Cope Rearrangements of Arylvinylhydroxylamines

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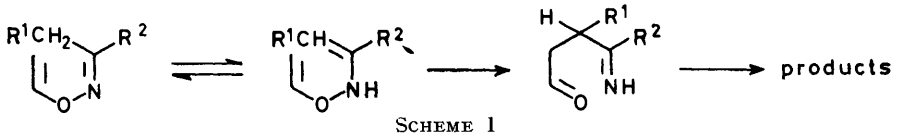
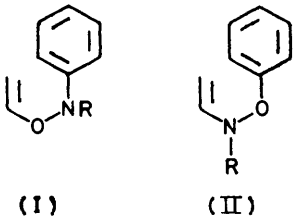
Addition of *N*-arylhydroxamic acids or *N*-aryl-*N*-hydroxycarbamates to dimethyl but-2-ynedioate gives *N*-acyl-*N*-aryl-*O*-(1,2-bismethoxycarbonylvinyl)hydroxylamines, which rearrange spontaneously to dimethyl (2-acylaminophenyl)oxalacetates. Addition of *O*-arylhydroxylamines to dimethyl but-2-ynedioate gives *O*-aryl-*N*-(1,2-bismethoxycarbonylvinyl)hydroxylamines, which also rearrange spontaneously and then cyclise to give 3-amino-4-methoxycarbonylcoumarins.

[3,3] SIGMATROPIC rearrangements which involve cleavage of nitrogen–oxygen bonds have been described by us.[1] The rearranging species were *O*-aryl- or *O*-vinyl-oximes and the reactions required either acidic catalysis or strong heating. We have assumed that the severe reaction conditions served only for tautomerization of the starting oximes (Scheme), whereas the rearrangement step itself would be expected to proceed very readily, or even spontaneously, as the cleaved N–O bond is relatively weak and highly polar.



SCHEME 1

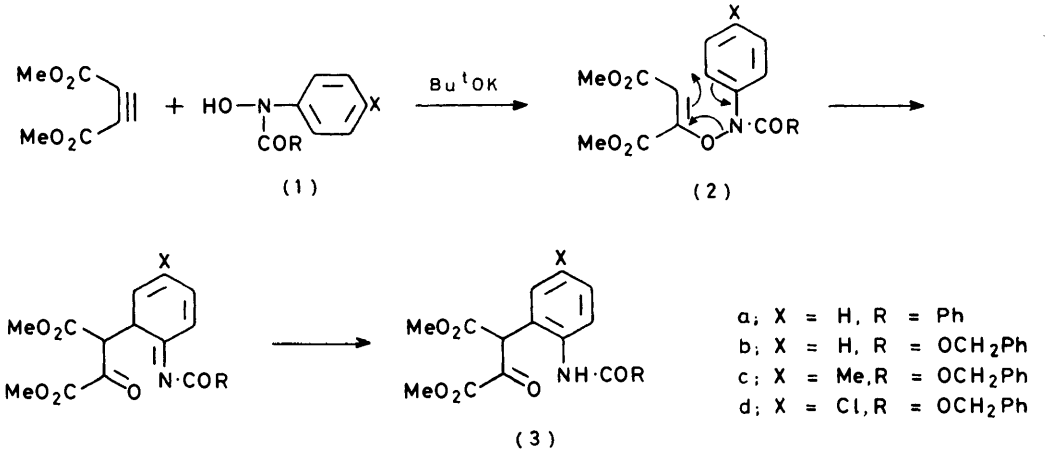


(I) (II)

In order to confirm this assumption it was of interest to prepare systems capable of undergoing the rearrangement without involving the oximes. This paper deals with two such systems: *N*-aryl-*O*-vinylhydroxylamines (I) and *O*-aryl-*N*-vinylhydroxylamines (II). The synthetic approach in both cases was the addition of suitable phenylhydroxylamines to dimethyl but-2-ynedioate (DMBD).

The addition of *N*-phenylhydroxylamine to DMBD, studied previously by several workers,[2-4] gives a mixture of products, all of which arise from initial addition through nitrogen. Formation of the required *N*-aryl-*O*-vinylhydroxylamines (I) would, however, require addition through oxygen. Suitable candidates for this mode of addition are the *N*-arylhydroxamic acids, as the acyl group would mask the nitrogen and activate the oxygen. Double addition involving the carbonyl group, as reported [5] for the reaction of *N*-unsubstituted hydroxamic acids with acetylenes, would also be impossible.

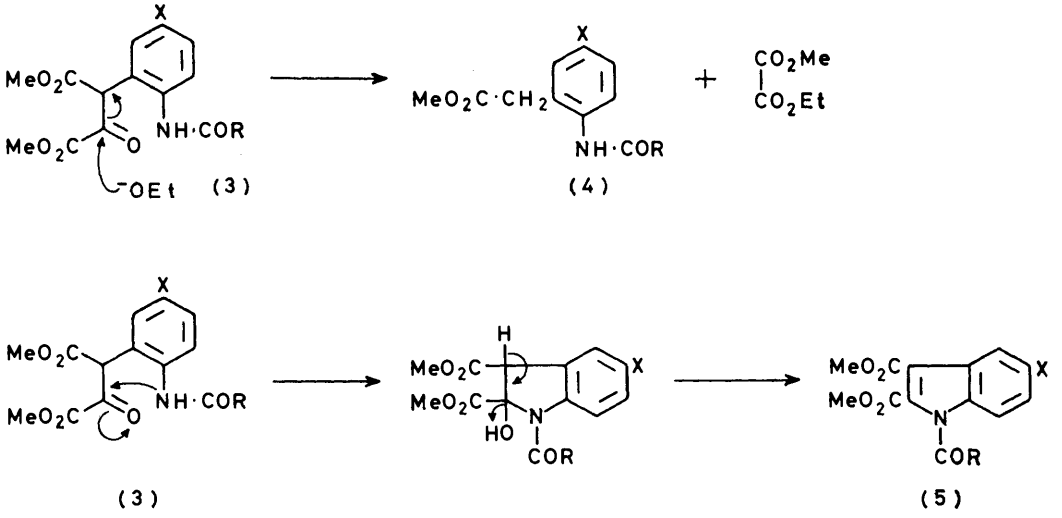
The base catalysed (Bu^tOK) addition of *N*-phenylbenzohydroxamic acid (1a) to DMBD in dimethyl sulphoxide gave a 1 : 1 adduct (67% yield). Its i.r. spectrum showed the presence of an NH (3 340 cm^{-1}) and three types of carbonyl group [1 670 (amide), 1 710 (ketone), and 1 730 cm^{-1} (ester)]. The n.m.r. spectrum showed a one-proton singlet at δ 5.53, two methyl ester singlets at δ 3.73 and 3.38, and a nine-proton multiplet at δ 7.1—7.9. The spectral data combined with the



[1] T. Sheradsky and G. Salemnick, *J. Org. Chem.*, 1971, **36**, 1061, and references cited therein.
[2] E. H. Huntress, T. E. Leslie, and W. M. Nearon, *J. Amer. Chem. Soc.*, 1956, **78**, 419.
[3] W. C. Agosta, *J. Org. Chem.*, 1961, **26**, 1724.
[4] E. Winterfeldt, W. Krohn, and H. U. Stracke, *Chem. Ber.*, 1964, **102**, 2346.
[5] F. M. W. Chen and T. P. Forrest, *Canad. J. Chem.*, 1973, **51**, 1368.

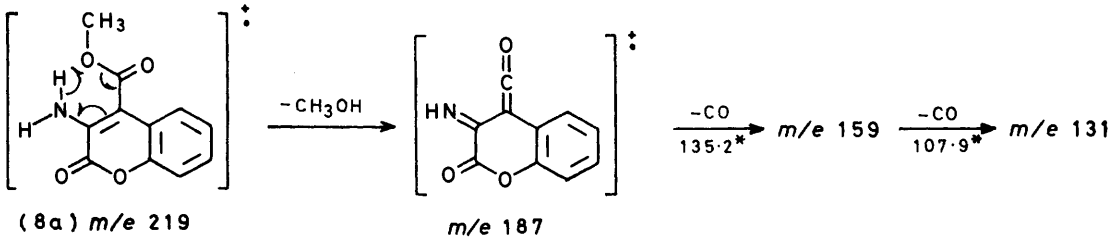
chemical evidence described below led to its identification as dimethyl (2-benzoylaminophenyl)oxalacetate (3a). The formation of (3a) suggests that the initial adduct (2a) rearranged as expected, under the mild addition conditions.

Similar results were obtained in the additions of benzyl *N*-hydroxy-*N*-phenylcarbamate (1b) and its *p*-methyl (1c) and *p*-chloro (1d) derivatives, which yielded the corresponding benzyloxycarbonyl derivatives of dimethyl (2-aminophenyl)oxalacetate (3b—d). The benzyl carbamates were selected as reaction components with the intention to remove the benzyloxycarbonyl group while retaining the ester functions. Catalytic hydrogenation or acidolysis (HBr–HOAc) of (3b) gave similar mixtures of products, and the spectra indicated that all the three possible cyclizations involving the amino-group (with the carbonyl and the two ester groups) had occurred simultaneously.



On carrying out the additions of compounds (1) to DMBD in refluxing ethanol, with potassium hydroxide or sodium ethoxide as catalysts, the reaction proceeded one step further and gave two series of products. The major ones [the only product in the case of (1a)] were the corresponding methyl (2-acylaminophenyl)acetates (4a—d) formed by retro-Claisen cleavage of compounds (3). The minor ones were *N*-benzyloxycarbonyl-2,3-bismethoxycarbonylindoles (5b—d) formed by cyclization and dehydration of (3b—d). Attempts to induce the cyclization of compounds (3) to the indoles (4) by treatment with a series of bases under various conditions failed: the indoles were formed in very small yields. The probable reason is anion formation in the oxo-ester portion of the molecule in preference to or in addition to formation of the amide anion required for the cyclization.

For the preparation of *O*-aryl-*N*-vinylhydroxylamines (II) we tried the addition of *O*-phenylhydroxylamine (6a) to DMBD.[6] The uncatalysed reaction in ethanol or ether at room temperature yielded a single product. Elemental analyses and the mass spectrum indicated addition with loss of the elements of methanol. The i.r. spectrum showed the presence of a primary amino group (3 340 and 3 450 cm^{-1}), two carbonyls (1 665 and 1 730 cm^{-1}), and a 1,2-disubstituted benzene (755 cm^{-1}). The n.m.r. showed signals for one methyl ester (δ 4.05) and four aromatic protons (7.6—7.7), and the broad two-proton peak of the amino group (δ 7.2; exchangeable with D_2O). The material also exhibited high wavelength (356 nm) u.v. absorption. The only reasonable structure which accommodates all these data is that of 3-amino-4-methoxycarbonylcoumarin (8a). This structure is further supported by the mass spectrum, which showed an initial loss of methanol typical of anthranilic and similar esters,[7] followed by two consecutive losses of CO.[8] Substituted coumarins (8b—e) were obtained in a similar manner from the hydroxylamines (6b—e). A

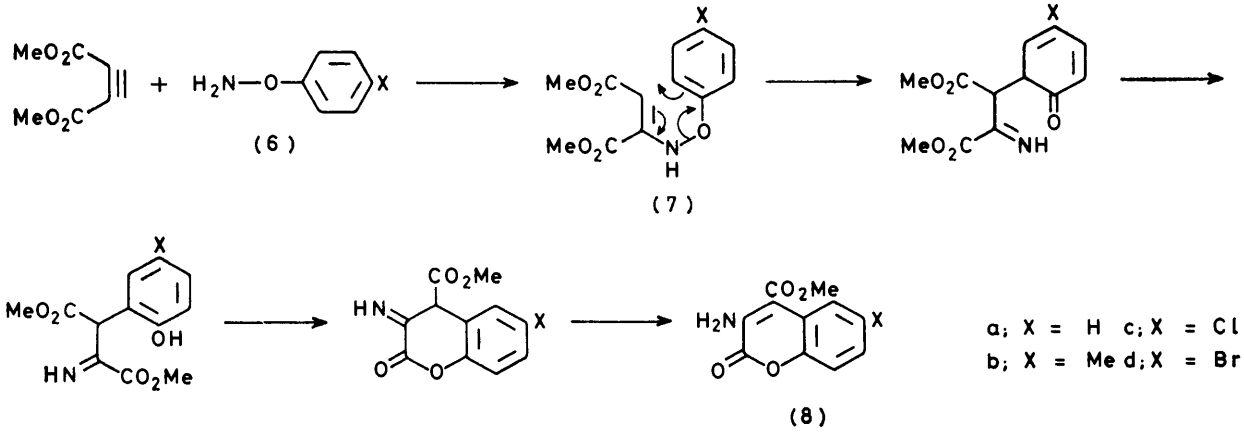


(8a) *m/e* 219 *m/e* 187

[6] Preliminary communication, T. Sheradsky and S. Lewinter, *Tetrahedron Letters*, 1972, 3491.

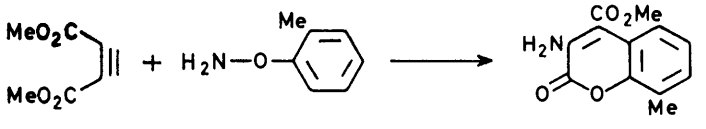
[7] E. M. Emery, *Analyt. Chem.*, 1960, **32**, 1495.

[8] C. S. Barnes and J. L. Occolowitz, *Austral. J. Chem.*, 1964, **17**, 975.



(6) (7) (8)

a; X = H c; X = Cl
b; X = Me d; X = Br

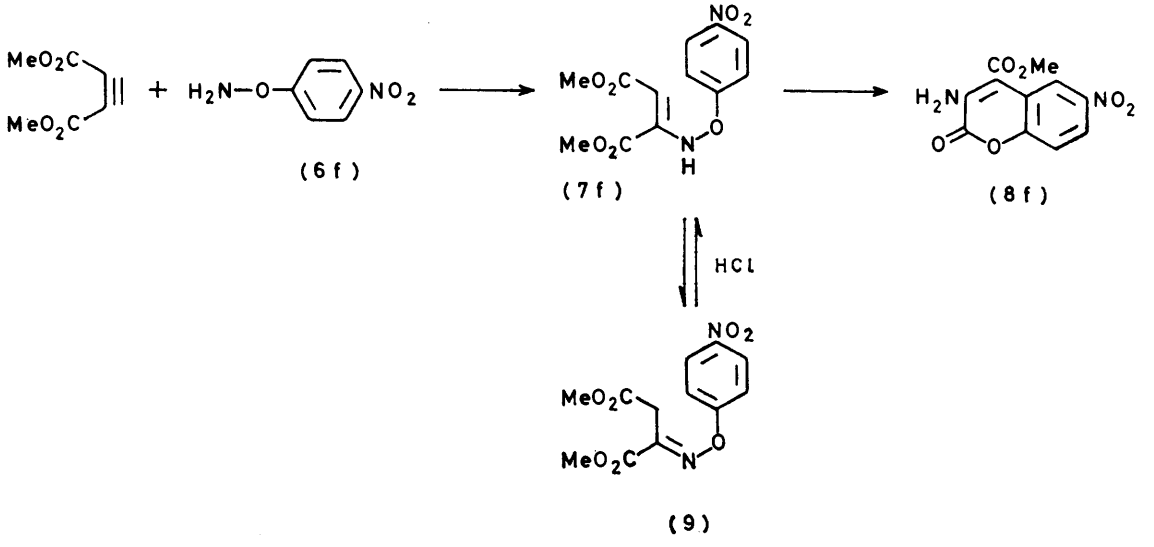


(6e) (8e)

3-Amino-4-methoxycarbonylcoumarins

(8)	Substituent	Yield (%)	M.p. (°C)	$\nu_{max.}$/cm^{-1} NH$_2$	$\nu_{max.}$/cm^{-1} C=O	$\lambda_{max.}$/nm (ε)	Found (%)	Formula	Calc. (%)
a	H	80	151	3 340	1 665	250 (11 000)	C 60.05	$C_{11}H_9NO_4$	C 60.3
				3 450	1 730	356 (10 500)	H 4.1		H 4.1
							N 6.7		N 6.4
b	6-Me	78	120	3 330	1 680	252 (13 000)	C 61.4	$C_{12}H_{11}NO_4$	C 61.8
				3 450	1 720	261 (12 000)	H 5.0		H 4.75
							N 5.65		N 6.0
c	6-Cl	86	177	3 340	1 675	258 (11 800)	C 51.9	$C_{11}H_8ClNO_4$	C 52.2
				3 460	1 740	357 (12 200)	H 3.6		H 3.2
							N 5.4		N 5.5
d	6-Br	80	191	3 340	1 680	258 (11 300)	C 44.4	$C_{11}H_8BrNO_4$	C 44.3
				3 450	1 725	357 (12 100)	H 2.8		H 2.7
							N 4.6		N 4.7
e	8-Me	82	124	3 340	1 680	256 (10 800)	C 61.5	$C_{12}H_{11}NO_4$	C 61.8
				3 460	1 720	356 (10 400)	H 4.7		H 4.75
							N 6.05		N 6.0
f	6-NO_2	10 (70) [a]	226	3 300	1 680	262 (22 000)	C 49.95	$C_{11}H_8N_2O_6$	C 50.0
				3 410	1 740	350 (13 000)	H 3.2		H 3.05
							N 10.8		N 10.6

[a] See text.



(6f) (7f) (8f) (9)

mechanism which accounts for their formation is shown. The adducts (7) undergo the expected rearrangement followed by aromatization and lactonization.

The addition proceeded directly to compounds (8) even at −30 °C, and no intermediates were isolated. In the hope that the rearrangement step, which involves an electrophilic attack on the ring, would be slower we also tried the addition of *O*-(*p*-nitrophenyl)hydroxylamine (6f) to DMBD. Reaction in this case occurred only in refluxing ethanol, giving two products. The minor one (10%) was 3-amino-4-methoxycarbonyl-6-nitrocoumarin (8f). The major product (60%) was the unrearranged adduct. Its i.r. spectrum showed no NH absorption and the n.m.r. spectrum showed a two-proton singlet at δ 3.83. These data indicate that this isolated adduct is not the *N*-vinylhydroxylamine (7f) but its tautomer, the *O*-phenyloxime (9). Compound (9) could not be converted into (8f) under the addition conditions (refluxing ethanol), but treatment with ethanolic hydrogen chloride transformed it quantitatively into (8f).

These results confirm the prediction outlined in the introduction. Nitrogen–oxygen bonds, when forming part of a Cope system, are highly unstable, and rearrangements involving their cleavage occur spontaneously.

EXPERIMENTAL

M.p.s were taken with a Thomas–Hoover apparatus. N.m.r. spectra were recorded with a Varian T-60 or EM-360 spectrometer (solvent $CDCl_3$ with Me_4Si as internal standard). I.r. spectra were taken with a Perkin-Elmer 157 spectrometer (KBr pellets or Nujol mulls) and u.v. spectra with a Unicam SP 800 spectrometer (ethanolic solutions).

Benzyl N-*Hydroxy*-N-*phenylcarbamate* (1b).—To a solution of *N*-phenylhydroxylamine (10.9 g, 0.1 mol) in ether containing potassium carbonate (6.4 g) and water (4 ml), benzyl chloroformate (17.05 g, 0.1 mol) was added dropwise during 1 h with stirring and cooling (ice-bath). Stirring was continued for 1 h and the ether layer was separated, washed twice with 0.1N-hydrochloric acid and then with saturated brine and concentrated. Addition of petroleum (b.p 40—60 °C) caused precipitation of the product, which was recrystallized from ether–petroleum (yield 23.6 g, 96.5%), m.p. 84° (lit.,[9] 82°). Similarly prepared were *benzyl* N-*hydroxy*-N-(4-*tolyl*)*carbamate* (1c) from *N*-(*p*-tolyl)hydroxylamine and benzyl chloroformate (yield 72%), m.p. 44° (Found: C, 69.9; H, 6.1; N, 5.6. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%); and *benzyl* N-(*p*-*chlorophenyl*)-N-*hydroxycarbamate* (1d) from *N*-(*p*-chlorophenyl)hydroxylamine and benzyl chloroformate in 84% yield, m.p. 88° (Found: C, 60.5; H, 4.4; N, 5.2. $C_{14}H_{12}ClNO_3$ requires C, 60.55; H, 4.4; N, 5.05%).

Addition of Compounds (1) *to DMBD in Dimethyl Sulphoxide; General Procedure.*—A solution of the hydroxamic acid or *N*-hydroxycarbamate (1) (0.01 mol) and potassium t-butoxide (100 mg) in dry dimethyl sulphoxide (30 ml) was stirred at room temperature for 30 min, and DMBD (1.42 g, 0.01 mol) was added. The reaction was slightly exothermic and the solution turned dark red. Stirring was continued for 1 h, then the solution was poured into saturated brine and extracted several times with ethyl acetate. The combined extracts were washed with saturated brine, dried, and evaporated. The oily residue was chromatographed on silica gel (60 g) and gave the product (3) in the fractions eluted by dichloromethane–ethyl acetate (19 : 1). Compounds (3a, b, and d) solidified and were crystallized from chloroform–petroleum (b.p. 40—60 °C).

(*a*) *N*-Phenylbenzohydroxamic acid (1a) gave *dimethyl* (2-*benzoylaminophenyl*)*oxalacetate* (3a) (67%), m.p. 151—152° (see main text for spectral properties) (Found: C, 63.9; H, 4.8; N, 4.0. $C_{19}H_{17}NO_6$ requires C, 64.2; H, 4.8; N, 3.9%).

(*b*) Benzyl *N*-hydroxy-*N*-phenylcarbamate (1b) gave *dimethyl* (2-*benzyloxycarbonylaminophenyl*)*oxalacetate* (3b) (63%), m.p. 89°, δ 3.73 (3 H, s), 3.93 (3 H, s), 4.82 (1 H, s), 5.23 (2 H, s), 7.33 (5 H, s), and 6.8—7.9 (5 H, m), $\nu_{max.}$ 3 280 (NH) and 1 705, 1 725, and 1 735 cm^{-1} (C=O) (Found: C, 62.0; H, 4.9; N, 3.6. $C_{20}H_{19}NO_7$ requires C, 62.3; H, 5.0; N, 3.65%).

(*c*) Benzyl *N*-hydroxy-*N*-(4-tolyl)carbamate (1c) gave dimethyl (2-benzyloxycarbonylamino-5-methylphenyl)-oxalacetate (3d) (63%), which could not be induced to crystallize, δ 2.35 (3 H, s), 3.73 (3 H, s), 3.93 (3 H, s), 4.77 (1 H, s), 5.23 (2 H, s), 7.33 (5 H, s), and 7.1—7.9 (3 H, m).

(*d*) Benzyl *N*-(4-chlorophenyl)-*N*-hydroxycarbamate (1d) gave *dimethyl* (2-*benzyloxycarbonylamino*-5-*chlorophenyl*)-*oxalacetate* (3d) (57%), m.p. 79°, δ 3.75 (3 H, s), 3.93 (3 H, s), 4.72 (2 H, s), 5.20 (2 H, s), 7.33 (5 H, s), and 7.4—8.0 (3 H, m), $\nu_{max.}$ 3 310 (NH) and 1 705, 1 715, and 1 735 cm^{-1} (C=O) (Found: C, 57.3; H, 4.2; Cl, 8.4; N, 3.3. $C_{20}H_{18}ClNO_7$ requires C, 57.2; H, 4.3; Cl, 8.4; N, 3.3%).

Addition of Compounds (1) *to DMBD in Refluxing Ethanol; General Procedure.*—To a solution of compound (1) (0.01 mol) in absolute ethanol (30 ml), ethanolic potassium hydroxide or sodium ethoxide (1N; 0.5 ml) and DMBD (1.42 g, 0.01 mol) were added. The solution was refluxed for 4 h and evaporated to leave an oil. Purification was achieved by preparative t.l.c. on silica gel (plate thickness 2 mm; eluant CH_2Cl_2–EtOAc, 19 : 1).

Reaction of (1a) gave an 86% yield of methyl (2-benzoylaminophenyl)acetate (4a), m.p. 105° (lit.,[10] 108°), δ 3.68 (2 H, s), 3.73 (3 H, s), and 7.2—8.2 (9 H, m), $\nu_{max.}$ 3 260 (NH), 1 650, and 1 730 cm^{-1} (C=O).

The carbamates (1b—d) gave, in the first-eluted bands, the indoles (5), which were crystallized from chloroform–hexane: 1-*benzyl*-2,3-*dimethyl indole*-1,2,3-*tricarboxylate* (5b) from (1b) (8%), m.p. 114—115°, δ 3.67 (3 H, s), 3.88 (3 H, s), 5.40 (2 H, s), 7.40 (5 H, s), and 7.2—8.1 (4 H, m), $\nu_{max.}$ 1 710 and 1 750 cm^{-1} (C=O), $\lambda_{max.}$ 278 nm (ε 11 000) (Found: C, 64.0; H, 47.5; N, 3.0. $C_{19}H_{17}NO_6$ requires C, 64.2; H, 4.8; N, 3.9%); 1-*benzyl* 2,3-*dimethyl* 5-*methyl*-*indole*-1,2,3-*tricarboxylate* (5c) from (1c) (12%), m.p. 110—111°, δ 2.42 (3 H, s), 3.68 (3 H, s), 3.87 (3 H, s), 5.37 (2 H, s), 7.38 (5 H, s), and 7.2—8.1 (3 H, m), $\nu_{max.}$ 1 710 and 1 750 cm^{-1} (C=O), $\lambda_{max.}$ 279 nm (ε 10 500) (Found: C, 65.9; H, 5.0; N, 3.5. $C_{21}H_{19}NO_6$ requires C, 66.1; H, 5.0; N, 3.7%); 1-*benzyl* 2,3-*dimethyl* 5-*chloroindole*-1,2,3-*tricarboxylate* (5d) from (1d) (27%), m.p. 116—117°, δ 3.65 (3 H, s), 3.87 (3 H, s), 5.37 (2 H, s), 7.37 (5 H, s), and 7.2—8.1 (3 H, m), $\nu_{max.}$ 1 710 and 1 750 cm^{-1} (C=O), $\lambda_{max.}$ 277 (ε 11 600) (Found: C, 60.0; H, 4.0; N, 3.3. $C_{20}H_{16}ClNO_6$ requires C, 59.8; H, 4.0; N, 3.5%).

The second bands eluted contained the phenylacetates (4). Of these only *methyl* (2-*benzyloxycarbonylamino*-5-*chlorophenyl*)*acetate* (4d) was obtained crystalline (45%), m.p. 70—71° (from chloroform–hexane), δ 3.58 (2 H, s), 3.70 (3 H, s), 5.22 (2 H, s), 7.38 (5 H, s), and 7.3—8.2 (3 H, m),

[9] E. Boyland and R. Nery, *J. Chem. Soc.* (*C*), 1966, 346.
[10] P. W. Neber, *Ber.*, 1922, **55**, 826.

$\nu_{max.}$ 3 270 (NH) and 1 690 and 1 735 cm^{-1} (C=O) (Found: C, 60.9; H, 4.7; N, 4.05. $C_{17}H_{16}ClNO_4$ requires C, 61.2; H, 4.8; N, 4.2%).

O-*Arylhydroxylamines* (6a—e).—The procedure of Bumgardner and Lilly [11] was used. The hydroxylamines were isolated by passing dry hydrogen chloride through the organic layer of the reaction mixture and collecting the precipitated hydrochlorides. The free bases were regenerated by treatment with aqueous sodium hydrogen carbonate and extraction with ether (yields 10—15%). The method however, failed for *O*-(*p*-methoxyphenyl)- and of *O*-(1-naphthyl)-hydroxylamine.

3-*Amino*-4-*methoxycarbonylcoumarins* (8a—e); *General Procedure*.—A solution containing the *O*-arylhydroxylamine (0.01 mol) and DMBD (1.42 g, 0.01 mol) in ethanol (20 ml) was stirred at room temperature for 2 h. On cooling, the product (8) precipitated out and was crystallized from ethanol. Yields and properties of the products are given in the Table.

Addition of O-(4-*nitrophenyl*)*hydroxylamine* (6f) *to DMBD*. A solution of (6f) [12] (1.4 g, 0.01 mol) and DMBD (1.42 g, 0.01 mol) in ethanol (20 ml) was refluxed for 2 h. On cooling 3-*amino*-4-*methoxycarbonyl*-6-*nitrocoumarin* (8f) (0.26 g, 10%) precipitated out; m.p. 226° (see Table). The filtrate was concentrated to 5 ml and strongly cooled. *Dimethyl oxalacetate* O-(p-*nitrophenyl*)*oxime* (9) precipitated out as large prisms, m.p. 55° (1.8 g, 60%), δ 3.66 (3 H, s), 3.83 (2 H, s), 3.90 (3 H, s), 7.25 (2 H, d), and 8.10 (2 H, d, *J* 9 Hz), $\nu_{max.}$ 1 730 cm^{-1} (Found: C, 48.9; H, 4.2; N, 9.6. $C_{12}H_{12}NO_7$ requires C, 48.65; H, 4.1; N, 9.5%).

Compound (9) (0.5 g) in ethanolic hydrogen chloride (10%; 10 ml) was refluxed for 30 min. On cooling, the coumarin (8g) (0.45 g) precipitated out.

[7/179 *Received*, 2*nd February*, 1977]

[11] C. L. Bumgardner and R. L. Lilly, *Chem. and Ind.*, 1962, 559.
[12] T. Sheradsky, G. Salemnick, and Z. Nir, *Tetrahedron*, 1972, **28**, 3833.