Oxidation of Enamine-esters with Lead Tetra-acetate. Part 1. Products from Some *N*-Alkylaminofumarates

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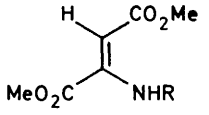
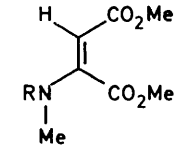
N-Methyl- and *N*-ethyl-aminofumarates are oxidised by lead tetra-acetate to mixtures of heterocyclic polyesters: pyrroles (4), pyridines (6), and pyrrolo[3,2-*b*]pyrroles (7). Some other *N*-alkylaminofumarates afford acyclic oxidative dimers, in which enamine molecules are linked through their β-carbon atoms. Dimers of one structure type (13) can be cyclised independently to (4) and (6).

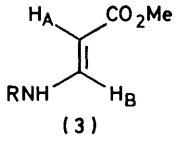
THE Michael adducts of primary and secondary amines and acetylenedicarboxylic esters serve as intermediates for the synthesis of a variety of nitrogen-containing heterocyclic systems, particularly pyrrole and quinoline derivatives.[1-7] A brief report[8] of the oxidation of dimethyl anilinofumarate (1h) with lead tetra-acetate



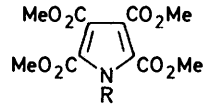
(1) a ; R = Me
b ; R = Et
c ; R = Pr^i
d ; R = cyclo-C_6H_{11}
e ; R = cyclo-C_7H_{13}
f ; R = Bu^s
g ; R = Bu^t
h ; R = Ph



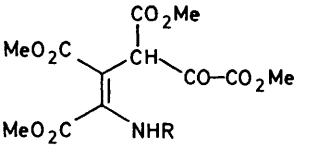
(2) a ; R = Me
b ; R = H



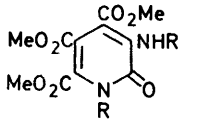
(3)



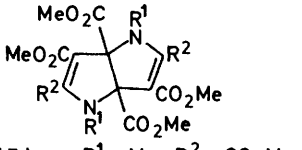
(4) a ; R = Me
b ; R = Et
c ; R = Pr^i
d ; R = cyclo-C_6H_{11}
e ; R = Ph



(5) a ; R = Me
b ; R = Et



(6) a ; R = Me
b ; R = Et
c ; R = Pr^i
d ; R = cyclo-C_6H_{11}



(7) a ; R^1 = Me, R^2 = CO_2Me
b ; R^1 = Et, R^2 = CO_2Me
(8) R^1 = Me, R^2 = CO_2H
(9) R^1 = Me, R^2 = H

(LTA) to give the *N*-phenylpyrrole tetraester (4e) prompted our investigation of similar oxidations of *N*-alkylaminofumarates.[9] Acetoxylation and oxidative cleavage of simpler enamines by LTA have been described, and imines capable of tautomerism to enamines react with LTA *via* the enamine form.[10]

RESULTS AND DISCUSSION

Heterocyclic Products.—Three products were obtained from the oxidation of dimethyl *N*-methylaminofumarate (1a) with LTA in dichloromethane, in the presence of trifluoroacetic acid at room temperature. The first product, the pyrrole-ester (4a), was identified from analysis and spectroscopic data and by comparison with a sample prepared by acid-catalysed cyclisation of the 1 : 2 adduct (5a) obtained from *N*-methylhydroxylamine and dimethyl acetylenedicarboxylate.[11] This product (4a) was more easily isolated and in higher yield (28%) when the enamine (1a) was treated with LTA in refluxing acetonitrile.

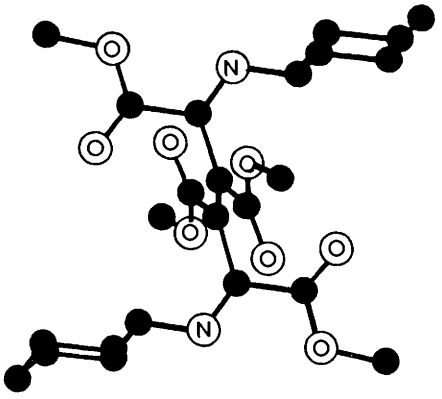
The second product was $C_{13}H_{16}N_2O_7$, with i.r. absorptions for N–H and C=O groups. The ^{1}H n.m.r. spectrum consisted of resonances for three inequivalent OMe groups, and NMe and NHMe groups. These data lead us to assign the pyridin-2-one structure (6a), which is also fully consistent with the ^{13}C n.m.r. spectrum (Table). An alternative formulation, the corresponding 2-methylaminopyridin-4-one-3,5,6-triester, would also be possible, except for the evidence of the mechanism of formation, which is discussed below.

The third product has the molecular formula $C_{20}H_{24}N_2O_{12}$ from elemental analysis and mass spectrometry. The ^{1}H n.m.r. spectrum consisted of four singlets of equal intensity, none of which was further resolved in the

^{13}C N.m.r. data for *N*-methyl compounds (p.p.m. downfield from internal $SiMe_4$)

Compd.	C=O	Other sp^2 carbon atoms	Ring sp^3 carbon atoms	OMe	NMe
(2a)	167.9	155.2(α)		52.8	39.7
	166.0	84.2(β) [a]		50.6	
(4a)	163.6 [b]	126.8(α) [b]		52.8 [b]	35.1
	160.5 [b]	119.6(β) [b]		52.4 [b]	
(6a)	167.0	137.8		53.1	34.1
	165.4	127.8		52.8	31.2
	163.0	112.3		52.3	
	157.9	107.1			
(7a)	167.5	157.4(α)	94.3	53.3 [b]	31.8
	163.9	86.2(β)		51.2	
	162.4				
(9)	168.9	156.0(α) [a]	96.1	53.2	34.1
	165.4	87.0(β)		50.7	

[a] Protonated =CH. [b] Relative intensity 2.



Projection drawing of the crystal structure of (10d)

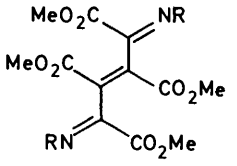
presence of a praseodymium shift reagent. This requires two-fold symmetry involving NMe and three inequivalent OMe groups, which is satisfied by the pyrrolo[3,2-*b*]-pyrrole structure (7a).[12] The u.v. absorption spectrum [$\lambda_{max.}(CH_2Cl_2)$ 285 nm (log ε 4.37)] is strikingly similar to that of dimethyl *NN*-dimethylaminomaleate (2a) [$\lambda_{max.}$ (EtOH) 282 nm (log ε 4.37)].[13] ^{13}C N.m.r. assignments (Table) were made in comparison with those for the model compound (2a), and the spectrum was fully in accord with the suggested structure (7a).

Careful saponification of the hexaester (7a) afforded a tetraester with the same two-fold symmetry (^{1}H n.m.r. spectrum). It was expected that the ester groups attached to bridgehead positions in structure (7) would be sterically hindered and that ester groups conjugated β to nitrogen atoms would be deactivated to nucleophilic attack, so that the hydrolysis product should be (8). This was confirmed by decarboxylation to give another tetraester, $C_{16}H_{20}N_2O_8$, for which the following evidence from n.m.r. spectra establishes structure (9). Assignments of OMe resonances for the hexaester (7a) (τ 6.10, 6.33, and 6.44 to ester groups at α, bridgehead, and β positions, respectively) are possible by comparison with the ^{1}H n.m.r. spectrum of the model compound (2a) (τ 6.15 and 6.45 for the ester groups at the α and β positions, respectively). Chemical shifts of the remaining OMe groups in the tetraester (9) (τ 6.34 and 6.43) therefore match those assigned to the bridgehead and β-ester groups in (7a). Also the vinyl hydrogen resonance (τ 2.70) in the spectrum of the tetraester (9) appears in almost the same position as that of the hydrogen atom H_B in *trans-N*-alkylaminoacrylic esters (3).[13] The ^{13}C n.m.r. spectrum of the tetraester (9) closely resembles that of the hexaester (7a) (Table), and off-resonance decoupling showed that the α-carbon of the enamine moiety was coupled to one hydrogen atom.

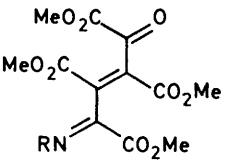
Oxidation of the enamine (1b) with LTA under the same conditions gave the corresponding heterocyclic products (6b) and (7b), the structures of which are proved by comparison of u.v., i.r. and n.m.r. spectroscopic data (see Experimental section) with those of the *N*-methyl compounds. The *N*-ethylpyrrole-ester (4b) was not identified as an oxidation product from (1b), but a sample was prepared from *N*-ethylhydroxylamine *via* addition of dimethyl acetylenedicarboxylate and cyclisation of the adduct (5b)

Acyclic Products.—The oxidation of dimethyl *N*-cyclohexylaminofumarate (1d) with LTA in dichloromethane afforded three products, all of different types from those described above. Using equimolar proportions of enamine (1d) and LTA we obtained an oxidative dimer, $C_{24}H_{34}N_2O_8$, in 14% yield. This formula was confirmed by high-resolution mass spectrometry. The ^{1}H n.m.r. spectrum of this compound showed resonances for the *N*-cyclohexyl group and for only two methyl ester environments. The two types of ester group were not resolved in the ^{13}C n.m.r. spectrum, which showed a single resonance for OMe, another singlet for C=O, and two other types of sp^2 carbon atoms (δ 152.5 and 139.4 p.p.m.). There were i.r. absorptions at 1 650w and 1 715s cm^{-1} in the carbonyl region. This evidence led us to suggest the structure (10d), which was confirmed by an *X*-ray crystallographic study carried out in Professor T. J. King's laboratory. The configuration at the central C=C bond is *trans* and the molecule is twisted (Figure) inhibiting conjugation of C=N with C=O bonds.

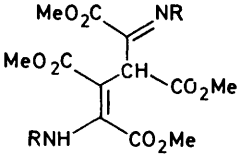
The second product obtained by LTA-oxidation of the enamine (1d) analysed for $C_{18}H_{23}NO_9$. Its i.r. absorption in the carbonyl region was more complicated than that of (10d), and both ^{1}H and ^{13}C n.m.r. spectra showed three resonances integrating for four OMe groups. This compound is still unidentified, although a possible structure which we are unable to confirm is that of the ketoester (11); *trans*-stereochemistry is assumed by analogy with (10d).



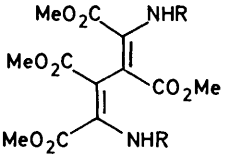
(10) a ; R = Pr^i
b ; R = Bu^s
c ; R = Bu^t
d ; R = cyclo–C_6H_{11}
e ; R = cyclo–C_7H_{13}



(11) R = cyclo–C_6H_{11}



(12)

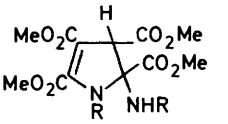


(13) a ; R = Pr^i
b ; R = cyclo–C_6H_{11}
c ; R = Bu^t

Slow addition of LTA to the enamine (1d) in refluxing acetonitrile afforded a third product, $C_{24}H_{36}N_2O_8$, in 11% yield. The same compound was readily formed by hydrogenation of (10d) over palladium, and it was re-oxidised to (10d) with LTA in dichloromethane. In

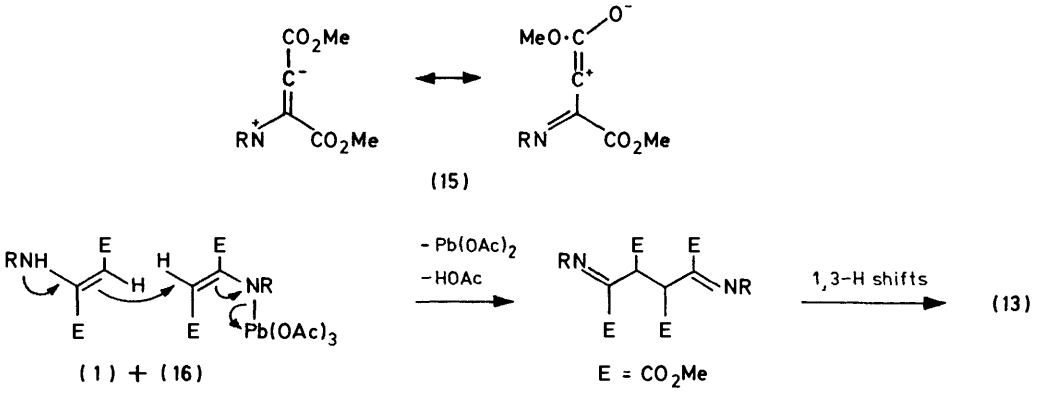
contrast to (10d), this new compound showed a group of four i.r. absorptions in the carbonyl region and four resonances for OMe groups in both ^1H and ^{13}C n.m.r. spectra. It must be an unsymmetrical dihydro-derivative of (10d), containing one aminofumarate moiety to account for the low-field position of an NH resonance (τ 1.30, br d) in the ^1H n.m.r. spectrum [*cf.* τ 1.95, br d, for the enamine (1d)]. We had earlier suggested[9] the structure (12) for this compound on account of a ^{13}C n.m.r. absorption (δ 152.3) in the same position as that assigned to the *C*=N atoms of the more oxidised dimer (10d). However, there is no evidence in the off-resonance ^{13}C n.m.r. spectrum of the presence of a tertiary CH other than those N–CH of the cyclohexyl groups. On the contrary, there are four resonances (δ 83.9, 91.7, 152.3, and 155.9) for non-protonated sp^2 carbon atoms (apart from those of C=O groups at even lower field), which look like those of two non-identical enamines [*cf.* values for the aminomaleate (2a) (Table) and corresponding values (86.2 and 151.1) for (1e) typical of aminofumarates (1)]. Structure (13b), containing maleate and fumarate moieties, is fully consistent with the ^{13}C n.m.r. spectrum. It is also consistent with the ^1H n.m.r. spectrum, if another broad doublet absorption (τ 5.58) is identified as that of the aminomaleate NH group; this is at higher field than that (τ 4.25) of compound (2b), but very close to that (τ 5.60) of the corresponding NH group in compound (5a).[11] Double-resonance experiments demonstrated convincingly that the two NH doublets were not a mutually coupled AB system, but that they were independently coupled to N–CH groups responsible for the broad resonance at τ 7.0. We are unable to explain why (13) should be preferred to a bis-fumarate structure, in view of the preference for the latter configuration shown by the enamines (1).[13]

A series of oxidative dimers (10; a—c and e) was obtained from the corresponding enamines (1c, f, g, and e) by treatment with LTA. I.r. and ^1H and ^{13}C n.m.r. spectra of all these compounds showed appropriate features in common with those of (10d). Some noteworthy features of the mass spectra of these compounds will be discussed elsewhere. Hydrogenation of two of these enedi-imines (10a and c) gave the corresponding dihydro-derivatives (13a and c) with appropriate i.r. and ^1H and ^{13}C n.m.r. characteristics matching those of (13b). One of these (13a) was also isolated by oxidation of the enamine (1c) with LTA in acetonitrile, and it was further oxidised by LTA in dichloromethane to give the same end-product (10a).



(14)

Rationalisation and Interrelation of these Products.— In the presence of trifluoroacetic acid the bis-enamines (13a and b) were readily converted into the corresponding pyrrole-esters (4c and d), which were characterised by analysis and spectra (see Experimental section).



(15)

(1) + (16)

E = CO_2Me

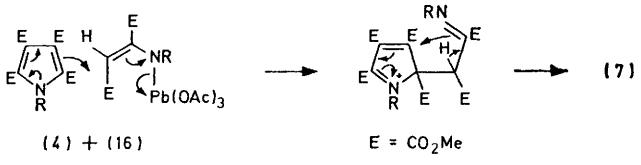
SCHEME 1

Cyclisation presumably occurs first to the dihydropyrrole (14), from which amine is eliminated to give the pyrrole (4). On the other hand, treatment of the bis-enamines (13a and b) with sodium methoxide in methanol prompted a different cyclisation to give the pyridinone derivatives (6c and d) analogous to the *N*-methyl and *N*-ethyl compounds described above. Neither of these cyclisations was achieved with the bis-enamine (13c) under comparable conditions of acidic or basic catalysis, possibly because of steric hindrance from the *N*-t-butyl group.

These results strongly suggest that the oxidative dimers (13) are the common intermediates for formation of the end-products (4), (6), and (10). Cyclisation is apparently easiest with primary *N*-alkyl groups, since only from the enamines (1a, b) are pyrrole and pyridinone derivatives, (4) and (6), isolated directly from the LTA oxidation. Enamines are ambident as nucleophiles, reacting either at the nitrogen or the β-carbon atom. A possible mechanism to account for the oxidative dimerisation (1) ⟶ (13) is shown in Scheme 1.

The LTA oxidation of phenylhydrazones to products derived *via* trapping of intermediate nitrile imines[14] led us to consider the possibility that plumbylated enamine

(16) decomposes to give a dipolar intermediate (15),* cycloaddition of which to the pyrrole (4) or its presumed precursor (14) could account for the formation of the bicyclic products (7). However, attempts to intercept such a dipole (15) by carrying out the oxidation of (1a) in the presence of acetonitrile, acrylonitrile, or benzonitrile still gave (7a) and no new products. A more likely mechanism is therefore one in which plumbylated enamine (16) couples to pyrrole (4) leading to pyrrolo-[3,2-*b*]pyrrole (7) as outlined in Scheme 2.



SCHEME 2

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls (unless otherwise stated), and absorptions are quoted only for the regions 1 600—1 800 and 3 000—3 500 cm^{-1}. ^1H N.m.r. spectra were obtained at 60 or 100 MHz (Perkin-Elmer R10, Varian A60A, or JEOL MH100 instruments) and ^{13}C n.m.r. spectra at 84.6 MHz (JEOL FX60) for solutions in deuteriochloroform (unless stated otherwise); ^{13}C chemical shifts are quoted in p.p.m. downfield from internal tetramethylsilane. Mass spectra were obtained by electron impact at 70 eV (A.E.I. MS12 and MS30 instruments); only those fragment ions with intensity >20% of the base peak are reported.

Lead tetra-acetate (LTA) was freshly recrystallised from acetic acid, washed with carbon tetrachloride and stored in a vacuum desiccator before use. Acetonitrile and dichloromethane were dried before use. Oxidation reactions in acetonitrile were worked up after confirming the absence of unreacted lead(IV); lead diacetate was filtered off, and the filtrate was concentrated by evaporation; carbon tetrachloride was added and then removed along with acetonitrile and acetic acid by rotary-evaporation to dryness. For reactions in dichloromethane removal of the precipitated lead diacetate by filtration was often less satisfactory, so the following procedure was used: the reaction mixture was poured into water, the dichloromethane layer was separated, washed with water and with aqueous sodium hydrogencarbonate, dried with $MgSO_4$, filtered, and rotary-evaporated to dryness.

Enamines (1) *and* (2).—The aminofumarate derivatives (1a—g) were prepared by reaction between dimethyl acetylenedicarboxylate and the appropriate primary amine in ethanol (in the case of methylamine) or ether (all others) at 0 °C. The solvent was evaporated and the residue was distilled *in vacuo* to give colourless or pale yellow oils, some of them (1a—d and g) already known [13,16] and others characterised as follows: *dimethyl* N-*cycloheptylaminofumarate* (1e), b.p. 136 °C at 2 mmHg (Found: C, 61.5; H, 8.3; N, 5.6. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.2; N, 5.5%), *m/e* 255 (M^+, 34%) and 160 (100); and *dimethyl* N-*s-butylaminofumarate* (1f), b.p. 106 °C at 0.3 mmHg (Found: C, 56.0; H, 8.0; N, 6.6. $C_{10}H_{17}NO_4$ requires C, 55.8; H, 7.9; N, 6.5%), *m/e* 215 (M^+, 100%) and 186 ([M − Et]$^+$, 72). ^1H N.m.r. spectra of all these compounds (1a—g) showed the following absorptions: τ 1.7—2.1 (br, NH), 5.0—5.3 (s, =CH), 6.2—6.4 (two singlets, OMe), and further absorptions appropriate to the *N*-alkyl group.

The crude product of the reaction between methylamine and dimethyl acetylenedicarboxylate was a mixture (*ca.* 2 : 3) of dimethyl *N*-methylaminomaleate (2b); τ 4.25 (br, 1 H, NH), 5.40 (1 H, s, =CH), 6.17 and 6.38 (each 3 H, s, OMe), and 7.25 (3 H, d, *J* 5 Hz, NMe), and the fumarate (1a): after distillation the presence of (2b) was no longer detectable. Dimethyl *NN*-dimethylaminomaleate (2a), m.p. 83—84 °C (lit.,[13] 83—84.5 °C) was obtained from dimethylamine and dimethyl acetylenedicarboxylate.

Oxidation of Dimethyl N-*Methylaminofumarate* (1a).—A solution of LTA (5.76 g) in dichloromethane (20 ml) containing trifluoroacetic acid (3.4 g) was added dropwise during 10 min to the enamine (1a) (4.5 g) in dichloromethane (10 ml) at 0 °C. The mixture was allowed to reach room temperature and to stand for 2 h. Work-up by the standard procedure gave an orange oil from which a solid separated on trituration with methanol. This solid was recrystallised from 1,2-dichloroethane–light petroleum to give *hexamethyl* 3a,6a-*dihydro*-1,4-*dimethylpyrrolo*[3,2-b]*pyrrole*-2,3,3a,-5,6,6a-*hexacarboxylate* (7a) (0.38 g, 9%), m.p. 264 °C (decomp.) (Found: C, 49.5; H, 4.8; N, 5.7%; *M* 484.1316. $C_{20}H_{24}N_2O_{12}$ requires C, 49.6; H, 5.0; N, 5.8%; *M* 484.1330); $\nu_{max.}$ 1 680, 1 740, and 1 760 cm^{-1}; τ 6.10, 6.33, and 6.44 (each 6 H, s, OMe) and 7.08 (6 H, s, NMe), *m/e* 485 (24%), 484 (M^+, 100), 425 ([M − CO_2Me]$^+$, 51), 420 (28), 409 (45), 393 (48), 381 (48), 366 (28), and 335 (27); *m** 373 (484→425). In a separate experiment without trifluoroacetic acid the yield of (7a) was increased to 12% [based on (1a)].

The methanolic mother-liquor from which the above product had separated was then concentrated by evaporation and chilled. A further crop of solid (2.0 g) was collected after 3 d and chromatographed on a column of type O alumina. Elution with toluene–ether (1 : 1 v/v) afforded first tetramethyl 1-methylpyrrole-2,3,4,5-tetracarboxylate (4a) (0.26 g, 6%), m.p. 123 °C (from methanol) (lit.,[17] m.p. 120—123 °C) (Found: C, 49.8; H, 4.8; N, 4.4. Calc. for $C_{13}H_{15}NO_8$: C, 49.8; H, 4.8; N, 4.5%); $\nu_{max.}$ 1 720 and 1 730 cm^{-1}; τ 5.94 (3 H, s, NMe) and 6.04 and 6.07 (each 6H s, OMe); *m/e* 313 (M^+, 34%) and 282 ([M − OMe]$^+$, 100), and then *trimethyl* 1-*methyl*-3-*methylamino*-2-*oxo*-1,2-*dihydropyridine*-4,5,6-*tricarboxylate* (6a) (1.70 g, 42%), m.p. 123 °C (from methanol), m.p. considerably depressed on admixture with (4a) (Found: C, 50.0; H, 5.1; N, 8.75. $C_{13}H_{16}N_2O_7$ requires C, 50.0; H, 5.1; N, 9.0%); $\nu_{max.}$ 1 600, 1 630, and 1 720 (C=O), and 3 320 (N–H) cm^{-1}; τ 3.85 (br, 1 H, NH, exchangeable), 6.19, 6.24, and 6.27 (each 3 H, s, OMe), 6.52 (3 H, s, NMe), and 7.13 (3 H, d, *J* 6 Hz, collapses to singlet after shaking with ^2H_2O, NH*Me*); *m/e* 312 (M^+, 89%), 281 (42), and 186 (100).

In a separate experiment oxidation of the enamine (1a) (3.5 g) with LTA (9.0 g) in refluxing acetonitrile afforded the pyrrole (4a) (0.9 g, 28%), m.p. 121—123 °C.

Oxidation of Dimethyl N-*Ethylaminofumarate* (1b).—The enamine (1b) (3.74 g) was treated with LTA (4.43 g) in dichloromethane containing trifluoroacetic acid (2.28 g) in the same way as described above. The reaction mixture was set aside for 20 h at room temperature before being worked

* The use of 1,3-dipolar addition reactions for the synthesis of some novel heterocyclic systems [including the 1,4-diazapentalene system [15]] is wrongly listed in index volumes of *Chem. Abs.* under pyrrolo[3,2-*b*]pyrrole derivatives instead of under pyrrolo[1,2-*a*]-imidazole.

up. The crude oil so obtained was triturated with ether–light petroleum, and the resulting solid was collected and recrystallised from methanol to give the *pyrrolo*[3,2-b]-*pyrrole* (7b) (0.37 g, 11%), m.p. 200 °C (Found: C, 51.5; H, 5.7; N, 5.2. $C_{22}H_{28}N_2O_{12}$ requires C, 51.6; H, 5.5; N, 5.4%); $\lambda_{max.}(CH_2Cl_2)$ 286 nm (log ε 4.30); $\nu_{max.}$ 1 675, 1 745, and 1 760 cm^{-1}; τ 5.95, 6.20, and 6.28 (each 6 H, s, OMe), 6.45 (4 H, q, *J* 7.5 Hz, CH_2), and 8.90 (6 H, t, CH_2Me); *m/e* 513 (24%), 512 (M^+, 100), 481 ($[M - OMe]^+$, 23), 453 ($[M - CO_2Me]^+$, 63), 437 (57), 421 (90), 409 (65), 394 (29), 389 (63), 363 (33), and 214 (34); *m** 401 (512→453), 391 (453→421), 369 (453→409), and 359 (421→389).

The ethereal liquor remaining after isolation of (7b) was kept at −20 °C. A second crop of crystals was collected and recrystallised from methanol to give the *pyridin-2-one* (6b) (0.5 g, 11%), m.p. 91 °C (Found: C, 52.9; H, 5.6; N, 8.5. $C_{15}H_{20}N_2O_7$ requires C, 52.9; H, 5.9; N, 8.2%); $\nu_{max.}$ 1 600, 1 640, and 1 715 (C=O), and 3 330 (N–H) cm^{-1}; τ 3.82 (br, 1 H, m, NH), 5.82 and 6.64 (each 2 H, q, *J* 7 Hz, CH_2), 6.00, 6.06, and 6.10 (each 3 H, s, OMe), and 8.63 and 8.71 (6 H, two overlapping t, CH_2Me), *m/e* 340 (M^+, 100%), 325 (20), 309 ($[M - OMe]^+$, 44), and 293 (81); *m** 281 (340 →309).

Tetramethyl 1-*Alkylpyrrole*-2,3,4,5-*tetracarboxylates* (4a and b).—*N*-Methylhydroxylamine (0.5 g) was added to dimethyl acetylenedicarboxylate (3.0 g) in refluxing methanol (20 ml). The solution was refluxed for 0.5 h, and cooled to give the 1 : 2 adduct (5a) (2.16 g, 61%), m.p. 179—181 °C (lit.,[11] 201 °C) (Found: C, 47.5; H, 5.3; N, 4.55. Calc. for $C_{13}H_{17}NO_9$: C, 47.2; H, 5.2; N, 4.2%); the i.r., ^1H n.m.r., and mass spectra are in agreement with those reported.[11] This compound (5a) (1.8 g) was dissolved in concentrated sulphuric acid (2 ml) at 0 °C. The solution was allowed to warm to room temperature and then poured into ice–water. The precipitate was collected, washed with water, sucked dry, and recrystallised from methanol to give the pyrrole-ester (4a) (1.3 g, 77%), m.p. 123 °C (lit.,[17] 120—123 °C), mixed m.p. with the sample obtained above showed no depression, and identical i.r. spectrum.

N-Ethylhydroxylamine [18] (1.5 g) was added to dimethyl acetylenedicarboxylate (7.0 g) in refluxing methanol (30 ml). The mixture was refluxed for 0.5 h and cooled, but no solid was obtained. Methanol was removed *in vacuo* and the residue was redissolved in toluene and refluxed 2 h. The solid which separated on cooling was collected and recrystallised from methanol, to give the 1 : 2 *adduct* (5b) (3.5 g, 41%), m.p. 116—117 °C (Found: C, 48.9; H, 5.3; N, 4.2. $C_{14}H_{19}NO_9$ requires C, 48.7; H, 5.5; N, 4.1%); $\nu_{max.}$ 1 600, 1 692, 1 750br, and 3 480 (N–H) cm^{-1}; τ 5.27 (1 H, s, tertiary CH), 5.93 (1 H, s, NH), 6.04, 6.10, 6.19, and 6.36 (each 3 H, s, OMe), 6.66 (2 H, q, *J* 7 Hz, CH_2), and 8.84 (3 H, t, CH_2Me); δ_C 172.6, 165.9, 163.2, 162.2, and 155.0 (C=O), 101.8 and 80.9 (C=C), 71.2 (tertiary CH), 54.0, 53.2, 52.5, and 51.1 (OMe), 41.6, and 12.7 (CH_2Me); *m/e* 345 (M^+, 3%) and 254 (100). This compound (3.0 g) was dissolved in concentrated sulphuric acid (18 ml) at 0 °C and the solution worked up as before to give the pyrrole-ester (4b) (2.6 g, 91%), m.p. 69—71 °C (from light petroleum, b.p. 60—80 °C) (lit.,[17] m.p. 66—68 °C); τ 5.52 (2 H, q, *J* 7 Hz, CH_2), 6.09 and 6.13 (each 6 H, s, OMe), and 8.61 (3 H, t, CH_2Me); *m/e* 327 (M^+, 30%), 296 ($[M - OMe]^+$, 66), 263 (35), 236 (100), 206 (27), and 149 (46).

Pyrrolo[3,2-b]*pyrrole Derivatives* (8) *and* (9).—The hexa-ester (7a) (0.5 g) was heated under reflux with sodium hydroxide (0.5 g) in water (10 ml) and methanol (10 ml) until all the solid had dissolved (0.5 h). The solution was cooled and acidified with dilute hydrochloric acid. Removal of methanol on the rotary evaporator caused a solid to separate from the remaining solution, which was collected, washed, and dried. A suitable solvent for recrystallisation was not found, but the solid was apparently the diacid (8); $\nu_{max.}$ 1 590, 1 650, 1 675, 1 720, and 1 740 (C=O), and 3 480 (O–H) cm^{-1}; τ (^2H_2O containing NaOH) 6.43 and 6.28 (each 6 H, s, OMe) and 7.13 (6 H, s, NMe). This compound (2.0 g), copper powder (0.75 g), and quinoline (2 ml) were heated at 150 °C for 15 min. The mixture was cooled and acidified with dilute hydrochloric acid. The solution was extracted with dichloromethane, the extract was washed successively with dilute hydrochloric acid, sodium hydrogencarbonate solution, and water, and dried ($MgSO_4$). The oil that remained after evaporation of dichloromethane was triturated with methanol to afford *tetramethyl* 3a,6a-*dihydro*-1,4-*dimethylpyrrolo*[3,2-b]*pyrrole*-3,3a,6,6a-*tetracarboxylate* (9) (0.72 g, 45%), m.p. 218 °C (from ethanol) (Found: C, 52.15; H, 5.4; N, 7.3. $C_{16}H_{20}N_2O_8$ requires C, 52.2; H, 5.4; N, 7.6%); $\nu_{max.}$ 1 610, 1 680, and 1 750 cm^{-1}; τ 2.70 (2 H, s, =CH), 6.34 and 6.43 (each 6 H, s, OMe), and 7.02 (6 H, s, NMe); *m/e* 368 (M^+, 82%), 337 ($[M - OMe]^+$, 25), 309 ($[M - CO_2Me]^+$, 100), 304 (50), 293 (46), 277 (90), 268 (34), 249 (73), 248 (25), 219 (50), 206 (34), and 132 (77); *m** 259.5 (368→309) and 248 (309→277).

Dimethyl trans-2,5-*Bisalkylimino*-3,4-*bis*(*methoxycarbonyl*)*hex*-3-*enedioate Derivatives* (10).—A solution of LTA (4.9 g) in dichloromethane (20 ml) was added slowly to the enamine (1d) (2.0 g) in dichloromethane (5 ml) at 0 °C. The solution was allowed to reach room temperature and set aside overnight. The usual work-up procedure gave an oil which solidified on trituration with ether. The solid was fractionally recrystallised from methanol to give the *bis*-N-*cyclohexylimino-derivative* (10d) (0.30 g), m.p. 156—157 °C (Found: C, 60.5; H, 7.1; N, 5.9; *M* 478.2313. $C_{24}H_{34}N_2O_8$ requires C, 60.25; H, 7.1; N, 5.9%; *M* 478.2315); $\nu_{max.}$ 1 650 (C=N) and 1 715 (C=O) cm^{-1}; τ 6.15 and 6.33 (each 6 H, s, OMe), 6.6 (2 H, br m, tertiary CH), and 8.0—9.0 (20 H, m, CH_2); δ_C 163.3 (C=O), 152.5 (C=N), 139.4 (C=C), 64.2 (C–N), 53.2 (MeO), and 32.5, 25.4, and 24.3 (CH_2). The methanolic mother-liquor subsequently yielded a second crop of crystals (0.29 g), recrystallisation of which from methanol afforded a second product, possibly the ketoester (11), m.p. 126 °C (Found: C, 54.6; H, 5.8; N, 3.6. $C_{18}H_{23}NO_9$ requires C, 54.4; H, 5.8; N, 3.5%).

Oxidation of the enamine (1e) (4.0 g) in the same way afforded the *enedi-imine* (10e) (0.35 g), m.p. 126—127 °C (from methanol) (Found: C, 61.5; H, 7.5; N, 5.6; *M* 506.2637. $C_{26}H_{38}N_2O_8$ requires C, 61.7; H, 7.5; N, 5.5%; *M* 506.2638); $\nu_{max.}$ 1 650 (C=N) and 1 720 (C=O) cm^{-1}; τ 6.16 and 6.34 (each 6 H, s, OMe), 6.5 (2 H, br m, tertiary CH), and 8.4 (24 H, br m, CH_2); δ_C 163.7 (C=O), 151.4 (C=N), 139.6 (C=C), 66.0 (C–N), 53.3 (MeO), and 34.7, 34.3, 28.5, 28.2, 25.2, and 25.1 (CH_2).

Oxidation of the enamine (1c) (4.0 g) in the same way afforded the *enedi-imine* (10a) (1.13 g, 28%), m.p. 181 °C (from methanol) (Found: C, 54.6; H, 6.6; N, 6.9. $C_{18}H_{26}N_2O_8$ requires C, 54.3; H, 6.5; N, 7.0%); $\nu_{max.}$ 1 650 (C=N) and 1 715 (C=O) cm^{-1}; τ 5.99 and 6.17 (each 6 H, s, OMe), 6.3 (2 H, br m, tertiary CH), and 8.77 (12 H, d, *J* 7 Hz, CMe); δ_C 163.0 (C=O), 152.0 (C=N), 139.3 (C=C), 55.5 (C–N), 53.2 (MeO), and 22.6 (CH_2).

Oxidation of the enamine (1f) (2.0 g) in the same way but

using LTA (5.5 g) afforded the *enedi-imine* (10b) (0.29 g), m.p. 149 °C (from methanol) (Found: C, 56.8; H, 7.3; N, 6.4. $C_{20}H_{30}N_2O_8$ requires C, 56.3; H, 7.0; N, 6.6%); $\nu_{max.}$ 1 650 (C=N) and 1 715 (C=O) cm^{-1}; τ 6.13 and 6.32 (each 6 H, s, OMe), 6.6 (2 H, br m, tertiary CH), 8.4 (4 H, br m, CH_2), 8.88 (6 H, d, J 6 Hz, Me), and 9.22 (6 H, t, J 7 Hz, Me); δ_C 163.7 (C=O), 153.1 (C=N), 139.6 (C=C), 61.7 (C–N), 53.2 and 52.7 (MeO), 30.5 (CH_2), and 20.3 and 10.7 (Me).

Oxidation of the enamine (1g) (2.0 g) in the same way using LTA (5.5 g) afforded the *enedi-imine* (10c) (0.49 g, 25%), m.p. 197 °C (from methanol) (Found: C, 56.5; H, 6.7; N, 6.4. $C_{20}H_{30}N_2O_8$ requires C, 56.3; H, 7.0; N, 6.6%); $\nu_{max.}$ 1 645 (C=N) and 1 715 (C=O) cm^{-1}; τ 6.20 and 6.36 (each 6 H, s, OMe) and 8.78 (18 H, s, CMe); δ_C 164.2 and 163.9 (C=O), 150.0 (C=N), 140.6 (C=C), 58.4 (C–N), 53.0 (MeO), and 29.4 (Me).

Bis-enamines (13).—A solution of LTA (4.43 g) in acetonitrile (60 ml) was added during 30 min to a solution of the enamine (1c) (4.02 g) in acetonitrile (20 ml); the mixture was stirred and heated under reflux during this addition and for 2 h further. A solid obtained by the usual work-up procedure was recrystallised from methanol to give *dimethyl* cis,trans-2,5-*bisisopropylamino*-3,4-*bis*(*methoxycarbonyl*)-*hexa*-2,4-*dienoate* (13a) (0.43g , 11%), m.p. 185 °C (Found: C, 53.7; H, 6.8; N, 6.8. $C_{18}H_{28}N_2O_8$ requires C, 54.0; H, 7.05; N, 7.0%); $\nu_{max.}$ 1 640, 1 680, and 1 730 (C=O), and 3 330 (N–H) cm^{-1}; τ 1.20 and 5.60 (each 1 H, br d, J 9 Hz, NH), 6.00, 6.13, 6.26, and 6.31 (each 3 H, s, OMe), 6.4—6.7 (2 H, m, NCH), 8.71 (6 H, d, J 6 Hz, $CHMe_2$), and 8.76 and 8.83 (each 3 H, overlapping d, J 6 Hz, $CHMe_2$); δ_C 170.8, 168.3, 166.1, and 163.8 (C=O), 155.8, 152.2, 91.9, and 84.0 (C=C), 52.4 and 51.0 (MeO), 47.8 and 46.8 (C–N), and 24.3 (Me), *m/e* 400 (M^+, 50%), 310 (20), 273 (55), 194 (27), 170 (58), 131 (31), 59 (21), and 43 ($[C_3H_7]^+$, 100). Further oxidation of this material with LTA in dichloromethane afforded the enedi-imine (10a), m.p. 180 °C, identical in respect of t.l.c., i.r. spectrum, and mixed m.p. with the product also obtained directly by LTA oxidation of the enamine (1c).

The enedi-imine (10a) (0.50 g) in methanol (20 ml) with 10% palladium–charcoal (50 mg) was shaken under hydrogen at atmospheric pressure. Absorption was apparently complete after 30 min, when the solution was filtered and the filtrate evaporated to give the bis-enamine (13a) (0.36 g), m.p. 185 °C (from methanol), identical in respect of t.l.c., i.r. spectrum and mixed m.p. with the sample obtained by LTA oxidation of the enamine (1c).

Oxidation of the enamine (1d) (4.82 g) with LTA (4.43 g) in refluxing acetonitrile as described above for the *N*-isopropyl compound gave the corresponding *bis-enamine* (13b) (0.55 g, 11%), m.p. 171 °C (from methanol) (Found: C, 60.2; H, 7.3; N, 6.05. $C_{24}H_{36}N_2O_8$ requires C, 60.0; H, 7.5; N, 5.8%); $\nu_{max.}$ 1 660, 1 685, 1 710, and 1 735 (C=O), and 3 400 (N–H) cm^{-1}; τ 1.30 and 5.58 (each 1 H, d, J 10 Hz, NH), 6.11, 6.23, 6.31, and 6.35 (each 3 H, s, OMe), 7.0 (2 H, br m, NCH), and 7.9—9.0 (20 H, m, CH_2); δ_C 170.9, 168.5, 166.2, and 163.9 (C=O), 155.9, 152.3, 91.7, and 83.9 (C=C), 54.6 and 53.9 (C–N), 52.4 and 51.1 (MeO), and 34.7, 34.5, 25.2, 25.0, and 24.6 (CH_2); *m/e* 480 (M^+, 29%), 312 (20), 241 (20), 240 (19), 209 (27), 170 (21), 83 ($[C_6H_{11}]^+$, 42), and 55 (100); *m** 181 (241→209), 121 (480→241), and 36.4 (83→55). Further oxidation of this material with LTA in dichloromethane gave the corresponding enedi-imine (10d), which was identified by t.l.c., i.r., and mixed m.p. comparison with the sample obtained directly by oxidation of the enamine (1d).

Hydrogenation of compound (10d) (0.56 g) in methanol (100 ml) over a palladium catalyst as described for the *N*-isopropyl compound (10a) afforded the bis-enamine (13b) (0.42 g), m.p. 171 °C, identical in respect of t.l.c., i.r. spectrum, and mixed m.p. with the sample obtained by oxidation of the enamine (1d).

Hydrogenation of the enedi-imine (10c) (1.0 g) in methanol (50 ml) in the presence of palladium–charcoal (0.1 g) by the same procedure gave an oil which eventually solidified. Recrystallisation from toluene–light petroleum afforded the *bis-enamine* (13c) (0.76 g), m.p. 134 °C (Found: C, 56.0; H, 7.4; N, 6.45. $C_{20}H_{32}N_2O_8$ requires C, 56.1; H, 7.5; N, 6.5%); $\nu_{max.}$ 1 580, 1 650, 1 695, and 1 715 (C=O), and 3 400 (N–H) cm^{-1}; τ 0.95 and 5.50 (each 1 H, s, NH), 6.18, 6.30, 6.40, and 6.45 (each 3 H, s, OMe), and 8.68 and 8.75 (each 9 H, s, Bu^t); δ_C 171.1, 168.7, 167.2, and 165.0 (C=O), 156.1, 152.1, 94.9, and 85.9 (C=C), 53.7 and 53.5 (C–N), 52.7 and 51.3 (MeO), and 30.7 and 30.4 (Me); *m/e* 429 (29%), 428 (M^+, 100), 230 (83), and 225 (96). Re-oxidation of this material (0.25 g) with LTA (0.26 g) in dichloromethane (10 ml) afforded (10c) (0.11 g), m.p. and mixed m.p. 199 °C, identical with the sample obtained by oxidation of the enamine (1g).

Cyclisation of Bis-enamines (13).—Trifluoroacetic acid (0.3 g) was added to a solution of compound (13a) (0.5 g) in dichloromethane (20 ml). After standing for 10 h at room temperature, the mixture was poured into ice–water; the organic phase was separated, washed, and dried ($MgSO_4$). Evaporation of dichloromethane left *tetramethyl* 1-*isopropyl*-*pyrrole*-2,3,4,5-*tetracarboxylate* (4c) (0.33 g, 77%), m.p. 90 °C (from toluene) (Found: C, 53.0; H, 5.6; N, 4.3. $C_{15}H_{19}NO_8$ requires C, 52.8; H, 5.6; N, 4.15%); $\nu_{max.}$ 1 708 and 1 735 cm^{-1} (C=O); τ 4.52 (1 H, septet, J 7 Hz, tertiary CH), 6.04 and 6.09 (each 6 H, s, OMe), and 8.46 (6 H, d, $CHMe_2$); δ_C 163.8 and 161.4 (C=O), 126.5 and 119.2 (C=C), 52.8 and 52.4 (MeO), 51.9 (C–N), and 21.9 (CH_3); *m/e* 341 (M^+, 20%), 268 (56), and 236 (100); *m** 208 (268→236).

The corresponding *pyrrole* (4d) (0.24 g, 60%) was obtained in the same way from compound (13b) (0.5 g) and recrystallised from toluene–light petroleum as needles, m.p. 60—62 °C (Found: C, 56.4; H, 6.0; N, 3.5. $C_{18}H_{23}NO_8$ requires C, 56.7; H, 6.1; N, 3.7%); $\nu_{max.}$ 1 705 and 1 735 cm^{-1} (C=O); τ 6.04 and 6.10 (each 6 H, s, OMe), 6.20 (1 H, m, tertiary CH), and 7.9—9.0 (10 H, m, CH_2); δ 163.9 and 161.5 (C=O), 126.6 and 119.1 (C=C), 60.1 (C–N), 52.8 and 52.4 (MeO), and 32.2, 26.3, and 25.1 (CH_2); *m/e* 381 (M^+, 20%), 349 (20), 317 (50), 268 (96), 236 (100), 206 (20), and 179 (23); *m** 320 (381→349), 288 (349→317), 208 (268→236), and 180 (236→206).

Sodium (73 mg) was allowed to react with methanol (15 ml) and to this solution was added compound (13a) (1.16 g) in methanol (10 ml). The solution was set aside for 10 h at room temperature and it was then rotary-evaporated to dryness. The residue was treated with aqueous acetic acid and then extracted with dichloromethane; the extract was separated, washed, dried ($MgSO_4$), and rotary-evaporated to dryness. This residue was recrystallised from methanol below 0 °C to give *trimethyl* 1-*isopropyl*-3-*isopropylamino*-2-*oxo*-1,2-*dihydropyridine*-4,5,6-*tricarboxylate* (6c) (0.54 g, 59%) as pale yellow flakes, m.p. 89—90 °C (Found: C, 55.3; H, 6.7; N, 7.4. $C_{17}H_{24}N_2O_7$ requires C, 55.4; H, 6.6; N, 7.6%); $\nu_{max.}$ 1 640, 1 675, and 1 730 (C=O), and 3 330 (N–H) cm^{-1}; τ 4.0 (1 H, br m, NH), 5.6—6.2 (2 H, m,

2 × C*H*Me$_2$), 6.05, 6.12, and 6.16 (each 3 H, s, OMe), and 8.40 and 8.84 (each 3 H, s, OMe), and 8.40 and 8.84 (each 6 H, d, *J* 7 Hz, CH*Me*$_2$); δ_C 167.4, 165.7, 163.5, and 157.9 (C=O), 137.0, 128.1, 111.7, and 107.4 (C=C), 56.6 and 45.0 (C–N), 53.2, 52.7, and 52.4 (MeO), and 23.5 and 19.5 (Me); *m/e* 368 (M^+, 44%), 325 (44), and 293 (100); *m** 264 (325→293).

The corresponding *pyridinone* (6d) (0.32 g, 49%) was obtained in the same way from the bis-enamine (13b) (0.70 g) and recrystallised from aqueous methanol as yellow needles, m.p. 115 °C (Found: C, 61.5; H, 7.1; N, 6.2. $C_{23}H_{32}N_2O_7$ requires C, 61.7; H, 6.9; N, 6.3%); $\nu_{max.}$ 1 605, 1 630, and 1 720 (C=O), and 3 400 (N–H) cm^{-1}; τ 3.9 (1 H, NH, br, exchangeable in ^2H_2O), 6.10, 6.17, and 6.21 (each 3 H, s, OMe), 6.5 and 7.5 (each 1 H, br m, CHN) and 7.9—9.1 (20 H, m, CH_2); δ_C 167.4, 165.8, 163.7, and 158.1 (C=O), 136.8, 128.3, 111.8, and 107.4 (C=C), 65.5 and 52.1 (C–N), 53.2, 52.8, and 52.4 (MeO), and 33.8, 28.6, 26.4, 25.6, 25.1, 24.7, and 24.3 (CH_2); *m/e* 448 (M^+, 84%), 366 (64), 365 (80), 333 (33), 301 (29), 291 (49), 284 (40), 253 (28), 248 (24), 192 (23), 83 (21), 82 (25), 81 (29), 67 (57), 55 (100), and 54 (47); *m** 304 (365→333) and 272 (333→301).

We thank Professor T. J. King for providing the structure of compound (10d) by *X*-ray diffraction and Dr. A. J. G. Crawshaw for n.m.r. spectra and discussions thereof.

[9/216 *Received*, 12*th February*, 1979]

REFERENCES

[1] J. B. Hendrickson and R. Rees, *J. Amer. Chem. Soc.*, 1961, **83**, 1250; J. B. Hendrickson, R. Rees, and J. F. Templeton, *ibid.*, 1964, **86**, 107.
[2] D. S. James and P. E. Fanta, *J. Org. Chem.*, 1962, **27**, 3346.
[3] S. K. Khetan, J. G. Hiriyakkavanar, and M. V. George, *Tetrahedron*, 1968, **24**, 1567; S. K. Khetan and M. V. George, *ibid.*, 1969, **25**, 527; S. K. Khetan and M. V. George, *Canad. J. Chem.*, 1969, **47**, 3545; R. K. Gupta and M. V. George, *Indian J. Chem.*, 1972, 875; K. Nagarajan, M. D. Nair, R. K. Shah, and J. A. Desai, *ibid.*, 1973, 112.
[4] N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocyclic Chem.*, 1966, **3**, 222; N. D. Heindel and T. F. Lemke, *ibid.*, p. 389; E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, 1967, **32**, 1666; N. D. Heindel, I. S. Bechara, T. F. Lemke, and V. B. Fish, *ibid.*, p. 4155; N. D. Heindel, *ibid.*, 1970, **35**, 3138; C. F. Beam, C. A. Park, N. D. Heindel, and W. P. Fives, *J. Heterocyclic Chem.*, 1977, **14**, 703.
[5] E. H. Huntress, T. E. Lesslie, and W. M. Hearon, *J. Amer. Chem. Soc.*, 1956, **78**, 419; C. Agosta, *J. Org. Chem.*, 1961, **26**, 1724.
[6] *Cf.* C. F. Huebner, L. Dorfman, M. H. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *J. Org. Chem.*, 1963, **28**, 3134; N. Anglelide, C. Draghici, and D. Raileanu, *Tetrahedron*, 1974, **30**, 623.
[7] M. V. George, S. K. Khetan, and R. K. Gupta, *Adv. Heterocyclic Chem.*, 1976, **19**, 279, and references therein.
[8] S. K. Khetan, *Chem. Comm.*, 1972, 917.
[9] Preliminary Communication: R. M. Carr, R. O. C. Norman, and J. M. Vernon, *J.C.S. Chem. Comm.*, 1977, 854.
[10] F. Corbani, B. Rindone, and C. Scolastico, *Tetrahedron*, 1973, **29**, 3253; 1975, **31**, 455.
[11] E. Winterfeldt, W. Krohn, and H.-U. Strache, *Chem. Ber.*, 1969, **102**, 2346.
[12] Previous syntheses of this ring system: H. Hemetsberger and D. Knittel, *Monatsh.*, 1972, **103**, 194; R. Schwesinger, Dissertation, University of Freiburg, 1975, cited by H. Prinzbach, R. Schwesinger, and M. Breuniger, *Angew. Chem. Internat. Edn.*, 1975, **14**, 347.
[13] R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, 1966, **99**, 2526.
[14] W. A. F. Gladstone, *Chem. Comm.*, 1969, 179; W. A. F. Gladstone, J. B. Aylward, and R. O. C. Norman, *J. Chem. Soc.* (*C*), 1969, 2587; J. B. Aylward, *ibid.*, 1970, 1494.
[15] N. A. Fedoruk, *Diss. Abs. B*, 1966, **27**, 748 (*Chem. Abs.*, 1967, **66**, 37797d).
[16] G. Domschke, *J. prakt. Chem.*, 1969, **311**, 786, 807.
[17] R. Scarpati and V. Davinola, *Rend. Accad. Sci. fis. mat.* (*Napoli*), 1960, **27**, 81 (*Chem. Abs.*, 1964, **61**, 13269h).
[18] H. Feuer, B. F. Vincent, jun., and R. S. Bartlett, *J. Org. Chem.*, 1965, **30**, 2877.