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OXIDATION OF ARYLOXYAMINOALCOHOLS WITH ACTIVATED DIMETHYLSULFOXIDE; A NOVEL C-N OXIDATION FACILITATED BY NEIGHBORING GROUP EFFECT

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Abstract: Oxidation of aryloxy-ß-aminopropanols (1) with "activated" dimethylsulfoxide (DMSO) was found to provide a convenient "one-pot" method to synthesize aryloxy-ß-aminoketo-oximes (3), without isolation of the unstable ketones 2. Assignment of Z and E stereoisomers of oximes 3 was based on ^{1}H-and ^{13}C-NMR studies. Spontaneous isomerization of 3 was also observed and discussed.

Dioxime derivatives 6 and 7 were first isolated as by-products in the oxidation of compounds 1 and an improved synthetic method for 6 was developed. The novel C-N oxidation step involved in the formation of 6 from 1 was rationalized on the basis of neighboring group effect.

Introduction

Oxidation with dimethylsulfoxide (DMSO) activated by dicyclohexylcarbodiimide (DCC) (known as Pfitzner-Moffatt oxidation [1,2]) is a widely accepted and convenient method for the conversion of alcohols into aldehydes or ketones respectively, under mild conditions. The method, however, fails to yield the expected product from aryloxyamino-alcohols 1, due to the chemical instability of the resulting aryloxyaminoketones 2[3]. We have recently prepared representative aryloxyaminoketone-oximes (3) using a multi-step synthetic sequence.

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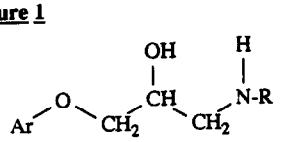
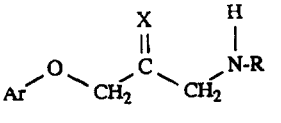
Compound 3a was found to be remarkably active in lowering intraocular pressure in rabbits.[3] It was established that this activity is due to a hydrolysis-reduction sequence in the iris-ciliary body within the eye, forming the active amino alcohol exclusively at the site of action. With the aim of synthesizing numerous further analogs of structure 3, the possibility of direct oxidation of 1 was reinvestigated.

Figure 1



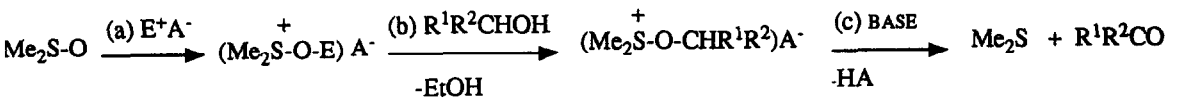
1



2 X = O; 3 X = NOH

Mechanistic studies on the Pfitzner-Moffatt oxidation (as well as on modifications thereof) have been reviewed[2,4]. The reaction sequence was found to include: (a) "activation" of DMSO by a suitable electrophilic reagent; (b) electrophilic attack by the acyloxysulfonium cation thus formed on an alcohol to give an intermediate alkoxysulfonium salt; and (c) deprotonation of the latter accompanied by its decomposition to form the carbonyl product and dimethylsulfide (Scheme 1). In addition to DCC several other electrophilic reagents have been reported [2,4,5,6] as "activators". Some of these are very active electrophiles and allow the oxidation to be performed at temperatures as low as -20°C to -78°C.

SCHEME 1



In our present studies oxidation of 1 with DMSO - oxalyl chloride reagent was investigated. We found that the electrophilic attack of the DMSO/$(COCl)_2$ reagent on the secondary alcohol moiety of 1 took place smoothly at both -40°C and -70°C. To avoid the possibility of reaction at the secondary amine site, hydrohalide salts of 1 were used.

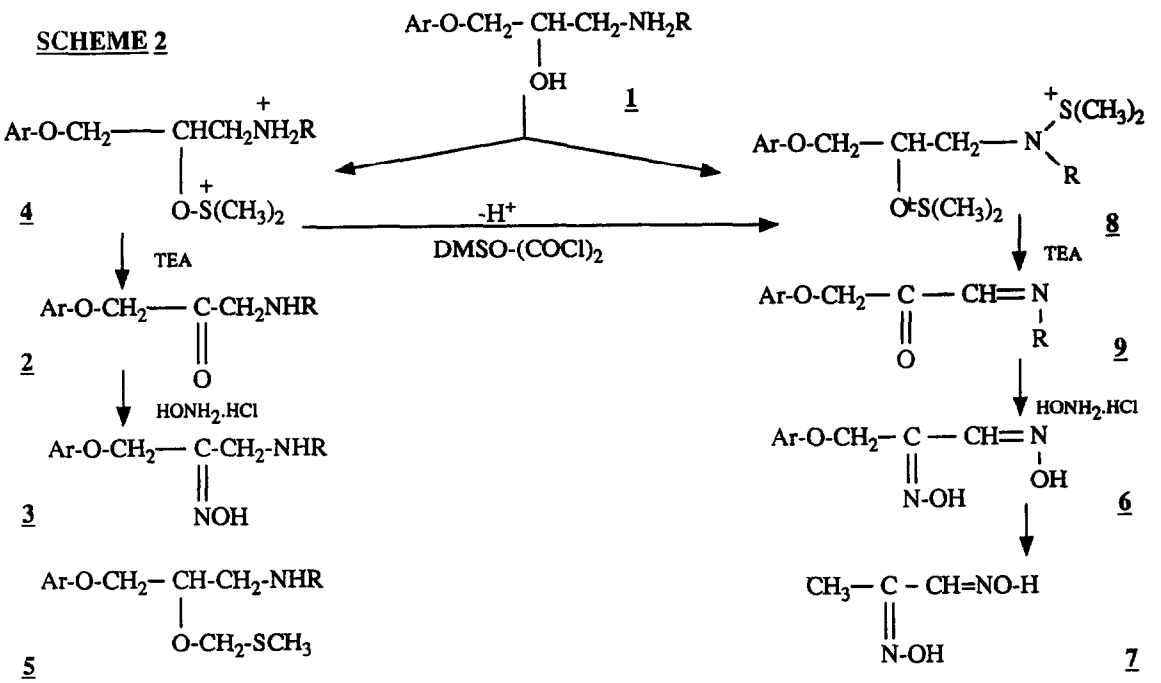
In fact, formation of the acyloxysulfonium reagent (obtained from the reaction of DMSO with $(COCl)_2$) proved to be faster at both temperatures than O-acylation of 1 by $(COCl)_2$; thus, solutions of salts of 1 and DMSO were treated with $(COCl)_2$, avoiding the need to prepare the reagent in advance. Decomposition of the intermediate alkoxysulfonium salts 4 was best brought about by triethylamine (TEA). Deprotonation of 4 with any proton-containing base such as Amberlite® (basic) ion-exchange resin or reaction in protic media resulted almost exclusively in reformation of 1. Interestingly, even slow (dropwise) addition of TEA brought about significant formation of 1, possibly because of the liberated secondary amine moiety in 4 acting as a nucleophile concurrently with TEA as proton scavenger.

The aryloxyaminoketones 2 thus formed were found to have very limited stability at temperatures at or above 0°C, thus, they were preferably transformed *in situ* into the more stable ketonoxime derivatives 3. Compounds 3 were isolated as their acid-addition salts (oxalates or hydrochlorides) as mixtures of stereoisomers in moderate to good yields (Table 1, Method A).

Formation of the methylthiomethylether of structure 5 as a by-product was anticipated on the basis of earlier reports,[4,5] but this compound was never detected in our investigation. Instead, a by-product isolated in significant yield in all cases proved to be the dione-dioxime 6 (Table 4). In some cases minor amounts of pyruvaldehyde-dioxime 7 were also isolated.

The formation of 6 can best be rationalized as the result of electrophilic attacks by the acyloxysulfonium reagent on both the OH and the NH groups of 1 (the latter being set free partly from its salt by dissociation facilitated by the highly proton-accepting DMSO). Double proton-elimination from the intermediate 8 thus formed can lead to the formation of 9, from which trivial condensation with hydroxylamine can give 6.

SCHEME 2



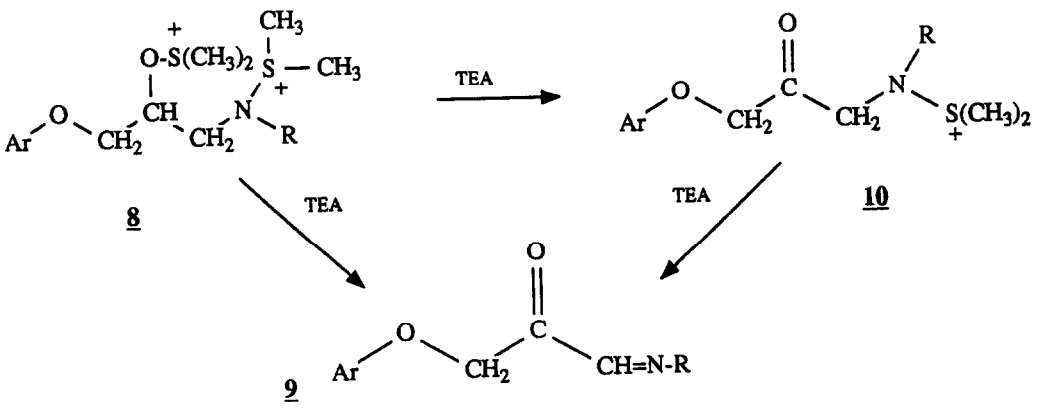
The suggested mechanism is shown in Scheme 2. Supporting the above rationalization are the findings that:

a. 6 was obtained almost exclusively when the free bases of 1 were reacted with DMSO/$(COCl)_2$; and, **b.** formation of 6 was virtually avoided and the yield of 3 was significantly enhanced when salts of 1 were exposed to DMSO/$(COCl)_2$ oxidation in the presence of excess acid (Table 1, Method B).

Although DMSO-oxidation of R^1R^2CH-OH type alcohols is widely known, oxidation of an amine with an analogous structure (R^1R^2CH-NHR) has not been reported. In fact, DMSO-oxidation of simple secondary amines such as N-isopropyl-benzylamine and N-methylbenzylamine was attempted but failed. Since electrophilic attack of the reagent is at least as likely on an NH as on an OH group, deprotonation is apparently selectively favored in the case of an alcohol. Deprotonation of intermediates such as 4 or 8 requires a positive polarization of the carbon(s) adjacent to the heteroatom(s). The electron-withdrawing effect of the positively charged sulfur is obviously well transferable through an O-bridge, but the same is not true of an NR-bridge (due to the lesser electronegativity of the N as compared to that of O, as well as to the electron-supporting effect of the R-group), thus rendering the oxidation of simple secondary amines impossible. In the specific case of the 2-aminoalcohol derivatives of this study, however, proton elimination from the $-CH_2$-N moiety may well be facilitated by the electron-withdrawing neighboring group in either intermediate 8 or 10. The novel C-N oxidation step involved in the formation of 6 from 1 can thus be attributed to a specific neighboring group effect.

Formation of 7 is likely to be the result of a reductive or redox splitting of either 6 or intermediates thereof (8, 9 or 10), (Scheme 3) the mechanism of which is yet to be investigated.

SCHEME 3



Compounds 3 and 6 were isolated as mixtures of stereoisomers (Figure 2) in most cases, as indicated by their NMR spectra.The isomer ratio was estimated by ^{1}H-NMR and determined analytically by HPLC (see Experimental and Table 1.). Pure isomers of compounds 3 were isolated by fractional recrystallization or isomerization (see later). Structural assignment of the

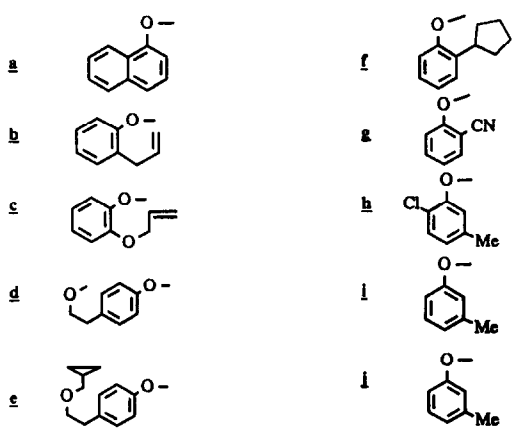
stereoisomeric oximes 3 and 6 was based on their ^{1}H-NMR and ^{13}C-NMR spectra. Configurational analysis of isomeric ketone oximes using NMR-techniques has been reported[7-12]. In a systematic study of ^{1}H-NMR spectra of relatively simple ketone oximes (and other ketone derivatives) the shielding effects attributed to the lone pair of electrons on the N in the C=N bond have been established[7]. Thus, alpha-protons cis to the oximino-hydroxy group were found down-field relative to those in trans configuration[7-9]. In the ^{13}C-NMR spectra, on the other hand, the shielding effects were found to be the reverse: carbons cis to the oximino-O-atom appeared to be more shielded than the respective trans carbons, an effect interpreted as steric compression shift [10-12].

Table 1. Physical data for compounds **3a-3j**.

	Salt	R'	Yield(%) method A	B	Solvent	M.P.°C Z	E	T_R(min.) Z	E	%MeCN[h]
3a	HCl	i	68	64	i-PrOH	170-171 (f,i)	189-191 (j)	5.5	4 6	30
	oxalate (a)		53		MeOH		152-158			
3b	HCl	i	62	78	MeCN	118-120 (k)	154-156 (l)	5.6	4 7	30
	oxalate (a,b)			60	MeCN	142-145 (a)				
3c	HCl	i	38	51	i-PrOH		130-133(b,e)	3 7	3.0	30
	oxalate (b)		45		MeCN	118-120 (e)				
3d	HCl	i	48	71	MeCN	129-131	164-168	7.1	5.3	20
3e	HCl	i	60	82	i-PrOH		168-170	5.7	4.7	30
3f	HCl	t	39	62	MeCN		179-181	7 0	6.1	40
3g	HCl	t	55	52	MeCN		189-191	5 9	4.0	20
3h	HCl	t	6 (c)	47 (d)	MeCN	164-166 (g)		6.9	6.0	30
3i	HCl	i	57	67	i-PrOH		183-185	3.2	2.6	30
3j	HCl	dmp	59	78	i-PrOH	155-158		3.0	2.6	40

a: Neutral salt (molar ratio 1.2); b: Acidic salt (molar ratio 1:1); c: From 1h base; d: Method C (see experimental); e: Z:E ratio 3.1; f: Base m.p. 127-129°C (CCl_4); g: Base m.p. 162-164°C (EtOH).
. h. %MeCN (v/v) in mobile phase;Mass spectra - m/z (%): l.272 (6); 115 (100), 144 (73), 72 (62), 128 (56), 56 (53), 143 (48), 129 (40), 116 (36); j: 272 (7), 115 (100), 129 (68), 144 (64), 143 (47), 72 (45), 56 (35), 183 (31), 116 (30); k: 262 (10), 173 (100), 105 (92), 133 (65), 134 (60), 131 (59), 115 (49), 130 (42). 247 (38); l: 262 (12), 105 (100), 173 (95), 133 (70), 72 (67), 131 (64), 134 (63), 130 (60), 115 (53). ' Structures of the Ar groups are given below.' i = i-Pr; t = t-Bu;
dmp = 2-(3,4-dimethoxyphenyl)ethyl.

Structure of Ar groups in compounds 3 &6 a-i :



The ^{1}H-NMR spectra of compounds 3 (especially their salts) reflect only slight shielding effects on the OCH_2 and NCH_2 groups. These are inconclusive in most cases, and sometimes even controversial, inasmuch as the opposite assignation could be deduced from the ^{1}H-NMR data of some of compounds 3 and those of their respective salts (e.g. 3g and 3h in Table 2).

These discrepancies can probably be attributed to the secondary amine group, the protonation of which can strongly influence and occasionally outweigh the

shielding effects of the =NOH moiety. In the ^{13}C-NMR spectra, on the other hand, this influence was not found; the same significant and conclusive shielding effects were observed on both the bases and salts (cf. Table 3), allowing unequivocal assignment of the isomer with the more shielded O<u>C</u>H$_2$ and more deshielded N<u>C</u>H$_2$ as having the Z configuration. This assignment is also in agreement with that deduced from the ^{1}H-NMR spectra of the free bases (cf. Table 2).

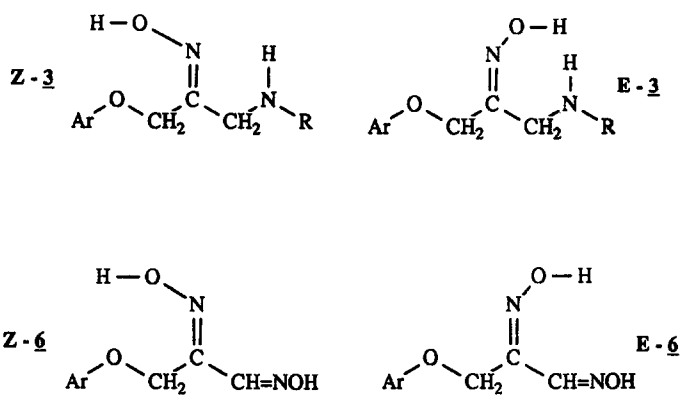
Table 2. ^{1}H-NMR chemical shift data for Z and E stereoisomers of compounds **3** in DMSO

		Z			E		
		NO<u>H</u>	OC<u>H</u>$_2$	NC<u>H</u>$_2$	NO<u>H</u>	OC<u>H</u>$_2$	NC<u>H</u>$_2$
3a	HCl	12.10	5.19	3.98	12.30	5.12	3.91
	base	11.10	5.07	3.41	11.10	4.82	3.57
3b	HCl	12.05	5.00	3.85	12.20	4.93	3.80
	base	11.10	4.87	3.34	11.10	4.62	3.49
3c	HCl	11.95	4.98	3.85	12.20	4.87	3.85
	base	-	4.91	3.22	-	4.63	3.33
3d	HCl	11.97	4.94	3.80	12.20	4.85	3.80
	base	-	4.90	3.19		4.55	3.31
3e	HCl	11.97	4.94	3.75	12.20	4.87	3.80
	base	-	4.90	*x*	-	4.56	3.31
3f	HCl	11.98	4.98	3.75	12.20	4.94	3.75
	base	-	4.94	3.35	-	4.66	3.46
3g	HCl	12.10	5.20	3.80	12.30	5.26	3.80
	base	-	5.08	3.40	-	4.89	3.50
3h	HCl	12.05	5.10	3.80	12.20	5.22	3.80
	base	11.13	4.91	3.36	-	4.76	3.50
3i	HCl	11.90	4.91	3.75	12.10	4.84	3.75
	base	-	4.90	3.24	-	4.56	3.31
3j	HCl	12.00	4.91	3.85	12.40	4.84	3.85
	base	-	4.87	3.32	-	4.55	3.47

x = overlapping signal.

In a similar fashion, analysis of combined ^{13}C- and ^{1}H-NMR spectra was applied to compounds <u>6</u>. Although four configurational isomers of <u>6</u> are possible, (Figure 2) only two of them were actually found in each case investigated. These were assigned to the Z-E isomersalong the ketonoxime moiety, on the basis of two

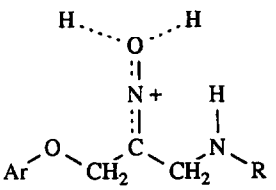
Figure 2



distinctly different O<u>C</u>H$_2$ signals in the ^{13}C-NMR, indicating the same shielding effects as found in compounds 3 (cf. Tables 3 2and 5). No indication of isomerism about the aldoxime group was found; its actual configuration is not yet determined.

Spontaneous isomerization of HCl-salts of compounds 3 was also observed in solution; it was not observed in compounds 6 or in oxalates or bases of 3. The isomerization of 3 was found to be facilitated in aprotic solvents, much slower in protic media and, especially, by addition of hydrochloric acid. Acid-catalyzed isomerization was in most cases found to result in formation of the opposite isomers in solutions and in suspensions, respectively. (In suspension, clearly the less soluble isomer is forming).

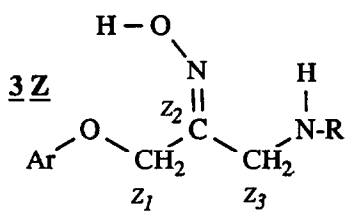
Figure 3



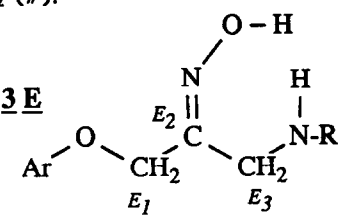
11

Isomerization of oximes is known to proceed via inversion rather than rotation about the double bond[13]. Based on detailed AM-1 calculations of the possible routes, acid-catalysis of the process can best be interpreted by protonation of the oxime-oxygen leading to a coplanar transition state such as 11 with low activation energy[14] (Figure 3). Through 11 the isomeric equilibrium shifts towards the thermodynamically more stable isomer (Z in all cases) in solution, but towards the less soluble isomer (E in most cases; Z in 3a and 3j) in suspension. Probably due to insolubility, no isomerization of 3h was observed.

Table 3. Relevant ^{13}C-NMR data of stereoisomers of 3 (#).



3 Z



3 E

		Z_1	Z_2	Z_3	E_1	E_2	E_3
3a	HCl	61.47	148.50	42.58	67.49	147.32	37.27
	base	61.08	154 25	46.32	67 55	154.78	40/96
3b	HCl	61.32	148.53	42.38	67.26	147.41	36.96
	base	61.09	154.30	46.26	67 28	154 77	40.88
3c	HCl	62.53	148.74	42.57	68.64	147.41	37.10
3d	*	61.20	148.8	42.6	67.23	147.38	37.11
3e	*	61.26	148.9	42.54	67.22	147.38	37.11
3f	*	61.40	148.86	39 (*)	67.36	147.61	34.02
3g	*	62.46	147.78	39 (*)	67.71	146.45	33.91
3h	*	62.07	148.24	39.67	——	——	- - - - - -
	base	61.62	154.5	42.41	68.0	**	36.80
3i	HCl	61.18	148.73	42.55	67.10	147.38	37.12
3i	*	61.31	148.65	45.36	67.18	147.27	40.05

*#: Strucures of Ar, R given above (see Table 1); *: overlap with DMSO-d$_6$ signals; ** not detected due to low solubility.*

Table 4. ^{1}H-NMR data for compounds **6a-i** (a).

		E			Z		
	Yield(%)(b)	NOH	CHN	OCH_2	NOH	CHN	OCH_2
6a	15 (c)	11.92, 12.00	8.36	5.04	11.62, 12.27	7.84	5.10
6b	28 (d)	11.82, 11.95	8.24	4.80	11.56, 12.16	7.72	4.86
6c	23 (e)	11.82, 11.98	8.30	4.83	11.62, 12.17	7.79	4.88
6d	25 (c)	11.67, 11.82	8.22	4.75	11.44, 12.02	7.70	4.81
6e	24 (f)	11.86, 12.01	8.26	4.79	11.64, 12.21	7.77	4.86
6f	15 (d)	11.87, 11.98	8.26	4.79	11.58, 12.20	7.74	4.86
6g	10 (c)	12.00, 12.07	8.31	5.05	11.70, 12.37	7.81	5.05[e]
6h	14 (g)	11.95, 12.04	8.31	4.91	11.68, 12.29	7.82	4.95
6i	25 (h)	11.78, 11.91	8.25	4.77	11.54, 12.12	7.72	4.82

*a: structure designations for **a-i** given above (see Table 1); b: isolated crude yield as by-products in Method A (isomeric mixtures); c: admixed with 50-65% of Z; d: admixed with 15-20% of Z; e: m.p. 125-127°C (E:Z ratio 3:1); f: m.p. 152-154°C (E isomer); g: m.p. 129-130°C (E:Z ratio 4:1); h: m.p. 117-119°C (E:Z ratio 3:2).*

Table 5. ^{13}C-NMR shift data for compounds **6a,c,d,e,g,h** and **i**.

		C1(Ar)	OCH_2	C=N	CH=N
6a	E	153.88	65.90	147.57	138.48
	Z	154.00	57.42	150.59	145.86
6c	E	148.23 (x)	66.17	147.73	138.84
	Z	148.28	57.56	150.75	145.84
6d	E	156.75	65.26	147.53	138.76
	Z	156.86	56.79	150.67	145.78
6e	E	156.75	66.27	147.59	138.75
	Z	156.86	56.78	150.66	145.76
6g	E	159.87	66.12	146.69	138.50
	Z	159.9	57.84	149.61	145.54
6h	E	153.46	66.14	147.24	138.07
	Z	153.56	57.62	150.18	145.67
6i	E	158.44	65.20	147.67	138.85
	Z	158.54	56.69	150.72	145.84

x: arbitrary assignment.

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. All new compounds gave satisfactory microanalytical data for C, H, N (and Cl). ^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz) spectrometer, ^{13}C-NMR spectra on a Varian VXR-300 FT spectrometer in DMSO-d_6 solutions with TMS and DMSO-d_6 internal standard, respectively. Mass spectra (EI) were recorded on a Kratos MS80RFA instrument operated at 70 eV electron energy and 200°C source temperature.

Synthesis of 1-aryloxy-3-(substituted)-amino-propanone-2-oximes (3)

Method A

A solution of 3mmol of the appropriate 1.HCl (1d-oxalate) in 1.2-2.0 ml (17-28 mmol) of DMSO was diluted with 10 ml of dichloromethane and cooled to about -60°C. A solution of 0.37 ml (4.24 mmol), of oxalyl chloride in 5 ml of dichloromethane was added dropwise below -50°C and stirring was continued for an additional 30-60 min. below -40°C (precipitation occurs). The mixture was cooled below -60°C again and a solution of 1.70 ml (12.25 mmol) of triethylamine was added at once (temperature rises to about -40°C; the precipitate dissolves, then precipitation starts again). The reaction mixture was stirred for an additional 1-1.5 hr. below -25°C, then a solution of 0.71g (10 mmol) of hydroxylamine hydrochloride in 1 ml of water and 3 ml of ethanol was added. The temperature was allowed to rise to ambient, and the resulting clear solution was stirred for 6-18 hrs at room temperature. It was then shaken with 60 ml of 5% sodium hydrogen carbonate solution; the water phase was extracted with ether, the combined organic phases were washed with water, dried over magnesium sulfate and evaporated below 30-40°C. The remaining oil was dissolved in ether and acidified with ethereal hydrogen chloride (or, alternatively, with ethereal oxalic acid solution); the precipitated solid was filtered off, washed with ether and dried.

Method B

A solution of 3mmol of the appropriate 1.HCl (oxalate in case of 1d) in 1.2-2.0 ml (17-28 mmol) of DMSO was diluted with a solution of 0.1-0.2g (1-2 mmol) of concentrated H_2SO_4 in 10 ml of dichloromethane and cooled to about -60°C. A solution of 0.38 ml (0.55g; 4.35 mmol) of oxalyl chloride in 5 ml of dichloromethane was added dropwise below -50°C, and stirring was continued for an additional 40-50 min. below -40°C (precipitation occurs). The mixture was cooled below -60°C again and a solution of 2.0 ml (1.45 g; 14.35 mmol) of triethylamine was added at once (temperature rises to about -35°C, precipitate dissolves, then precipitation starts again). The mixture was stirred for an additional 1 hr. at -25 to -45°C, then a solution of 0.7g (10 mmol) of hydroxylamine hydrochloride in 1 ml of water and 3 ml of ethanol was added. The temperature was allowed to rise to ambient, the resulting clear solution was stirred overnight at room temperature, then shaken with 60 ml of 5% sodium hydrogen carbonate solution. The aqueous phase was extracted with dichloromethane, the combined organic phases were washed with water, dried over magnesium sulfate and evaporated below 30-40°C. The resulting oil was dissolved in ether and acidified with ethereal hydrogen chloride (or, alternatively, with ethereal

oxalic acid solution). The precipitated solid was filtered off, washed with ether and dried.

Method C

A solution of 3.0 ml (42 mmol) of DMSO in 10 ml of dichloromethane was cooled to -60°C. A solution of 1.30 ml (14.9 mmol) of oxalyl chloride in 10 ml of dichloromethane was added dropwise while stirring and cooling to maintain the temperature below -45°C, and stirring was continued for 30 min. A solution of 1.5g (15 mmol) of sulfuric acid in 10 ml of dichloromethane was then added and the mixture was stirred for 20 min. (precipitation occurs), followed by dropwise addition of 2.72g (10 mmol) of 1h, dissolved in 10 ml of dichloromethane (all below -45°C). Stirring of the thick slurry was continued for 40 min. below -45°C, then it was cooled to -70°C and 7.0 ml (50 mmol) of triethylamine was added at once with vigorous shaking below -40°C. Stirring (and occasional shaking) of the thick reaction mixture was continued for an additional 1 hr, then a solution of 2.1g (30 mmol) of hydroxylamine hydrochloride in 3 ml of water and 10 ml of ethanol was added at -20°C. The reaction temperature was allowed to rise to ambient, and the mixture (containing some undissolved material) was stirred overnight, then it was shaken with 100 ml of 5% sodium hydrogen carbonate solution. The precipitated solid was filtered off, washed and dried to give 0.55g (20%) of 3h.

The two-phase filtrate was separated, the water phase was washed with dichloromethane, the combined organic phases were washed with water, dried and evaporated. The solid residue was taken up with ether, filtered, washed and dried to give a further 1.50g (40%) of 3h. The two fractions of 3h thus obtained were combined, dissolved in 50 ml of warm methanol, and the solution was acidified with ethereal hydrochloric acid and evaporated in vacuum. The residue was taken up with ethyl acetate, filtered, washed and dried to give 1.50g (78%, 47% overall) of 3h. HCl. Data for compounds 3 are listed in Tables 1-3.

Isolation of 3-aryloxy-2-oxopropanal dioxime (6) and pyruvaldehyde dioxime (7)

The ethereal mother liquors from the synthesis (Method A) of compounds 3 were washed with water, dried over magnesium sulfate and evaporated. The residual solidified oils were recrystallized twice from benzene to give compounds 6, analytically pure.

The crude compounds 6a, b, d, f and g were isolated mixed with various amounts of pyruvaldehyde dioxime 7. In these cases the residue was first recrystallized from toluene to isolate 7, which was further purified by recrystallization from toluene; mp. 154-157°C (lit.[15] m.p. 157°C); calcd. C 35.29, H 5.92, N 27.44%; found C 35.24, H 5.83, N

27.49%; ^{1}H-NMR (DMSO-d_6): 11.48, 11.38 (2 s, NOH's, 2H), 7.63 (s, CH=N, 1H), 1.91 (s, CH_3, 3H); ^{13}C-NMR (DMSO-d_6): 152.03 (C=N), 147.56 (CH=N), 9.31 (CH_3).
The toluene mother liquor of compound Z was evaporated to about 2/3 volume, cooled, filtered and evaporated to dryness. The residue was recrystallized from benzene to give 6. Data for compounds 6 isolated in this way are listed in Tables 4 and 5.

Improved synthesis of 3-(1-naphthyl)oxy-2-propanal dioxime 6a

A solution of 2.5 ml (35 mmol) of DMSO in 20 ml of dichloromethane was cooled below -60°C, and treated dropwise with a solution of 0.7 ml (8 mmol) of oxalyl chloride in 10 ml of dichloromethane while stirring and cooling to maintain the temperature below -55°C. After stirring the suspension thus obtained for 30 min. below -55°C, a solution of 0.76g (3 mmol) of 1a in 10 ml of dichloromethane was added dropwise and stirred for an additional 30 min. below -55°C. To the clear solution 2.5 ml (18 mmol) of triethylamine was added and stirred for a further 1 hr below -40°C. The slurry thus obtained was treated with a solution of 1.05g (15 mmol) of hydroxylamine hydrochloride in 1.5 ml of water and 5 ml of ethanol at -20°C. The temperature was then allowed to rise to ambient and the resulting solution was stirred overnight, then shaken with 60 ml of 5% sodium hydrogen carbonate solution. The water phase was extracted with ether, the organic phases were combined, washed with water, dried over magnesium sulfate and evaporated to give 0.54g (75%) of crude 6a (admixed with some Z). Separation of 6a and Z as well as purification thereof was described in the previous section.

High-performance liquid chromatography (HPLC)

HPLC separation of the Z and E isomers of compounds 3 was carried out on a system consisting of a Spectra Physics (Palo Alto, CA) SP 8810 precision isocratic pump, SP 8780 autosampler equipped with a Rheodyne Model 7125 injector valve (20 µl sample loop), a SP 8450 UV/VIS detector operated at 254 nm, and an SP 4290 integrator. A 5 cm x 4.6 mm i.d. Supelcosil LC-8-DB (5 µm) column (Supelco, Bellefonte, PA) was used. The mobile phase was a mixture of acetonitrile and an aqueous buffer solution containing 0.02 M monobasic potassium phosphate (adjusted to pH=3.0 with concentrated phosphoric acid) and 0.01% (v/v) triethylamine. Acetonitrile proportions (%v/v) used in the mobile phase and retention time (T_R) data are given in Table 1.

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