Synthetic Methods. Part 23.[1] Rearrangement of Some Hydroxamic Acids into Amides. A Self-Condensation Leading to Disproportionation

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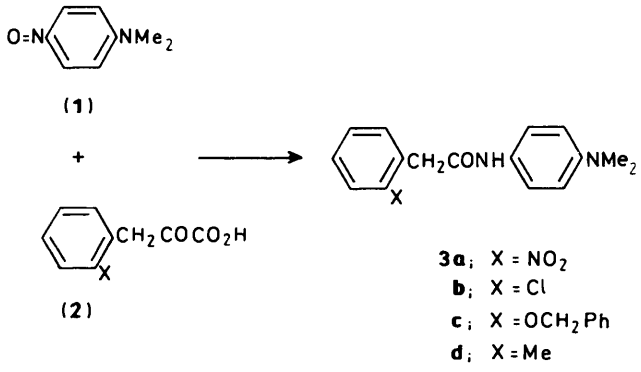
Pyruvic acids have been shown to react with *p*-nitroso-*N,N*-dimethylaniline (**1**) to produce *p*-dimethylaminoacetanilides (**3**) *via* the corresponding hydroxamic acids (**4**). Three such intermediates (**4a, c, d**) have been isolated and their structure proved by n.m.r. and mass spectroscopy and elemental analysis. Solutions of the hydroxamic acids (**4**) have been shown to undergo concentration-dependent self-condensation and disproportionation leading to the amides (**3**) and acids (**5**). Rational pathways for these transformations are discussed. Spectral correlations permit differentiation between the amides (**3**) and the corresponding hydroxamic acids (**4**).

Hydroxamic acids are of physiological interest since a number of antitumour antibiotics possess this functional group.[2]

Some years ago, one of us (M.R.) studied the reaction at room temperature of *p*-nitrosodimethylaniline (**1**) with arylpyruvic acids (**2**) and found that it proceeded readily to give CO_2 and the amides (**3**) in good yield.[3]



Intermediates in this conversion isolated for *o*-nitro- and *o*-chloro-phenylpyruvic acid (**2a, b**) were readily converted into (**3**) when heated in solution. Phenylpyruvic and *p*-nitrophenylpyruvic acids likewise reacted with *p*-nitroso-*N,N*-dimethylaniline (**1**) but without evidence for formation of an intermediate. The intermediate from (**2a**) was tentatively identified as the enol isomer of the amide (**3a**) since it formed a red colour with ferric chloride and was hydrolysed with dilute HCl to give *p*-dimethylaminoaniline and *o*-nitrophenylacetic acid. We have reinvestigated this reaction since it was felt that a more plausible structure for this intermediate was the hydroxamic acid (**4a**).

Results

Treatment of *o*-nitrophenylpyruvic acid (**2a**) with an equivalent amount of *p*-nitrosodimethylaniline (**1**) in ethanol or preferably in ether at room temperature gave immediate evolution of CO_2 and deposition of a yellow solid (m.p. 107 °C). The product formed in 70% yield is assigned structure (**4a**) on the basis of spectral and analytical evidence. The compound was unstable both in solution in various solvents with time and on chromatography; recrystallization from ethanol furnished the amide (**3a**). T.l.c. on silica gel showed three spots, one assignable to compound (**3a**) and the other to (**1**). Spectra of (**4a**) had to be measured as rapidly as possible, because of decomposition. The i.r. spectrum of (**4a**) showed characteristic broad OH (3 200 cm^{-1}) and C=O (1 640 cm^{-1}) absorption, while the amide (**3a**) showed sharp peaks at 3 310 and 1 655 cm^{-1}. ^1H N.m.r. (see Table 1) signals were consistent with structure (**4a**) and ^{13}C n.mr. results (see Table 2) indicated a carbonyl absorption at 164.4 p.p.m., characteristic of an amide type carbonyl [the C=O of (**3a**) is found at 167.7 p.p.m.]. Though the mass spectrum of (**4a**) suggested the presence of a mixture of (**3a**), (**1**), and *o*-nitrophenylacetic acid (**5a**), see discussion below, elemental analysis as well as a positive deep-red ferric chloride test were totally consistent with structure (**4a**) [neither (**3a**), (**1**) nor (**5a**) give this $FeCl_3$ test]. The compound formed a benzoate (**6**). The paucity of available mass spectral data[4] for hydroxamic acids or their esters, precluded a definitive correlation but the present

Table 1. ^1H N.m.r. chemical shifts (in p.p.m.)

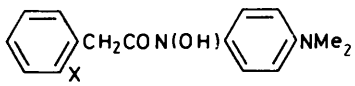
H	1	(4a)	(3a)	(5a)	(4c)	(3c)	(5c)	(4d)	(3d)	(5d)	Multiplicity (*J* in Hz)
2		7.35	7.58	7.36	7.22	*a*	*a*				bdd, 7.5, 1.5
3		7.57	7.62	7.61	6.89	6.98	6.93	*ca.* 7.15	*ca.* 7.15	*ca.* 7.15	td, 7.5, 1.5
4		7.44	7.46	7.49	7.21	*a*	7.22				ddd, 8, 7.5, 1.5
5		8.07	8.05	8.14	6.92	7.00	6.92				dd, 8, 1.5
7		3.90	3.97	4.07	3.57	3.71	3.71	3.56	3.72	3.65	s(H)
2′ + 6′	7.8[b]	7.32	7.32		7.00	7.10		7.18	7.21		AA′XX′ (2 H)
3′ + 5′	6.68	6.71	6.68		6.54	6.61		6.68	6.65		AA′XX′ (2 H)
4′NMe_2	3.18	3.01	2.90		2.95	2.87		3.01	2.89		7 (6 H)
2″ − 6″					*a*	*a*	*a*				
7″					5.00	5.14	5.06				
Other					8.87[c]			2.15[d]	2.35[d]	2.32[d]	

[a] 7.2—7.5 p.p.m. [b] Very broad due to slow NO rotation. [c] N-OH. [d] Ar-Me.

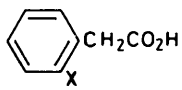
Table 2. ^{13}C N.m.r. chemical shifts (in p.p.m.)

	1[6]	(4a)	(3a)	(5a)	(4c)	(3c)	(5c)	(4d)	(3d)	(5d)
1		130.30	130.30	129.83	123.79	124.00	122.74	133.23	133.20	132.27
2		133.34	133.62	133.52	130.94	131.53	131.06	129.52[c]	130.91[c]	130.35[c]
3		133.34	133.32	133.37	120.81	121.53	120.87	126.01[d]	126.74	126.13[d]
4		128.36	128.41	128.52	128.26	128.78	128.78	127.07[d]	128.02[d]	127.54[d]
5		125.11	125.11	125.20	111.52	111.93	111.86	130.17[c]	130.59[c]	130.22[c]
6		148.72	148.87	148.74	150.36	156.13	156.54	136.53	137.40	136.87
7		37.57	41.65	39.74	33.47	40.16	36.00	36.22	42.73	38.75
8		164.44	166.72	173.99	166.09	168.83	177.48	165.81	168.73	175.36
1′	155.24	125.11	127.45		125.92	127.50		125.53	127.28	
2′ + 6′	*a*	128.86	121.79		128.54	121.34		128.62	121.92	
3′ + 5′	110.15	112.22	112.96		111.96	113.08		112.08	112.99	
4′	162.89	151.17	148.11		150.79	147.69		151.03	148.16	
4′-NMe_2	40.44	40.32	40.88		40.29	41.03		40.34	40.92	
1″					136.92	136.48	136.84			
2″ + 6″					127.68	127.50	127.02			
3″ + 5″					128.46	128.78	128.49			
4″					127.88	128.24	127.77			
7″					70.10	70.28	70.06	19.61[b]	19.54[b]	19.54[b]

[a] Too broad, not seen. [b] Ar-Me. [c] May be interchanged within the same column.



(4a-d)



(5a-d)

mass spectral fragmentation pattern for (**4a**) and (**6**) (see Table 3) was consistent with the assigned structures.

The decomposition of (**4a**) in $CDCl_3$, followed by n.m.r. spectroscopy gave equimolar amounts of (**3a**), (**5a**), and (**1**), the spectra of which were identical with those of authentic samples; the same compounds were also isolated on chromatography of (**4a**). Integration of the CH_2 and CH_3 region afforded a convenient way of determining the relative amounts of the four components as a function of time. The Figure shows that speed of decomposition is roughly proportional to concentration (*i.e.* a second-order type process), and that the reaction accelerates as it progresses, an indication that it is an autocatalytic process. Initial addition of acid and especially of base also speeds up the decomposition of (**4a**).

Since decomposition of the hydroxamic acid (**4a**) made its isolation difficult, we endeavoured to find more stable analogues. Thus, *o*-benzyloxyphenyl-(**2c**) and *o*-tolyl-pyruvic acid (**2d**) reacted with (**1**) to give the more stable hydroxamic acids (**4c**) and (**4d**) respectively, which could be crystallized from benzene. When heated in a solution, (**4c**) or (**4d**) were slowly converted into the amides (**3c**) or (**3d**) as well as to (**1**) and phenylacetic acids (**5c**) and (**5d**). These transformations, followed by n.m.r. spectroscopy, were reminiscent of the concentration dependent and autocatalytic disproportionation of (**4a**) (see Figure); (**4c**) and (**4d**) decomposed *ca.* 10 and 3 times slower respectively. Structure identification of (**4c**) and (**4d**) paralleled that of (**4a**), except that mass spectra showed both molecular ions and decomposition products.

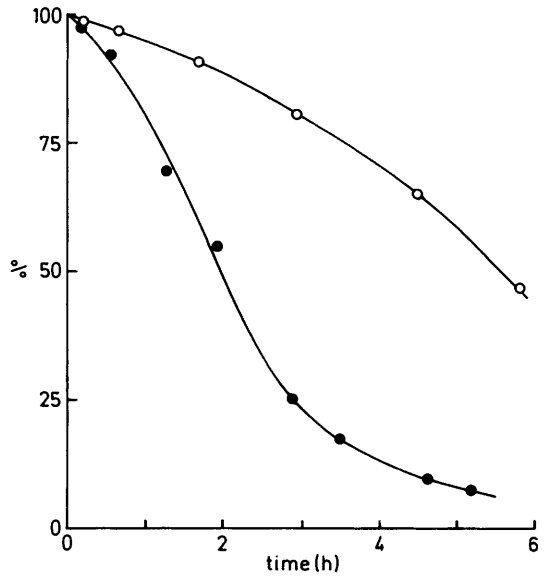
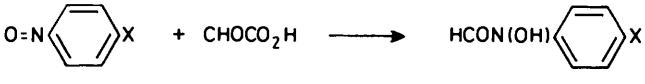


Figure. The disappearance of the hydroxamic acid (**4a**) as a function of time, at room temperature (24 ± 2 °C), for solutions 16 (○) and 30 mM(●) in $CDCl_3$, respectively.

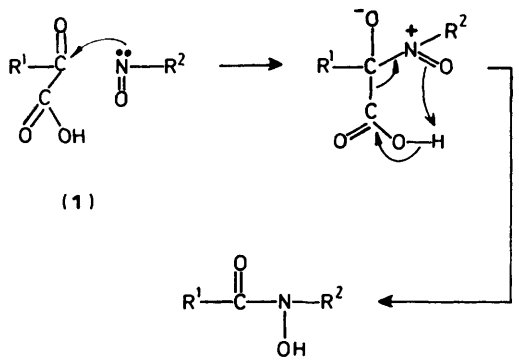
Discussion

Formation of the hydroxamic acid (**4**) upon treatment of the nitrosoaniline (**1**) with substituted acids (**2**) has analogy in the recently studied reaction of several nitrosobenzenes with glyoxylic acid leading to (**7**). A likely mechanism for formation of (**4**), based on one of those proposed by Corbett *et al.*,[4] is shown below. The decarboxylation becomes analogous to that of a β-keto acid. Unlike glyoxylic acid which reacted with



(7)

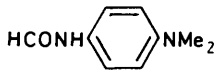
nitrosobenzene to give (**7**), phenyl-, or *o*-nitrophenyl-pyruvic acid did not react. This fact is consistent with the indicated mechanism in as much as the additional *p*-dimethylamino group in (**1**) provides the required increase in electron density for attack on the more hindered C=O of the phenylpyruvic acids as compared to glyoxylic acid. Furthermore, it is known that attack of nitrosobenzene on an aldehyde carbonyl occurs only on activation of the carbonyl group by aluminium isopropoxide.[5] In glyoxylic acid activation is provided by the adjacent carboxy group, while for reaction of keto acids (**2**) additional activation of the nitroso function by the dimethylamino group in (**1**) is required.



(1)

(4)

Transformation of the hydroxamic acid (**4**) into the amide (**3**) represents an apparent reductive process. In fact, Corbett *et al*[4b] had observed that, unlike other nitrosobenzenes, *p*-nitroso-*N*,*N*-dimethylaniline (**1**) reacted with glyoxylic acid to produce the amide (**8**) and they were able to show the transient intermediacy



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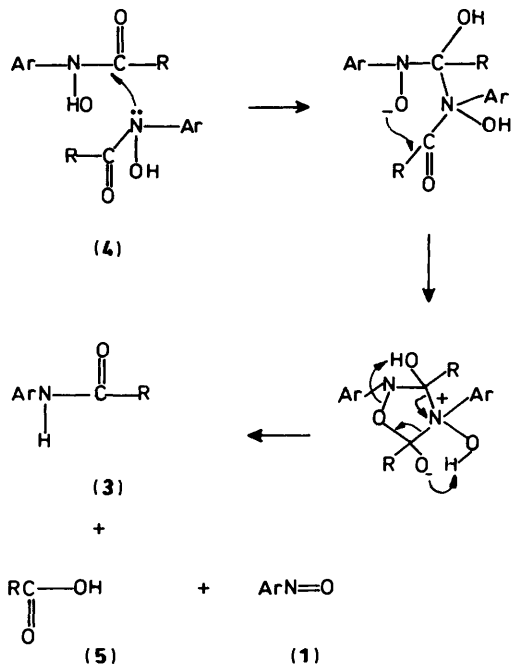

Scheme.

of (**7**) by careful analysis of the u.v. spectra. Because of the presence of glyoxylic acid they assumed that the hydroxamic acid was reduced by the aldehyde. In our case, it is clear that each of the hydroxamic acids (**4a**, **c**, **d**) is transformed to the amide (**3**) by itself in $CDCl_3$ or in other solvents, the rate of reaction being faster the more concentrated the solution (see Figure). Formation of the co-products (**1**) and (**5**) in equivalent amounts permits us to propose a rational pathway for this transformation as shown in the Scheme.

This mechanism explains why the only hydroxamic acids [*e.g.* (**4**)] that have so far been observed to rearrange into amides (**3**) are those that possess the electron-releasing dimethylamino substituent which facilitates attack by the nitrogen onto the carbonyl of (**4**). So far, the hydroxamic acids (**4**) that had a measurable lifetime all possessed *ortho* substituents in the phenylacetic portion. That the effect of the *ortho* substituent may be due to hydrogen-bonding to the *ortho* hetero atom (when X = NO_2, Cl, OCH_2Ph), was ruled out by the stability of hydroxamic acid (**4d**; X = Me), thus indicating a steric factor in the self-condensation. In the absence of an *ortho* substituent (X = H) we found only t.l.c. evidence for the presence of (**4**), the products being amide (**3**) and phenylacetic acid.

When we re-examined the reaction of pyruvic acid with *p*-nitroso-*N*,*N*-dimethylaniline (**1**), which was reported,[3a] to lead to 4,4′-bis(dimethylamino)azoxybenzene, we were able to isolate *p*-dimethylaminoacetanilide (**9**) by carrying out the reaction in ether instead of ethanol. The amide (**9**) in this case is probably formed *via* a hydroxamic acid in an analogous way as shown for (**3**). Apparently, the azoxybenzene formed in alcohol medium is a result of a subsequent transformation of (**1**).

The ^{13}C n.m.r. spectrum of the hydroxamic acids is similar to that of the corresponding amides. The major influences of the additional OH group are the shielding of C-7 (negative effect) and the deshielding of carbons 2′-, 4′-, and 6′-. The latter change must be attributed to decreased electron donation by the amidic nitrogen to the dimethylaminophenyl moiety. The n.m.r. data in Tables 1 (^1H) and 2 (^{13}C) may be useful to differentiate hydroxamic acids from amides in other cases.

The mass spectra of the amides (**3**) *versus* those of the analogous hydroxamic acids (**4**) also show useful differentiation patterns (see Tables 3a, 3b). The base peak of all hydroxamic acids (**4**) is a fragment ($MH^+ - O$) having the same molecular weight as the corresponding amides (**3**), but while the c.i. spectrum of (**3a**) shows virtually no fragmentation, a specific fragmentation pattern was observed for (**4a**). The intensity of the quasimolecular ion MH^+ of hydroxamic acids (**4**) increases in the series (**4a**), (**4c**), and (**4d**), consistent with the n.m.r. data on the relative stability of these compounds. Two compounds (**4c**), and (**4d**) exhibited a molecular ion peak in the electron impact mode (see Table 3b), which is quite rare for hydroxamic acids.

In conclusion, we have shown that the reaction of *p*-nitroso-*N*,*N*-dimethylaniline (**1**) with arylpyruvic acids (**2**) which produces arylacetamides (**3**), proceeds, at least in the case of the *ortho* substituted phenyl derivatives (**2a**, **c**, **d**), *via* isolable hydroxamic acid intermediates (**4**). The latter (usually upon

Table 3a. Mass spectra (c.i.) of hydroxamic acids (**4**)

Compd.	R^1	R^2	$(M+1)^+$/RA%	$(M-1)^+$/RA%	$MH^+ - O$/RA%	$MH^+ - O\text{-}CH_2$/RA%	$MH^+ - HF_2$/RA%	$MH^+ - R^1$/RA%
(**4a**)[a]	NO_2	H	316/0.24	314/2.6	300/100	286/7.6	151/1.27	270/2.3
(**4d**)[b]	Me	H	285/0.52	283/5.6	269/100	255/12	151/0.45	270/not found
(**4c**)[b]	OCH_2Ph	H	377/0.83	375/3.61	361/100	347/9.3	151/vw	270/55
(**6**)[a]	NO_2	COPh	420/2.62	418/not found			255/2	374/5.9

[a] C.i. reagent gas isobutane. [b] C.i. reagent gas methane. RA% = relative abundance as percentage of base peak BP.

Table 3b. Mass spectra (e.i.) of hydroxamic acids (**4**)

Compd.	R^1	M^+/e/RA%	$(M - O)^+ = A^+$/ RA%	$F_1{}^+$a.m.u./RA%	$(A - HF_1)^+$/ RA%	$(M - F_2)^+$/ RA%	$(A - F_2)^+$/RA%	Electron energy (eV)
(**4a**)	NO_2	315/not found	299/36	136/51	162/21	150/65	135/100	23
(**4d**)	Me	284/5.2	268/91	105/26	162/3.5	150/13	135/56	25
(**4c**)	OCH_2Ph	376/0.93	360/100	197/not found	162/3.3	150/3	135/5	19

Table 3c. Mass spectra (c.i.) of decomposition products (**3**) (in solution)

	(**3a**)	(**3d**)	(**3c**)	(**5a**)	(**5d**)	(**5c**)	(**1**)
MH^+/RA%	300[a]/100	269[b]/100	361[b] 3	182[a]/48.7	151[b]/100	243[b]/3.5	151[d]/100
$MH^+ - H_2O$/RA%				164/100	133/11	225/2.4	121[c]/0.5

[a] Separated compounds. [b] Mixture. [c] $MH^+ - NO$

warming in solution) underwent a rapid and unusual self-condensation leading to the amides (**3**) as well as to (**1**) and(**5**). Reaction pathways are proposed and spectral correlations are discussed.

Experimental

All m.p.s are uncorrected. ^1H and ^{13}C N.m.r. spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$–Me_4Si and are reported in δ values from Me_4Si. Mass spectra were recorded on a Finnagan-4021 quadrupole mass spectrometer in the c.i. mode unless otherwise indicated with isobutane as the reagent gas. The progress of reactions and the purity of the products were monitored by t.l.c. sheets pre-coated with silica gel (Merck Ar-5554) and eluted with dichloromethane–ether (5:1). For visualization of the compounds, u.v. light and I_2 were used. Column chromatography was carried out on silica gel 60 and *p*-nitroso-*N,N*-dimethylaniline (**1**) and *o*-nitrophenylpyruvic acid (**2a**) were synthesized by literature procedures.[7]

p′-*Dimethylamino*-N-*hydroxy*-o-*nitrophenylacetanilide*(**4a**).—A solution of compound (**1**) (0.37 g, 2.4 mmol) in ethanol or ether (10 ml) was added slowly to a stirred solution of (**2a**) (0.5 g, 2.4 mmol) in ethanol or ether (5 ml) at room temperature. After 10 min the title compound (**4a**) was filtered off; it had m.p. 107 °C and gave a deep red colour with $FeCl_3$ in ethanol (Found: C, 61.25; H, 5.5; N, 13.2%. $C_{16}H_{17}N_3O_4$ requires C, 60.95; H, 5.39; N, 13.33%).

Benzoylation of (**4a**) with benzoyl chloride in pyridine led to *N*-benzoyloxy-*p*′-dimethylamino-*o*-nitrophenylacetanilide (**6**) which was difficult to purify; it had m.p. *ca.* 20 °C (Found: N, 10.0. Calc. for $C_{23}H_{21}N_3O_5$: N, 10.02). Mass spectral fragmentation is consistent with the assigned structure.

p′-*Dimethylamino*-o-*nitrophenylacetanilide* (**3a**): *Isolation of Compounds* (**1**) and (**5**).—The acetanilide (**4a**) was heated in ethanol for a few minutes, and the solution cooled and filtered to give (**3a**), m.p. 207 °C (lit.,[3] 207 °C), *m/z* (300, MH^+, 100). Concentration of the filtered solution gave a residue which showed two spots on t.l.c. identical with authentic compounds (**1**) and (**5**). The mass spectrum (c.i.) of this solution also showed the presence of (**1**), *m/z* 151 (MH^+, 64%) and of (**5**), *m/z* 182 (MH^+, 49%) and 164 $MH^+ - H_2O$, 100). Chromatography on silica led to isolation of compounds (**1**) and (**5**).

p-*Dimethylaminoacetanilide* (**9**).—A solution of compound (**1**) (0.37 g, 2.5 mmol) in ether (10 ml) was added slowly to a stirred solution of pyruvic acid (0.22 g, 2.5 mmol) in anhydrous ether (5 ml) at room temperature. After 1 h the solution was concentrated and the residue was purified by chromatography on silica using dichloromethane–ether (3:2, v/v) to give the title compound, m.p. 135 °C (lit.,[8] 135—137 °C); *m/z* (e.i.) 178 (M^+, 100%) and 135 ($M^+ - COCH_3$, 95).

Kinetic Data on Compound (**4a**).—Solutions of hydroxamic acid (**4a**) in deuteriochloroform (9.5 and 24.0 mg/ml) were prepared and immediately examined by n.m.r. spectrometry. The kinetic data for the Figure were obtained by integration of n.m.r. signals in the spectra at 297 ± 1 K. The rate constant of the reaction was calculated from the plot of $1/c$ *vs.* t as $k = 5.5 \times 10^{-4}$ l mol^{-1} s^{-1}. After several hours integration of the signals (see Table 1 and 2) indicated disappearance of (**4a**) and formation of (**3a**), (**1**) and (**5**) in nearly equal amounts.

o-*Benzyloxyphenyl*-N-*hydroxy*-N-(p-*dimethylamino*)*phenylacetamide* (**4c**).—Compound (**1**) (0.75 g, 20 mmol) in ethanol (20 ml) was added to a solution of (**2c**) (1.35 g, 20 mmol) in ethanol (10 ml). After 24 h at room temperature the resulting solid was filtered off and recrystallized from ethanol or benzene to furnish (**4c**), m.p. 104 °C; *m/z* (e.i.) 376 (M^+) (Found: N, 7.75%. Calc. for $C_{23}H_{24}N_2O_3$; N, 7.44%).

o-*Benzyloxyphenyl*-N-(p-*dimethylamino*)*phenylacetamide* (**3c**): *Isolation of* (**1**) *and* (**5c**).—A solution of (**4c**) (0.5 g) in $CHCl_3$ (3 ml) was kept for 3 days at room temperature. The mixture was made alkaline with $NaHCO_3$ and extracted with ether. The dried organic layer when concentrated under reduced pressure provided a residue which was chromatographed over silica gel (CH_2Cl_2–Et_2O, 1/1) to give (**1**), m.p. 87 °C and (**3c**), m.p. 158 °C (from EtOH). The water layer was acidified with HCl (7%) and extracted with ether and the extract was concentrated under reduced pressure to afford (**5c**), m.p. 94 °C (from benzene); *m/z* (c.i.) 243 (M^+).

N-(p-*Dimethylaminophenyl*-N-*hydroxy*-o-*tolylacetamide* (**4d**).—This compound was obtained from (**2d**) by the same procedure as described for (**4c**). The crude product was purified by recrystallization from benzene; it had m.p. 98 °C; *m/z* (e.i.) 284 (M^+) (Found: C, 73.4; H, 7.05; N, 9.9. $C_{17}H_{20}N_2O_2$ requires C, 71.83; H, 7.04; N, 9.86).

N-(p-*Dimethylaminophenyl*)-o-*tolylacetamide* (**3d**): *Isolation of* (**1**) *and* (**5d**).—The amide (**3d**) was obtained from (**4d**) as described for the preparation of (**3c**); it had m.p. 160 °C. Isolation of (**1**) and (**5d**) was affected as described for (**3c**); they were identical with authentic samples; *m/z* (c.i.) of (**5c**): 151.

Acknowledgements

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