems.[3]



23



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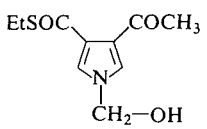

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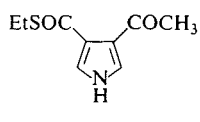

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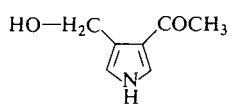


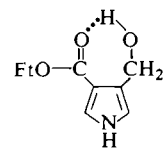
27

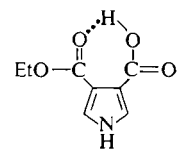
[3]The authors are indebted to Prof. Ch. Tamm who kindly provided an authentic specimen of Verrucarin E for comparison.

Confirmation of the proposed product structures is provided by their i.r., n.m.r., and mass spectral data. N.m.r. data for the trisubstituted pyrroles is given in Table 1.

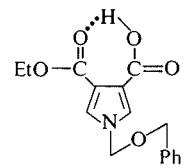
Data for the 3,4-disubstituted pyrroles, given in Table 2, require further comment. Since many of the compounds were of low solubility their spectra were determined in dimethyl sulfoxide-d_6 solution. In this solvent spin–spin coupling between the 1-proton and the α-protons was not apparent, except in those cases where the pyrrole had a CO_2H substituent, because of rapid exchange of the acidic 1-proton with the basic solvent. As a consequence the symmetrical disubstituted compounds exhibited a singlet absorption for the α-protons whilst the unsymmetrical ones gave an AB type quartet. In deuterochloroform solution these absorptions appear as A_2X and ABX respectively.

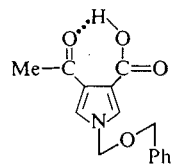
I.r. data for the compounds are reported in the Experimental. In certain compounds the C=O stretching vibration occurs at an anomalously low frequency, a result which we attribute to intramolecular hydrogen bonding. Compare the values in the Experimental for **4** (R = Me or Et) **16**, **17**, and **22**.





$*\nu_{max}$ 1670 cm^{-1} (Nujol) | 1625 (Nujol)





1635 ($CHCl_3$) | 1620 ($CHCl_3$)

*Stretching frequency of H-bonded carbonyl group

Most of the compounds reported exhibit an intense u.v. absorption in the 250 nm region. A further maximum below 215 nm was outside the useful range of the instrument used.

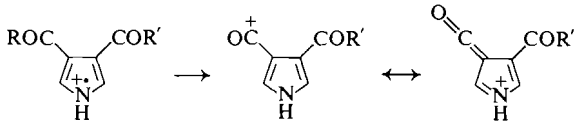
The major peaks in the mass spectra of some 2,4-disubstituted pyrroles are reported in Table 3. With the exception of the thiolesters the molecular ions are all of moderate abundance. The major fragmentation of each molecular ion

TABLE 1. N.m.r. data for trisubstituted pyrroles*

Substituent			τ-Value			
1	3	4	1-Substituent	α-H	3-Substituent	4-Substituent
CO_2Me	CO_2Me	CO_2Me	5.90	2.10	6.10	6.10
COPh	CO_2Me	CO_2Me	2.10 (m)	2.18	6.13	6.13
COPh	CO_2Et	CO_2Et	2.10 (m)	2.15	5.62 8.66	5.62 8.66
CH_2OH	CO_2Et	CO_2Et	4.68	2.64	5.72 8.68	5.72 8.68
CH_2OCH_2Ph	CO_2Et	CO_2Et	2.66 (br) 4.77 5.55	2.66	5.71 8.66	5.71 8.66
CH_2OCH_2Ph	CO_2H	CO_2H†	2.58 (br) 4.40 5.38	2.30	—	—
CH_2OCH_2Ph	CO_2Et	CO_2H	2.65 (br) 4.66 5.48	2.46§ 2.20§	5.59 8.62	— —
CH_2OCH_2Ph	CO_2Et	COMe	2.65 (br) 4.75 5.53	2.65 (br)	5.69 8.65	7.45
CH_2OCH_2Ph	CO_2H	COMe‡	2.58 (br) 4.35 5.33	2.30 (m)	—	7.35
CH_2OCH_2Ph	COMe	COSEt	2.63 4.75 5.50	2.63	7.51	6.94 8.65
CH_2OH	COMe	COSEt	4.6 (br)	2.63§ 2.55§	7.60	7.00 8.68
H	COMe	COSEt	—	2.50 (m)	7.51	7.00 8.70
H	COMe	CH_2OH	—	2.6 (q) 3.3 (m)	7.55	5.38

*In $CDCl_3$ except as noted.
†In $(CD_3)_2SO$.
‡In $(CD_3)_2CO$.
§$J_{2,5}$ = 2.6 Hz.

involves acylium ion formation. The subsequent major fragmentation of the ions **28** (R′ = OEt or SEt) appears to involve ejection of ethylene to give an ion to which may be ascribed structure **29***a* or *b* (X = O or S) (21). The corresponding ion **28**(R′ = OMe) undergoes a different fragmentation with the loss of CH_2O, to give the ion $C_6H_4NO_2^+$.



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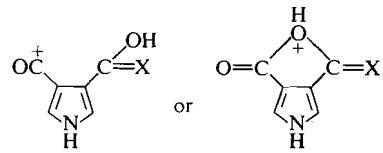
SCHEME 4



29*a* **29***b*

Experimental

Instruments and conditions were as described in ref. 22 except that i.r. spectra were determined in chloroform solution unless otherwise stated.

General Procedure for Diels–Alder Reactions

Dialkyl acetylenedicarboxylate (1.0 equiv) was added over 30 min to the 1-substituted pyrrole in a flask maintained at 190° and flushed with nitrogen. The reaction

TABLE 2. N.m.r. data for disubstituted pyrroles*

Substituents		τ-Value		
3	4	α-H	3-Substituent	4-Substituent
CO_2Me	CO_2Me	2.57	6.30	6.30
CO_2Et	CO_2Et	2.64	5.87 8.79	5.87 8.79
COSEt	COSEt	2.35	7.05 8.75	7.05 8.75
COPh	COPh	complex multiplet	2.0–2.7	
CO_2H	CO_2H	2.32 ($J_{1,2}$ = 3.0)	—	—
CO_2Me	CO_2H	2.40 ($J_{1,2}$ = 3.0) ($J_{2,5}$ = 2.2)	6.15	—
CO_2Me	CO_2Et	2.52	6.25	5.79 8.75
CO_2Me	COSEt	2.52	6.40	7.13 8.80
CO_2Me	CONHPh	2.53	6.83	2.1–2.6 (m)
CO_2Me	COC_6H_4OMe	2.42 ($J_{2,5}$ = 2.2)	6.46	6.12 2.18 2.92
CO_2Me	COC_6H_5	2.16 ($J_{2,5}$ = 2.2) 2.69	6.50	2.0–2.7(m)
CO_2Me	COEt	2.50 2.60	6.28	7.15 8.95
CO_2Me	CH_2OH	2.58 ($J_{2,5}$ = 2.3) 3.20	6.30	5.37(J=0.8)

*In $(CD_3)_2SO$.

TABLE 3. Mass spectral data for some disubstituted pyrroles

Substituents		Ion mass and abundance				
3	4					
(COR′)	(COR)	$M\cdot^+$	$(M\text{-}R')^+$	$(M\text{-}R)^+$	**29**	$C_6H_4NO_2^+$
CO_2Me	CO_2Me	183 (38)	152 (100)			122 (69)*
CO_2Et	CO_2Et	211 (22)	166 (40)		138 (100)†	—
COSEt	COSEt	243 (0.02)	182 (100)		154 (76)‡	—
COPh	COPh	275 (93)	198 (100)			—
CO_2Me	CO_2Et	197 (37)	166 (22)	152 (100)	138 (76)†	122 (51)*
CO_2Me	CO_2H	169 (43)	138 (100)	152 (100)		122 (12)*
CO_2Me	CONHPh	244 (39)	213 (4)	152 (100)		122 (53)*
CO_2Me	COSEt	217 (1)	186 (3)	152 (100)		122 (47)*
CO_2Me	COEt	181 (25)	150 (16)	152 (100)		122 (65)*
CO_2Me	COPh	229 (46)	198 (18)	152 (100)		122 (40)*
CO_2Me	COC_6H_4OMe	259 (18)	228 (6)	152 (26)		122 (18)*

M = 98.
†M* = 115.
‡M* = 130.

mixture was maintained at this temperature for a further 2 h prior to isolating the product.

Trimethyl 1,3,4-Pyrroletricarboxylate

Reaction of methyl 1-pyrrolecarboxylate (0.05 mol) and dimethyl acetylenedicarboxylate gave a dark oil which crystallized from methanol affording trimethyl 1,3,4-pyrroletricarboxylate, m.p. 67–68° (4.2 g, 35%) (lit. m.p. 69° (6)); ν_{max} 1775, 1745, and 1718 cm^{-1} (C=O); λ_{max} (MeOH) 247 nm (ε 7950).

Dimethyl 1-Benzoyl-3,4-pyrroledicarboxylate

1-Benzoylpyrrole (0.1 mol) and dimethyl acetylenedicarboxylate afforded an oil which was distilled to give recovered 1-benzoylpyrrole (4 g, 23%) and dimethyl 1-benzoyl-3,4-pyrroledicarboxylate (19.2 g, 67%), b.p. 210–212°/0.2 mm, which crystallized as needless, m.p. 115–116° (from MeOH); λ_{max} (MeOH) 229 (ε 17 600) and 253 nm (sh ε 9900).

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.7; H, 4.5. Found: C, 62.8; H, 4.4.

Diethyl 1-Benzoyl-3,4-pyrroledicarboxylate

Diethyl acetylenedicarboxylate similarly gave recovered 1-benzoylpyrrole (2.0 g, 25%) and diethyl 1-benzoyl-3,4-pyrroledicarboxylate b.p. 205–210°/0.2 mm, needles m.p. 65–66° (from petroleum (8.5 g, 54%); ν_{max} 1715 and 1732 sh cm^{-1} (C=O); λ_{max} (EtOH) 227 (ε 11 850) and 242 nm (sh ε 9750).

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.8; H, 5.4. Found: C, 64.9; H, 5.4.

Dimethyl 3,4-Pyrroledicarboxylate

Dimethyl 1-benzoyl-3,4-pyrroledicarboxylate (10.0 g) was added to KOH (1.5 g) in methanol (50 ml) and the mixture stirred at 5° for 3 h. The precipitated dimethyl 3,4-pyrroledicarboxylate was filtered and recrystallized from xylene to give needles (6.0 g, 94%), m.p. 242–243° (lit. m.p. 245° (6)); ν_{max} (Nujol mull) 1710 (C=O) and 3255 (N—H) cm^{-1}; λ_{max} (EtOH) 253 nm (ε 7900).

Diethyl 3,4-Pyrroledicarboxylate

Diethyl 1-benzoyl-3,4-pyrroledicarboxylate (3.15 g) was added to KOH (600 mg) in EtOH (65 ml) and the mixture was stirred at 20° for 2.5 h. The mixture was then cooled to 0° and the precipitated diethyl 3,4-pyrroledicarboxylate was collected by vacuum filtration. Recrystallization (from aqueous EtOH) gave plates, m.p. 151–152° (2.0 g, 95%) (lit. m.p. 153–154° (7)); λ_{max} (EtOH) 252 nm (ε 7500); ν_{max} 1730 and 1705 sh (C=O) and 3448 cm^{-1} (N—H).

3,4-Pyrroledicarboxylic Acid

Dimethyl 3,4-pyrroledicarboxylate (2.0 g), NaOH (20 g), and 50% aqueous MeOH (15 ml) were heated under reflux for 2 h. The resulting solution was poured onto ice and 3,4-pyrroledicarboxylic acid (1.55 g, 91%) was precipitated by addition of 2 *M* HCl. The acid had m.p. >300° (dec.) (lit. m.p. 290–292° dec. (6, 7)); ν_{max} (Nujol mull) 1590 (C=O), 2000–3000 (O—H), and 3160 cm^{-1} (N—H); λ_{max} (MeOH) 240 (ε 7900) and 259 nm (ε 7500).

3,4-Pyrroledicarbonyl Chloride

3,4-Pyrroledicarboxylic acid (155 mg), oxalyl chloride (1 ml), and dimethylformamide (1 drop) were heated under reflux in benzene (25 ml) for 30 min. Excess oxalyl chloride was distilled off leaving a homogenous, faintly yellow solution of pyrrole-3,4-dicarbonyl chloride.

Diethyl 3,4-Pyrroledithiolcarboxylate

The above diacid chloride solution, ethanethiol (1 ml), and pyridine (1 drop) were heated under reflux for 1 h. Cooling to 10° afforded diethyl pyrrole-3,4-dithiolcarboxylate as needles from benzene (160 mg, 66%), m.p. 179–180°; ν_{max} 1650 and 1640 cm^{-1} (C=O); λ_{max} (EtOH) 270 nm (ε 13 300).

Anal. Calcd. for $C_{10}H_{13}NO_2S_2$: C, 49.4; H, 5.4; N, 5.8. Found: C, 49.7; H, 5.2; N, 5.9.

3-Carbomethoxy-4-pyrrolecarboxylic Acid

Dimethyl 3,4-pyrroledicarboxylate (5.0 g) and methanolic KOH (1.53 g in 60 ml) were heated for 40 h on a steam bath. Water was added (10 ml) and the solution was filtered. Acidification of the filtrate afforded 3-carbomethoxy-4-pyrrolecarboxylic acid, m.p. 247–248° (from EtOH) (4.3 g, 93%); ν_{max} 1700 and 1625 (C=O) and 2500–3400 cm^{-1} (O—H); λ_{max} (EtOH) 245 (ε 8000) and 260 nm (ε 7350).

Anal. Calcd. for $C_7H_7NO_4$: C, 49.7; H, 4.2. Found: C, 49.9; H, 4.1.

3-Carbomethoxy-4-pyrrolecarbonyl Chloride

3-Carbomethoxy-4-pyrrolecarboxylic acid (1.0 g), oxalyl chloride (1.1 equiv), dimethylformamide (1 drop), and benzene (25 ml) were maintained at 50° for 2 h prior to cooling and filtering off the crude acid chloride (1.0 g, 90%); ν_{max} 1760 and 1715 cm^{-1} (C=O).

Ethyl 3-Carbomethoxy-4-pyrrolethiolcarboxylate

The above acid chloride (2.7 g), ethanethiol (1 ml), and benzene (30 ml) were heated under reflux for 2 h and then cooled to 10° to afford ethyl 3-carbomethoxy-4-pyrrolethiolcarboxylate, needles from benzene, m.p. 172.5–173° (2.3 g, 75%); ν_{max} 1710 and 1645 cm^{-1} (C=O); λ_{max} (EtOH) 255 (ε 9600) and 272 nm (7800).

Anal. Calcd. for $C_9H_{13}NO_3S$: C, 50.7; H, 5.2; N, 6.6. Found: C, 50.7; H, 5.0; N, 6.7.

3-Carbethoxy-4-carbomethoxypyrrole

The monoacid chloride (100 mg) and EtOH (5 ml) were heated under reflux for 1 h. Removal of excess EtOH afforded 3-carbethoxy-4-carbomethoxypyrrole, m.p. 159–160° (from $CHCl_3$) (97 mg, 92%); ν_{max} 1730 br cm^{-1} (C=O); λ_{max} (EtOH) 252 nm (ε 8500).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.9; H, 5.6. Found: C, 54.9; H, 5.8.

3-Carbomethoxy-4-pyrrolecarboxanilide

3-Carbomethoxypyrrole-4-carbonyl chloride (100 mg), aniline (100 mg), and benzene (5 ml) were heated under reflux for 2 h. The mixture was cooled and filtered to afford 3-carbomethoxy-4-pyrrolecarboxanilide (105 mg, 85%). Sublimation (180°/0.1 mm) gave an analytical sample, m.p. 216–217°.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 64.0; H, 4.9. Found: C, 63.9; H, 4.8.

3-Carbomethoxy-4-hydroxymethylpyrrole

Ethyl 3-carbomethoxy-4-pyrrolethiolcarboxylate (300 mg) in EtOH (75 ml) was cooled to 0° and W5 Raney nickel (2 g) was added. After 40 min in a Parr hydrogenator at 25° and 30 p.s.i. of hydrogen, the catalyst was removed

by filtration through a Celite pad and washed with EtOH (200 ml). Concentration of the filtrate and washings yielded 3-carbomethoxy-4-hydroxymethylpyrrole, m.p. 94–95° (from EtOH) (148 mg, 68%); ν_{max} 1690 (C=O) and 3450 cm^{-1} (N—H).

Anal. Calcd. for $C_7H_9NO_3$: C, 54.2; H, 5.8. Found: C, 54.1; H, 5.9.

3-Propionyl-4-carbomethoxypyrrole

3-Carbomethoxypyrrole-4-carbonyl chloride (1.0 g) was added to a benzene solution of diethylcadmium (0.15 mol). The mixture was heated under reflux for 4 h and then poured onto ice – 6 *M* H_2SO_4. The benzene layer was separated and the aqueous layer was extracted with ethyl acetate. The organic solutions were washed with $NaHCO_3$ solution and then dried ($MgSO_4$). The solvent was removed and the product was chromatographed on basic alumina (Brockmann activity III). Elution with ethyl acetate gave 3-propionyl-4-carbomethoxypyrrole, m.p. 179–180° (from ethyl acetate) (0.38 g, 36%); ν_{max} 1720 and 1675 (C=O) and 3450 cm^{-1} (N—H); λ_{max} (EtOH) 253 nm (ε 7000).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.7; H, 6.1. Found: C, 59.8; H, 6.0.

3-Benzoyl-4-carbomethoxypyrrole

3-Carbomethoxy-4-pyrrolecarboxylic acid (420 mg) was converted to the acid chloride in benzene solution. The flask was flushed with nitrogen, aluminum chloride (700 mg) was added, and the mixture was heated under reflux for 10 h. The product was poured onto ice–HCl, extracted into ethyl acetate, and washed with $NaHCO_3$ solution. Chromatography on neutral alumina (Brockmann activity I), eluting with ethyl acetate afforded 3-benzoyl-4-carbomethoxypyrrole, m.p. 163–164° (130 mg, 23%); ν_{max} 1717 and 1655 (C=O) and 3445 cm^{-1} (N—H).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.1; H, 4.8. Found: C, 67.9; H, 5.0.

3-p-Anisoyl-4-carbomethoxypyrrole

3-Carbomethoxypyrrole-4-carboxylic acid (420 mg) similarly gave 3-*p*-anisoyl-4-carbomethoxypyrrole, m.p. 179–180° (from ethyl acetate) (306 mg, 47%); ν_{max} 1715, 1645 (C=O) and 3445 cm^{-1} (N—H); λ_{max} (EtOH) 218 (ε 8600) and 283 nm (ε 9000).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.9; H, 5.0. Found: C, 64.6; H, 5.2.

3,4-Dibenzoylpyrrole

3,4-Pyrroledicarboxylic acid (155 mg) was converted to the diacid chloride in benzene solution (40 ml) as described earlier. Aluminum chloride (260 mg) was added and the mixture was stirred for 18 h at 50°. The product, 3,4-dibenzoylpyrrole m.p. 223–224° (from ethyl acetate) (94 mg, 34%), was isolated as above; ν_{max} 1650 (C=O) and 3445 cm^{-1} (N—H).

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.5; H, 4.7. Found: C, 78.6; H, 4.9.

Diethyl 1-Hydroxymethyl-3,4-pyrroledicarboxylate

Diethyl 3,4-pyrroledicarboxylate (211 mg), aqueous formaldehyde (5 ml of 37%), tetrahydrofuran (5 ml), and benzyltrimethylammonium hydroxide (0.2 ml) were heated under reflux for 5 h. The mixture was poured onto ice and extracted with ethyl acetate, washed with water, and dried ($MgSO_4$). Removal of the solvent afforded diethyl 1-hydroxymethyl-3,4-pyrroledicarboxylate, m.p. 85–86° (from $CHCl_3$–petroleum) (205 mg, 85%); ν_{max} 1725 br (C=O) 3350 br (O—H bonded), and 3560 cm^{-1} (O—H free); λ_{max} (EtOH) 250 nm (ε 6700).

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.7; H, 6.2. Found: C, 54.8; H, 6.1.

Elimination of Formaldehyde from Diethyl 1-Hydroxymethyl-3,4-pyrroledicarboxylate

Diethyl 1-hydroxymethyl-3,4-pyrroledicarboxylate (150 mg), tetrahydrofuran (3 ml), water (10 ml), and benzyltrimethylammonium hydroxide (0.1 ml) were heated under reflux for 3 h. The mixture was diluted with water and the organic material extracted into ethyl acetate and dried ($MgSO_4$). Removal of the solvent gave a product which was shown (i.r. and n.m.r.) to be diethyl 3,4-pyrroledicarboxylate.

Diethyl 1-Benzoyloxymethyl-3,4-pyrroledicarboxylate

Diethyl 3,4-pyrroledicarboxylate (1.05 g) in dry tetrahydrofuran (50 ml) was treated with 1 equiv of sodium hydride. The solution was heated under reflux for 2 h then cooled to 0° and benzyl chloromethyl ether (800 mg) in tetrahydrofuran (10 ml) was added over 15 min. The solution was allowed to reach 25°, stirred overnight, and then heated under reflux for 2 h prior to filtration. The filtrate was concentrated and, after chromatography on neutral alumina, gave diethyl 1-benzyloxymethyl-3,4-pyrroledicarboxylate as a viscous liquid (1.48 g, 90%); ν_{max} 1725 br cm^{-1}.

1-Benzyloxymethyl-3,4-pyrroledicarboxylic Acid

Diethyl 1-benzyloxymethyl-3,4-pyrroledicarboxylate (450 mg) was heated under reflux with aqueous alcoholic potassium hydroxide (12 ml of 10% solution) for 45 min. The mixture was allowed to stand for a further 1 h at 25° prior to acidification with 2 *M* HCl and subsequent extraction into ethyl acetate. Extraction of the organic acid into $NaHCO_3$ solution and re-precipitation afforded 1-benzyloxymethyl-3,4-pyrroledicarboxylic acid, m.p. 143–144° (from 5:1 aqueous-ethanol) (250 mg, 67%); ν_{max} 1720 and 1645 (C=O), 3200–2200 cm^{-1} (O—H); λ_{max} (EtOH) 257 nm (ε 7400).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.0; H, 4.7; N, 5.1. Found: C, 61.0; H, 4.8; N, 5.2.

1-Benzyloxymethyl-3,4-pyrroledicarboxylic Anhydride

1-Benzyloxymethyl-3,4-pyrroledicarboxylic acid (125 mg) and dicyclohexylcarbodiimide (110 mg) were added to dichloroethane (25 ml). The mixture was heated under reflux for 90 min. The initial suspension became homogeneous prior to precipitation of the dicyclohexylurea. Filtration and concentration of the filtrate afforded a product (95 mg, 81%), m.p. 72–80°; ν_{max} 1785, 1835, and 1855 cm^{-1}, average molecular weight in dichloroethane: 308 (calcd. 257). Attempted recrystallization from various solvents failed to sharpen the melting point.

1-Benzyloxymethyl-3-carbethoxy-4-pyrrolecarboxylic Acid

Diethyl 1-benzyloxymethyl-3,4-pyrroledicarboxylate (6.5 g), potassium hydroxide (1.10 g), and EtOH (50 ml) were heated under reflux for 18 h. The product was poured into water and extracted with ether. The aqueous layer was separated, acidified, and filtered to afford 1-benzyloxymethyl-3-carbethoxy-4-pyrrolecarboxylic acid, m.p. 82–83° (from ether) (4.8 g, 81%); ν_{max} 1712 and

1635 cm^{-1} (C=O); λ_{max} (EtOH) 247 (ε 7650) and 260 nm (7300).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.3; H, 5.6. Found: C, 63.5; H, 5.6.

Ethyl 1-Benzyloxymethyl-3-acetyl-4-pyrrolecarboxylate

The above half-acid (1.50 g) was heated under reflux with a benzene solution (80 ml) of oxalyl chloride (0.65 g) and dimethylformamide (1 drop). A solution of dimethylcadmium was prepared from magnesium (0.48 g) and methyl iodide (1.4 ml) to form a Grignard reagent in ether (50 ml), followed by the addition of cadmium chloride (1.83 g). This mixture was heated under reflux for 2 h prior to replacing the ether by benzene (50 ml). The above acid chloride was added to the dimethylcadmium solution over 15 min and the mixture was then heated under reflux for 3.5 h prior to pouring onto ice–HCl. The organic material was extracted into a large volume of ethyl acetate, washed with $NaHCO_3$ solution, dried ($MgSO_4$) and filtered through a short column of activity I basic alumina. Removal of the solvent afforded ethyl 1-benzyloxymethyl-3-acetylpyrrole-4-carboxylate as a viscous liquid (800 mg, 54%), ν_{max} 1710 and 1665 (C=O) cm^{-1}.

1-Benzyloxymethyl-3-acetyl-4-pyrrolecarboxylic Acid

The above keto-ester (200 mg) was heated under reflux for 2.5 h with a solution of KOH (500 mg) in aqueous ethanol (3 ml, 1:1). The solution was poured into water, acidified with 2 *M* HCl, and the resulting 1-benzyloxymethyl-3-acetyl-4-pyrrolecarboxylic acid was filtered off giving a solid m.p. 149–150° (from aqueous EtOH), (140 mg, 78%); ν_{max} 1710 and 1620 cm^{-1} (C=O); λ_{max} (EtOH) 262 nm (ε 10 300).

Anal. Calcd. for $C_{16}H_{17}NO_5$; C, 63.4; H, 5.6. Found: C, 63.5; H, 5.7.

Attempted Hydrogenolysis of the Benzyloxymethyl Substituent in **22**

Uncontrolled hydrogenolysis of ethyl 1-benzyloxymethyl-3-acetyl-4-pyrrolecarboxylate (**22**) (150 mg) in EtOH (20 ml) in the presence of 10% palladium-on-carbon (25 mg) resulted in complete hydrogenolysis of the benzyl group and complete reduction of the acetyl group as shown in the n.m.r. of the product. When hydrogenolysis under these conditions was stopped after the uptake of 1 mol equiv of hydrogen (2.5 h), the n.m.r. of the product showed the absence of acetyl group but retention of a benzyl group. The α-proton resonances occurred as doublets (J = 2.2 Hz) at τ 2.55 and 3.27.

Hydrogenolysis of **22** (100 mg) in tetrahydrofuran (40 ml) in the presence of 10% palladium-on-carbon (35 mg) and triethylamine (1 drop) for 4 h resulted in recovery of a product, the n.m.r. spectrum of which indicated that it was mainly **22** although a little reduction of the acetyl group was apparent in the spectrum.

Hydrogenolysis of **22** (50 mg) in EtOH (6 ml) in the presence of 10% palladium-on-carbon (20 mg) and sulfur–quinoline poison solution (0.1 ml) for 4 h resulted in complete reduction of the acetyl but retention of the benzyl as shown by the n.m.r. spectrum.

Hydrogenolysis of **22** (100 mg) in the presence of W5 Raney nickel (~200 mg) in EtOH (15 ml) under 30 p.s.i. for 1 h resulted in recovery of unchanged **22**.

Ethyl 1-Benzyloxymethyl-3-acetyl-4-pyrrolethiolcarboxylate

1-Benzyloxymethyl-3-acetyl-4-pyrrolecarboxylic acid (275 mg) was heated under reflux for 2 h in a benzene solution (25 ml) of oxalyl chloride (135 mg) and dimethylformamide (1 drop). A solution of sodium ethanthioxide was prepared by adding ethanethiol (65 mg) to 50 mg of 58% sodium hydroxide in 25 ml of benzene. The above acid chloride was then added to the sodium ethanthioxide solution and the mixture was refluxed for 1 h. The reaction mixture was then cooled and the precipitated inorganic salt was removed by filtration and washed with benzene (100 ml). The filtrate was then evaporated *in vacuo*, and the yellow viscous liquid thus obtained was filtered through a short column of neutral alumina (Brockmann activity I) using ether as eluant. Removal of solvent gave ethyl 1-benzyloxymethyl-3-acetyl-4-pyrrolethiolcarboxylate as a pale yellow viscous oil (225 mg, 71%); ν_{max} 1665 and 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{19}NO_3S$: C, 64.4; H, 6.0; N, 4.4. Found: C, 64.2; H, 6.0; N, 4.5.

Ethyl 1-Hydroxymethyl-3-acetyl-4-pyrrolethiocarboxylate

Ethyl 1-benzyloxymethyl-3-acetyl-4-pyrrolethiolcarboxylate (160 mg) in anhydrous benzene (15 ml) was stirred at 40 °C for 30 min with aluminum chloride (140 mg). The solution was then cooled in ice and the excess aluminum chloride was slowly destroyed through addition of ice-cold water. The organic layer was separated, dried ($MgSO_4$) and evaporated *in vacuo*. The benzyl chloride formed was distilled under vacuum, the reddish gum obtained crystallized from ether–petroleum (92 mg, 81%), m.p. 89–91°; ν_{max} 3400 br (O—H), 1665, and 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.9; H, 5.7. Found: C, 52.8; H, 5.9.

Ethyl 3-Acetyl-4-pyrrolethiolcarboxylate

Ethyl 1-hydroxymethyl-3-acetyl-4-pyrrolethiolcarboxylate (60 mg) in aqueous tetrahydrofuran (13 ml of 10:3) was heated under reflux with benzyltrimethylammonium hydroxide (0.2 ml). The mixture was then evaporated to half-bulk, diluted with water (20 ml), and extracted twice with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), and evaporated *in vacuo* affording ethyl 3-acetyl-4-pyrrolethiolcarboxylate as a white powder, (44 mg, 85%). Recrystallization from ether – petroleum ether gave an analytical sample, m.p. 118–120°; ν_{max} 3440 (N—H free), 3250 (N—H bonded), 1665 and 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_9H_{11}NO_2S$: C, 54.8; H, 5.8; N, 7.1. Found: C, 54.8; H, 5.6; N, 7.2.

3-Acetyl-4-hydroxymethylpyrrole

Ethyl 3-acetyl-4-pyrrolethiolcarboxylate (30 mg) in absolute methanol (20 ml) was cooled to 0° and W5 Raney nickel (about 800 mg) was added. The mixture was shaken in a Parr hydrogenator for 70 min at 25° and 30 p.s.i. of hydrogen. The catalyst was then removed by collection on a Celite pad and was washed with ethanol (250 ml). The filtrate and washings were combined and removed *in vacuo* affording a pink gum. Preparative t.l.c. (silica gel GF-254 chloroform–methanol, 97:3) of the crude product resulted in the isolation of pure 3-acetyl-4-hydroxymethylpyrrole (15 mg, 71%), m.p. 88–90°

(lit. (3, 4) 90.5–91°). The i.r., u.v., and p.m.r. spectra were identical with those of natural Verrucarin E. The R_f values of the synthetic product were in agreement with those reported for the natural compound using chloroform–methanol, 97:3; or 92:8; as well as ethyl acetate as eluants.

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