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ALKYLATION OF ENAMINES BY α-HALOKETOXIMES

SYNTHESIS AND PROPERTIES OF SOME 6-HYDROXY-5,6-DIHYDRO-1,2,4*H*-OXAZINES RING-CHAIN TAUTOMERISM OF γ-OXIMINO CARBONYL COMPOUNDS*

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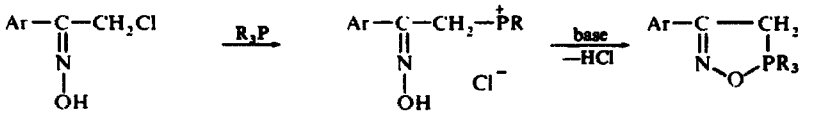
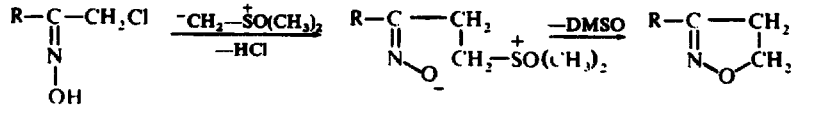
Abstract—Alkylation of several enamines by phenacyl or *p*-bromophenacyl bromide oxime affords the corresponding alkylated immonium salts III. Mild hydrolysis of these salts in most cases yields the unknown 6-hydroxy-4,5-dihydro-1,2,4*H*-oxazines (VI). Spectroscopic observation shows that some of these compounds exist in solution only in the cyclic form, some in a ring-chain tautomeric equilibrium with the corresponding γ-oximino carbonyl compounds V. When two dissymmetric centers are present in VI rapid epimerization can be observed at C-6, probably through the open chain form. The chemical behaviour of oxazines VI has been investigated. A Beckmann fragmentation has been observed on one of these oxazines (VIg) when treated with trifluoroacetic acid.

OXIMES of α-halocarbonyl compounds are attacked by several classes of nucleophiles such as amines,[1] alkoxides,[1a] phosphines,[2, 3] carbanions[4, 5] etc. to give the corresponding α-substituted oximes. When the group replacing the halogen is sensitive to nucleophilic reagents it can undergo an intra-molecular attack by the oximic oxygen to give O,N-heterocycles. Two cases reported[2, 3, 5, 6], where 5-membered heterocycles were obtained by this route, are illustrated in Eq. 1 and 2.



Eq 1



Eq 2

It was considered possible to obtain 6-membered heterocycles by a similar scheme, by reacting α-haloketoximes with nucleophiles so as to give oximes bearing an electrophilic centre in position 4 with respect to the oximino group. Enamines were chosen as reagents with the special requirements. These compounds could be potential

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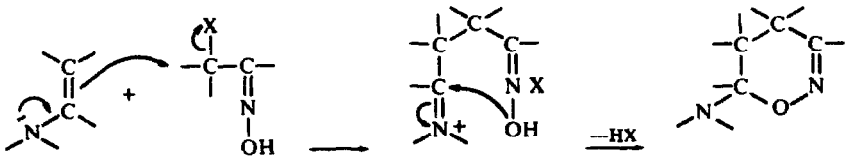
† In alphabetical order.

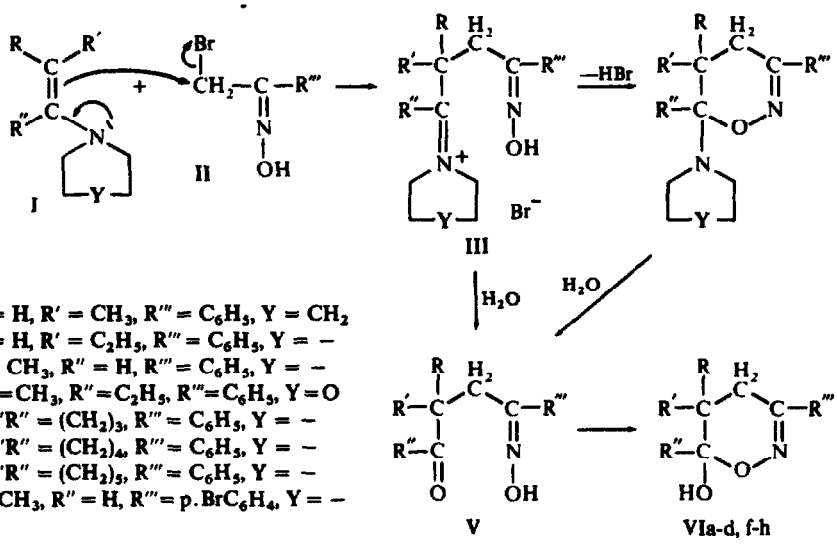
starting material for the synthesis of 1,2-oxazines (IV) through the intermediate oximes III, according to the following scheme:



I II III IV

X = halogen

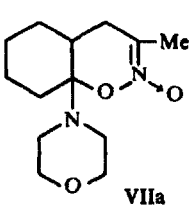
Actually α-haloketoximes (II) react easily with enamines (I) to give salts of structure III (Chart 1). These salts, upon treatment with base in an anhydrous medium can be



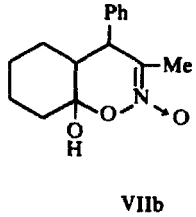
a: R = R″ = H, R′ = CH_3, R‴ = C_6H_5, Y = CH_2
b: R = R″ = H, R′ = C_2H_5, R‴ = C_6H_5, Y = –
c: R = R′ = CH_3, R″ = H, R‴ = C_6H_5, Y = –
d: R = H, R′ = CH_3, R″ = C_2H_5, R‴ = C_6H_5, Y = O
e: R = H, R′R″ = $(CH_2)_3$, R‴ = C_6H_5, Y = –
f: R = H, R′R″ = $(CH_2)_4$, R‴ = C_6H_5, Y = –
g: R = H, R′R″ = $(CH_2)_5$, R‴ = C_6H_5, Y = –
h: R = R′ = CH_3, R″ = H, R‴ = p.BrC_6H_4, Y = –

CHART 1

converted into the corresponding cyclic compounds, the 1,2-oxazines IV, bearing an amino function at C-6, as shown for IIIf (see below).● More easily, when simply dissolved in water or hydroalcoholic mixtures, the salts III undergo hydrolysis to give 6-hydroxy-5,6-dihydro-1,2,4*H*-oxazines (VI) in good yields, very probably



VIIa



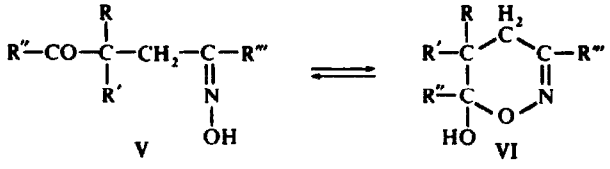
VIIb

● No 6-amino-5,6-dihydro-1,2,4*H*-oxazine is reported in the literature. Only recently the N-oxide VIIa of a compound related to this class of heterocycles has been reported. It has been obtained by reaction of 2-nitropropene with morpholinocyclohexene.[7a] In a similar way the related compound VIIb has been obtained from the reaction of 2-nitro-1-phenylpropene with cyclohexanone.[7b,c]

through the oximes V.▲ By this new method several examples of hemiacetal-like heterocycles of structure VI, not yet known,■ were obtained in order to study their physico-chemical properties and chemical behaviour.

According to the scheme (Chart 1) we synthesized seven 6-hydroxy-5,6-dihydro-1,2,4*H*-oxazines starting from the easily available ω-bromoacetophenone oximes IIa and IIh. The enamines employed were the pyrrolidino enamines of butyraldehyde (Ib), isobutyraldehyde (Ic), cyclopentanone (Ie), cyclohexanone (If), cycloheptanone (Ig), the piperidino enamine of propionaldehyde (Ia) and the morpholino enamine of diethylketone (Id). The first step of the synthesis was performed in benzene. In three cases (IIIe, IIIf, IIIg) the intermediate salts III, obtained as a precipitate, were isolated and purified by crystallization from anhydrous methanol and then hydrolysed. In the other cases III as the crude reaction mixture, was hydrolysed in water or water–ethanol after elimination of the solvent. The resulting 6-hydroxy-5,6-dihydro-1,2,4*H*-oxazines were purified by chromatography on silica gel and by crystallization. Some of their properties are summarized in Table 1.

6-Hydroxy-5,6-dihydro-1,2,4*H*-oxazines (VI) are the ring tautomers of the mono oximes of saturated γ-dicarbonyl compounds V, in the same way as pyranose sugars are the ring tautomers of γ-hydroxy-carbonyl compounds:



V VI

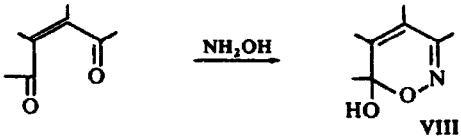
This tautomerism has been revealed by the IR and NMR spectra* which show at room temperature that some of these compounds exist in the cyclic form, some in the open chain form and some, finally, in both forms (Table 2).† In seven out of nine of these compounds (VI*a–d*, VI*f–h*) only the cyclic form was observed in the solid state (no C=O stretching band in the IR). Five of these products, VI*a,b,c,h* (from enamines of aldehydes) and VI*f* (from cyclohexanone enamine) exist in the cyclic form only also

* See the following section for a full discussion of the structures.

† An analogous case of ring-chain tautomerism has been shown to exist between VIIb and the corresponding γ-nitroketone [7b,c,d]

▲ The question whether these oximes would be formed by direct hydrolysis of the immonium salts or through the aminooxazines IV was not ascertained.

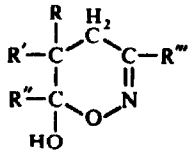
■ As far as we know, only three examples of 1,2-oxazines bearing an OH group on the C atom α to the oxygen (VIII) have been reported, all bearing two double bonds in the ring.[8–10] They were obtained from



VIII

unsaturated 1,4-dicarbonyl compounds and hydroxylamine. On the contrary, simple 5,6-dihydro-1,2,4*H*-oxazines, with no OH in position 6 are known.[11–17] In addition, several 1,2-oxazines condensed with aromatic nuclei (2,3-benzoxazines, pyridoxazines, etc.) are also reported in the literature.[11, 12, 18, 19]

TABLE 1. 6-HYDROXY-5,6-DIHYDRO-1,2,4*H*-OXAZINES



VI

6-Hydroxy-5,6-dihydro-1,2,4*H*-oxazines

	R	R′	R″	R‴	Yields[a] %	m.p.	IR (cm^{-1})[b] (nujol)	UV (EtOH) λ, nm	UV (EtOH) ε	% Analysis calc. C	calc. H	calc. N	found C	found H	found N
a	H	CH_3	H	C_6H_5	55	106°[d]	1565, 1610	246	10000	69·1	6·8	7·3	69·2	6·8	7·3
b	H	C_2H_5	H	C_6H_5	64	114°[c]	1575, 1615	245	10600	70·2	7·4	6·8	69·9	7·3	6·7
c	CH_3	CH_3	H	C_6H_5	90	144°[c]	1575, 1615	245	10700	70·2	7·4	6·8	70·1	7·4	6·6
d	H	CH_3	C_2H_5	C_6H_5	49	86°[e]	1575, 1615	246	9040	71·2	7·8	6·6	70·8	7·9	6·3
f	H	—$(CH_2)_4$—		C_6H_5	(92)	138°[c]	1570, 1605	245	9900	72.7	7·4	6·1	73·0	7·6	6·0
g	H	—$(CH_2)_5$—		C_6H_5	(77)	108°[e]	1565, 1610	245	9300	73·4	7·8	5·7	73·7	7·9	5·7
h	CH_3	CH_3	H	p.BrC_6H_4	61	79°[e]	1580, 1600	255	15500	50·7	4·9	4·9	50·7	5·0	4·9[f]

[a] Yields were calculated on the α-halo oximes II; when in brackets they were calculated on the intermediate salts III.

[b] Only the bands between 1550 and 1650 cm^{-1} are reported here. The bands are of low intensity.

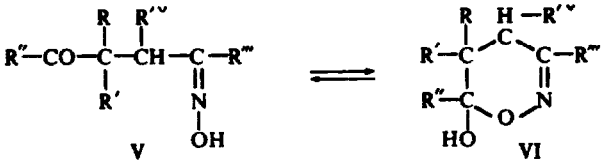
[c] From EtOH.

[d] From benzene or EtOH.

[e] From benzene.

[f] Found: Br, 28·2. Calc. Br, 28·1%.

TABLE 2. THE PREFERRED FORM OF γ-DICARBONYL COMPOUNDS MONO OXIMES



V VI

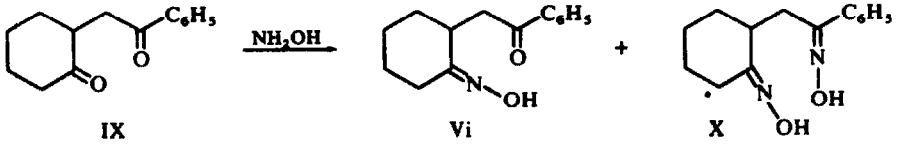
	R	R′	R″	R‴	R⁗	In solid	In soln[a]
a	H	Me	H	Ph	H	VI	VI[b]
b	H	Et	H	Ph	H	VI	VI[b]
c	Me	Me	H	Ph	H	VI	VI
d	H	Me	Et	Ph	H	VI	V(59%) + VI(41%)
e	H	$-(CH_2)_3-$		Ph	H	V	V(90%) + VI(10%)
f	H	$-(CH_2)_4-$		Ph	H	VI	VI
g	H	$-(CH_2)_5-$		Ph	H	VI	V(64%) + VI(36%)
h	Me	Me	H	p.BrC_6H_4	H	VI	VI
i	H	H	Ph	$-(CH_2)_4-$		V	V

[a] In DMSO-d_6, at room temp.
[b] Two epimers in equilibrium.

in solution, both in polar and non polar solvents (NMR in DMSO-d_6: OH at ~6 ppm, C-6 proton at ~5 ppm; IR: no C=O band in $CHCl_3$ solution). Compounds VIa and VIb exist in solution as a mixture of the two possible diastereoisomers in equilibrium, as shown by the NMR spectra. Solutions of VId and VIg show the cyclic and the open-chain forms in equilibrium [C=O band in $CHCl_3$; 2 OH peaks in DMSO-d_6, at ~6 ppm (C—OH) and ~11 ppm (N=OH)]. The relative abundance of the two forms could be deduced from the NMR spectra.

The product of hydrolysis of IIIe exists only in the open chain form Ve in solid state (strong band at 1745 cm^{-1}), but an equilibrium between cyclic and open chain forms is present in DMSO-d_6 solution.

Finally, one example of a γ-dicarbonyl compound mono oxime which exists in the open chain form only, both in the solid and in solution, has been obtained from 2-phenacylcyclohexanone (IX), during an attempt to synthesize VIf by oximation. The



IX Vi X

only product we could isolate, beside the dioxime X, was a mono oxime in the open chain form Vi (strong band at 1695 cm^{-1} in solid; OH only at 10·2 ppm in DMSO-d_6).

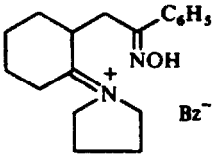
The chemical behaviour of 6-hydroxy-5,6-dihydro-1,2,4*H*-oxazines, as indicated in a following section, is in accord with their structure VI being in equilibrium with the corresponding open chain form V.

Structures and physico-chemical properties

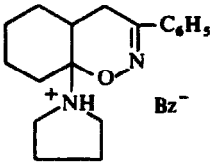
(a) *Immonium salts* (III). The structures of the immonium salts obtained from

enamines and ω-bromoacetophenone oxime were determined on the basis of their spectroscopic characteristics, as shown for IIIf:

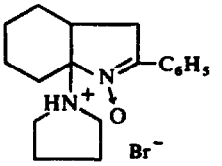
Compound IIIf gave analytical values corresponding to a formula $C_{18}H_{25}BrN_2O$, confirmed by mass spectrometry. Of the three possible structures IIIf, III'f and III"f, corresponding to this formula, only the first can be justified by the spectroscopica



IIIf



III'f

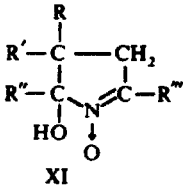


III"f

data. A strong band in the IR spectrum at 1665 cm^{-1} (stretching vibration of C=N) strongly suggests an immonium salt structure,[20, 21a] so excluding the alternatives III'f and III"f. The absence of this band in all of the many compounds related to this work which still contain the system C_6H_5—C=N—O, excludes the possibility that this absorption could be due to the C=N stretching of the C=N—O grouping. On the other hand, in the "double bonds" stretching region, at 1610 and 1570 cm^{-1}, two distinct bands of low intensity appear, the former can be assigned to the C=C stretching of the aromatic nucleus and the latter to the C=N stretching of the C=N—O grouping. Bands of this type and in this region have been reported for many compounds containing the Ar—C=N—O system.[22–24] The alternative structure III"f was discarded on the basis of the UV spectrum which shows λ_{max}^{EtOH} 247 nm (ε 11500). In fact 2-phenyl-Δ'-pyrroline N-oxide, of closely related structure, has been reported to absorb, in methanol, at 221 and 288 nm,[25] whereas many oximes of aromatic ketones and other related compounds are known to absorb at 240–250 nm.[26] The NMR spectrum is also in accord with structure IIIf. In fact the spectrum in DMSO-d_6 shows a complex signal (~10 H) between 1·2 and 2·3 ppm (3 CH_2 of the cyclohexane ring plus 2 CH_2 of pyrrolidine) and a broad signal (4 H) between 3·5 and 4·2 ppm (CH_2—$\overset{+}{N}$—CH_2).* The signals of the other three non aromatic protons, between 2·3 and 3·5 ppm, are partially overlapped with the solvent absorption. The OH proton falls at 11·7 ppm.

The structures of the other immonium salts were determined in a similar manner.

(b) 6-*Hydroxy*-5,6-*dihydro*-1,2,4H-*oxazines* (VI). As stated, the hydrolysis of the immonium salts III afforded the corresponding 6-hydroxy-5,6-dihydro-1,2,4*H*-oxazines (VI*a–d*, *f–h*). The isomeric open chain structure V for these hydrolysis products in the solid state was excluded by their IR spectra in nujol which show no carbonyl absorption. The alternative nitronic structure XI, which is possible, was



XI

* These values are close to the corresponding values of other immonium salts.[20b]

discarded on the basis of the UV spectra which show a maximum in ethanol at 245–255 nm for all compounds.[25*]

The existence of two dissymmetric centres in VI*a,b,d,f,g* implies that these compounds could be present in two diastereoisomeric forms. Actually in the solid state they consist of only one epimer. In fact they all were obtained, sometimes almost quantitatively, as solids of sharp m.p., which resisted fractionation by chromatographic techniques and appeared unitary on TLC. Moreover their NMR spectra in DMSO-d_6, registered *immediately after dissolution*, show only one OH signal (at ~6 ppm) integrating for 1 H, thus supporting the previous indication that these products exist in only one of the two possible epimeric forms.† On the other hand the spectroscopic investigation has shown that, when in solution, all these compounds except VIf, which still seems to be unitary, undergo an equilibration either between the two possible diastereoisomeric forms or between the cyclic and the open chain form. This will be discussed in some detail for each compound:

The NMR spectrum of VIa in DMSO-d_6 (Fig. 1A), registered immediately after the compound was dissolved, shows only the signals corresponding to one of the two possible diastereoisomers of the cyclic form: the Me appears as a doublet centred at 1·02 ppm (J = 6·0 c/s); the H-6 gives rise to a doublet of doublets centred at 5·25 ppm (J_{HCCH} = 2·0 c/s, J_{HCOH} = 4·2 c/s) and the OH appears as a doublet at 6·91 ppm (J = 4·2 c/s) each line of the doublet being slightly split (J = 0·7 c/s) because of further coupling with H-5. On treatment with D_2O the doublet disappears while the signal at 5·25 ppm changes into a doublet (J = 2·0 c/s). The small value of the J_{HCCH} suggests an axial-equatorial or di-equatorial interaction ($\phi \cong 60°$) in a half-chair conformation of the ring.[27] On the other hand the existence of a significant coupling between the OH and H-5 implies $\phi \cong 180°$ or 0°.[31] The combination of these two findings is indicative of a predominant half-chair conformation with a *cis* configuration of H-6 (equatorial) and H-5 (axial) and a *trans* relationship of OH and H-5 (both axial). We will call this isomer the "*trans*" epimer.

The spectrum of VIa after a short period of time, registers a diminution of all the signals except the aromatic ones, together with a simultaneous appearance of new lines. This process stops after a few hours, when the disappearance of the first spectrum is about 50%. The new lines in the spectrum clearly correspond to what one would expect from the other possible diastereoisomer of VIa, arising from the epimerization at the anomeric centre C-6, which we call the "*cis*" epimer. In fact the new spectrum (Fig. 1B) shows a doublet at 0·97 ppm (J = 6·6 c/s) for the Me; the H-6 gives rise to a doublet of doublets (apparently a triplet) centred at 4·98 ppm (J_{HCCH} = 4·4 c/s; J_{HCOH} = 4·8 c/s) and the OH appears as a doublet at 7·05 ppm (J = 4·8 c/s). On treatment with D_2O the doublet disappears, while the signal at 4·98 changes into a doublet (J = 4·5 c/s). The value of $J_{H-5,H-6}$ is too low for a *trans* diaxial interaction which one should expect if a predominant chair conformation with the largest groups in an equatorial position were postulated. On the other hand this low

* The LAH reduction of VIa to the γ-hydroxyketoxime XVa is a further proof against the N-oxide structure XI. In fact nitrones are known to be reduced by LAH to the corresponding secondary amines[21b] or hydroxylamines.[21c]

† It is well known[27–30] that DMSO-d_6 is a very useful solvent for the NMR spectroscopy of hydroxylic compounds because DMSO reduces the rate of proton exchange. Consequently this solvent facilitates the separation of the signals arising from different hydroxyls and permits observation of hydroxyl protons splitting.

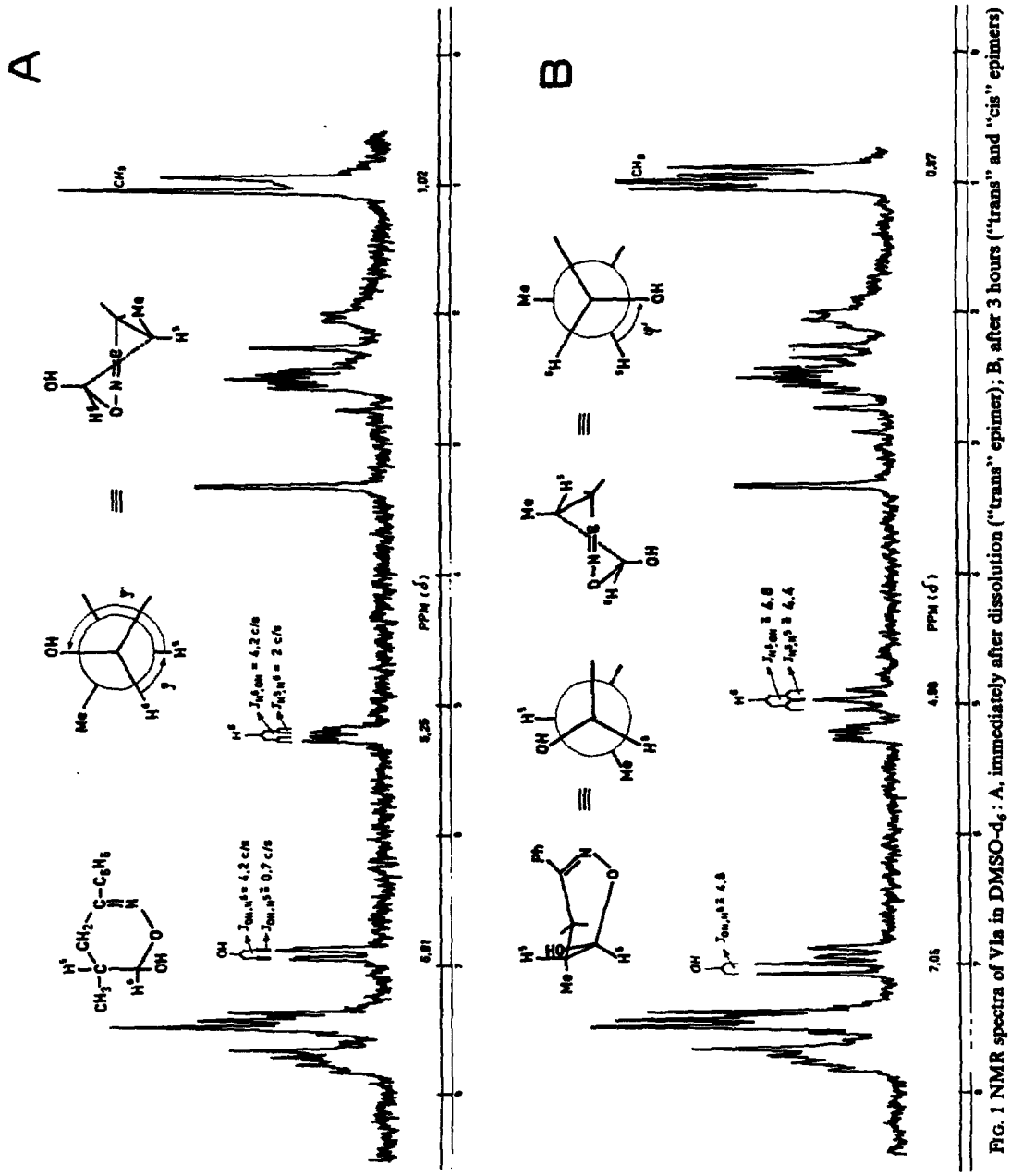


FIG. 1 NMR spectra of VIa in DMSO-d_6; A, immediately after dissolution ("trans" epimer); B, after 3 hours ("trans" and "cis" epimers)

value could be possible in a boat conformation.* Moreover one can not exclude a substantial contribution of a chair conformation with both OH and Me predominantly in a *trans* diaxial position. In this case the dihedral angle ϕ' ($\sim 60°$) between OH and H-5 should justify the absence of J_{HCCOH}.[31] A trace of TFA added to a fresh solution of VIa in DMSO-d_6 speeds up the epimerization which is the 1:1 equilibrium in a few seconds, whereas a solution of VIa in pure TFA shows only one of the two epimers (or both epimers in a very fast equilibrium). The same 1:1 equilibrium between the two epimers of VIa is reached very rapidly in $CDCl_3$, benzene-d_6 and pyridine-d_5, as revealed by NMR measurements, even in absence of a trace of TFA. The strong retardation of the epimerization in DMSO is in line with the observed inhibition induced by this solvent in the related phenomenon of mutarotation of sugars.[29] No trace of the tautomeric open chain form (the possible intermediate in the epimerization) could be detected in solution, either by NMR (lack of any —CHO and oximic protons) or by IR measurements (lack of any C=O band in $CHCl_3$ solution).

The rapid epimerization of VIa in many solvents accounts for the fact that only one of the two possible diastereoisomers, evidently the less soluble, could be isolated from its solutions by crystallization.

Compound VIb is similar in behaviour to VIa. The NMR spectrum in DMSO-d_6 (Table 3) shows a slow equilibration between the two possible anomers analogous to that observed for VIa. The spectrum of the compound, registered immediately after the dissolution, shows almost exclusively the signals of only one of the two epimers, precisely the "*trans*" one, as shown by the presence of a significant J_{HCCOH}. The *trans/cis* ratio at equilibrium, reached after a few hours at room temperature, was 56:44.

As for VIc and VIh, both devoid of the asymmetric centre at C-5, their NMR spectra in DMSO-d_6 and in $CDCl_3$ (Table 3) shows the existence of a unique species for both compounds. Here also, as for VIa and VIb, no tautomeric open chain form was observed by NMR and IR measurements.

Even VIf, even though possessing two dissymmetric centres, probably exists in solution as a sole cyclic species, as shown by IR (no C=O band in $CHCl_3$ solution) and and by NMR (only one slightly broadened OH signal (1 H) at 6·08 ppm in DMSO-d_6).

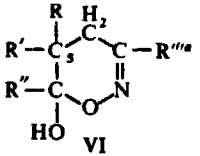
An equilibrium between cyclic and open chain form was observed in solution in the case of VId and VIg. The IR spectra of these compounds, devoid of any C=O band in nujol, shows a strong carbonyl absorption near 1700 cm^{-1}, when dissolved in $CHCl_3$ or DMSO. The NMR spectra in DMSO-d_6, taken immediately after dissolution, shows only one OH signal at ~ 6 ppm, corresponding to the cyclic form. A slow decrease in this signal was then observed together with a simultaneous appearance of another OH signal at ~ 11 ppm. At the equilibrium, reached after a few hours, the ratio of the former *versus* the latter signal is 41:59 for VId and 36:64 for VIg, the sum of the two signals integrated for 1 H. The peak at 11 ppm clearly corresponds to the oximic open chain form V of the oxazines. The value of the chemical shift is in accord with the report[30, 2] that OH protons in aromatic oximes fall at 11–12·5 ppm.† No evidence for any appearance of the other possible epimer was obtained, as no other OH peak appears in the spectra, either of VId and VIg, even after two days.

A similar tautomeric equilibration was also shown by the product of hydrolysis of

* Boat forms in cyclohexene do not usually differ much from chair forms in energy.[32]

† See also the spectra of IIIf–h, Ve, Vi, XVa and XVc.

TABLE 3. NMR SPECTRA OF 6-HYDROXY-5,6-DIHYDRO-1,2,4*H*-OXAZINES



VI

Compound	solvent	Chemical shift, δ, ppm; J, c/s											
		R		R'		J	R''		$J_{H'OH}$	$J_{H-5'H-6}$	OH	$J_{OH'H-6}$	$J_{OH,H-5}$
VIa cis[b]	DMSO-d_6	H		CH_3	0·97 (d)	6·6	H	4·98 (dd)	4·8	4·4	7·05 (d)	4·8	0
VIa trans[b]	DMSO-d_6	H		CH_3	1·02 (d)	6·0	H	5·25 (dd)	4·2	2·0	6·91 (dd)	4·2	0·7
VIa[c]	$CDCl_3$	H		CH_3	1·03 (d)	6·8	H	5·17 (d)		3·4	4·03		
					1·12 (d)	6·0		5·37 (d)		2·0	4·28		
VIa[c]	benzene-d_6	H		CH_3	0·80 (d)	6·1	H	5·03 (d)		3·6			
					0·89 (d)	6·0		5·22 (d)		2·3	4·4–5·3		
VIa[c]	pyridine-d_6	H		CH_3	1·10 (d)	6·7	H	5·42 (d)		4·3			
					1·21 (d)	5·5		5·67 (d)		2·3			
VIa	CF_3COOH	H		CH_3	1·32 (d)	6·8	H	5·87 (d)		2·3			
VIb cis[b]	DMSO-d_6	H		C_2H_5			H	5·08 (m)	4·7	4·5	7·04	4·6	0
VIb trans[b]	DMSO-d_6	H		C_2H_5			H	5·31 (dd)	4·0	1·7	6·89	4·0	0·7
VIb[c]	$CDCl_3$	H		C_2H_5			H	5·30 (m)		3·0[d]	4·06 (m)		
								5·48 (m)		1·8[d]	3·80 (m)		
VIc	DMSO-d_6	CH_3	0·90 (s)	CH_3	1·02 (s)		H	4·87 (d)	4·1		6·93 (d)	4·1	
VIc[e]	$CDCl_3$	CH_3	1·06 (s)	CH_3	1·12 (s)		H	5·02 (s)			3·7–4·2		
VId	DMSO-d_6	H		CH_3			C_2H_5				6·14 (d)		1·2
VIe	DMSO-d_6	H			—$(CH_2)_3$—						6·62		
VIf	DMSO-d_6	H			—$(CH_2)_4$—						6·08		
VIg	DMSO-d_6	H			—$(CH_2)_5$—						6·18		
VIh[f]	$CDCl_3$	CH_3	0·98 (s)	CH_3	1·10 (s)		H	5·01 (s)			4·1–4·5		

[a] R''' = C_6H_5 for VIa–VIg; R''' = p.BrC_6H_4 for VIh.

[b] "*cis*" and "*trans*" relationship between OH and H-5.

[c] When two signals for one group are reported, they correspond to the *cis* and *trans* epimers. The analysis of the spectrum did not permit which signal to attribute to which epimer.

[d] Measured after exchange with D_2O.

[e] The methylene protons appear as an AB system (δ_A = 2·25; δ_B = 2·60; J_{AB} = 17 c/s).

[f] The methylene protons appear as an AB system (δ_A = 2·18; δ_B = 2·53; J_{AB} = 17·5 c/s).

the immonium salt IIIe, which exists in the solid in the open chain form Ve (strong carbonyl band at 1745 cm^{-1}). The NMR spectrum in DMSO-d_6, immediately after dissolution, shows the oximic OH peak at 11·2 ppm. A slow equilibration then takes place, whereby a certain amount (~10%) of the tautomeric cyclic form VI was obtained, as shown from the appearance of a small OH peak (~0·1 H) at 6·62 ppm, together with a consistent decreasing of the peak at 11·2 ppm.

On the contrary, no trace of any tautomeric equilibrium could be detected for the mono oxime Vi which exists only in the open chain form both in solid (C=O band at 1695 cm^{-1}) and in DMSO-d_6 solution (only one peak at 10·2 ppm).†

Chemical behaviour

The chemical behaviour of the immonium salts III and 1,2-oxazines VI is consistent with the proposed structures.

When a cold solution of IIIf in anhydrous methanol was percolated through a basic ion-exchange resin, a compound was obtained of formula $C_{18}H_{24}N_2O$ (analysis and mass spectrum) whose IR spectrum did not show either the band at 1670 cm^{-1} ($C=\overset{+}{N}$) or the OH band in the 3000 cm^{-1} region. Its NMR spectrum in $CDCl_3$ is in accord with the structural formula IVf [M(12 H) between 1·1 and 2·0 ppm; M(3 H) at 2·0–2·7 ppm, for the $CH-CH_2-C=N$ group; M(4 H) at 2·7–3·1 ppm, for the CH_2-N-CH_2 protons; M(5 H) at 7·2–7·9 ppm (aromatics)]. Evidently IVf originated from an intramolecular attack of the oximate anion on the $C=\overset{+}{N}$ group, the high yield of the reaction showing the oximate anion to be a much more powerful nucleophile than methanol.

When dissolved in aqueous ethanol IVf underwent hydrolysis, giving VIf.

The chemical behaviour of 6-hydroxy-5,6-dihydro-1,2,4*H*-oxazines has been investigated mainly via VIa (Chart 2). Acetylation of this compound with acetic

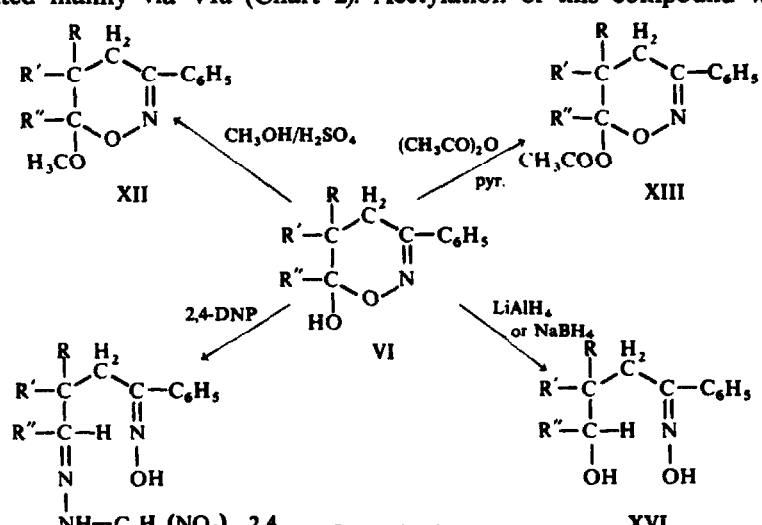


CHART 2

† The OH proton of cyclohexanone oxime falls at 10·02 ppm.[30]

anhydride in pyridine gave a mixture of two epimeric acetates (XIIIa), as shown by the NMR spectrum of the reaction mixture in $CDCl_3$: two Me doublets overlapped at 1·12 ppm (J = 0·7 c/s); two Ac singlets overlapped at 2·08 ppm; two doublets of the anomeric protons at 6·19 ppm (J = 2·5 c/s) and 6·38 ppm (J = 1·9 c/s) in a 4:1 ratio. The ratio of the two epimers did not change appreciably after crystallizatior from hexane.

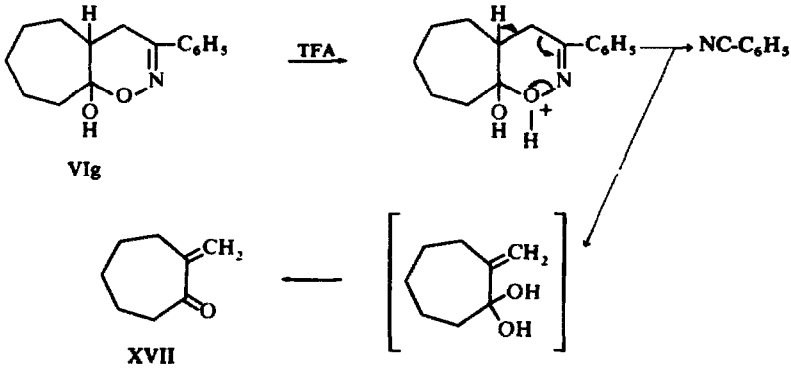
Compound XIIIa gave two different spots on TLC. Yet an attempt of separation by chromatography on silica gel failed.

On treatment with anhydrous methanol in presence of sulphuric acid VIa afforded a 2:3 mixture of the two epimeric methyl ethers (XIIa), as shown by the NMR spectrum. In this case one of the two epimers could be obtained in pure form after preliminary chromatography on silica gel: the liquid mixture of the two isomers obtained from the chromatography solidified in part on standing. The crystals resulted to be the less abundant isomer. Its NMR spectrum in $CDCl_3$ shows a doublet for the CH_3—C at 1·10 ppm (J = 6·1 c/s), a singlet for the MeO at 3·47 ppm and a doublet for the anomeric proton at 4·84 ppm (J = 2 c/s). The corresponding signals of the other epimer, determined from the spectrum of the mixture, are a doublet at 1·07 ppm (J = 6·7 c/s), a singlet at 3·50 ppm and a doublet at 4·70 ppm (J = 2·5 c/s).

The gas chromatography of the mixture of the methyl ethers did not permit the separation of the second epimer, as both anomers show the same retention time.

Both LAH and $NaBH_4$ reductions of VIa afforded the corresponding open chain γ-hydroxy ketoxime XVIa. Similar treatment of VIc with LAH afforded the oxime XVIc. On treatment with 2,4-dinitrophenylhydrazine in acidic (HCl) ethanol, VIa gave the 2,4-DNP XVa of the corresponding open chain aldehyde. VIa, VIb and VIc gave positive Fehling and Tollens tests.

An interesting reaction was observed when a solution of VIg in cold DMSO-d_6 was treated with TFA: a spontaneous heating took place and the NMR spectrum of the solution does not show any signals of VIg; instead two doublets of an AB system appear at 5·31 and 5·91 ppm ($J \cong 2$ c/s), each integrating for 1 H, the former showing further long range coupling; the pattern and the chemical shifts, characteristic of a methylene on a quaternary C atom, suggest that a Beckmann fragmentation had occurred similar to that observed with certain oximes containing a tertiary α-carbon or other groups having exceptional stability as cations.[33–34] The reaction can be outlined as follows:



Actually, when the reaction was repeated on larger amounts of VIg, a mixture of benzonitrile and 2-methylenecyclohexanone XVII was isolated, identified by IR spectrum and by mass/VPC analysis.

An attempt to repeat this reaction using VIf in DMSO and TFA failed, the product being substantially unaffected.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined on a Beckmann DK2 spectrophotometer in 95% EtOH; λ_{max} (nm) and ε are reported. IR spectra were determined in nujol with a Perkin–Elmer Mod. 137 Infracord spectrophotometer. Only predominant peaks are reported (cm^{-1}). NMR spectra were recorded on a Varian A-60 instrument. Chemical shifts were measured in ppm (δ) from TMS as internal standard. Mass spectra were measured on a Hitachi–Perkin–Elmer RMU6D (single focus) spectrometer at 70 eV. Combination mass/VPC experiments were performed on a 270 Perkin–Elmer spectrometer with I.P. 80 V and C.T. 250°, using a column filled with Bentone 34-Carbowax 20M at 120° (He as a carrier gas). TLC were performed on silica gel HF_{254} (Merck-Darmstadt) using hexane–ether as solvent. Column chromatography on silica gel 0·05–0·20 mm (Merck Darmstadt).

Immonium salts IIIe, IIIf *and* IIIg *from the reaction of* ω-*bromoacetophenone oxime*

(a) *With* 1-N-*pyrrolidinocyclopentene.* To a soln of ω-bromoacetophenone oxime[3] (19·8 g, 0·09 mole) in dry benzene (250 ml) 1-N-pyrrolidinocyclopentene[35–36] (12·0 g, 0·09 mole) was added with stirring at room temp. Heat evolution was observed and an oily ppt of IIIe was obtained which solidified on standing. The crystals (31·5 g, 100% yield) were purified by rapid crystallization from a little EtOH or anhyd MeOH; m.p. 203°; NMR (DMSO-d_6): 1·2–2·3 (8H,m, 2 C—CH_2CH_2—C), 2·5–3·4 (m's overlapped with solvent signals), 3·4–4·2 (4H,m,CH_2—$\overset{+}{N}$—CH_2), 7·2–8·0 (5H,m,C_6H_5), 11·7 (1H,s,OH). (Found: C, 58·7; H, 6·7; N, 8·1. $C_{17}H_{23}BrN_2O$ requires: C, 58·1; H, 6·6; N, 8·0%).

(b) *With* 1-N-*pyrrolidinocyclohexene.* By the same procedure as under (a), IIIf was obtained in 70% yield from 4·0 g (0·026 mole) of 1-N-pyrrolidinocyclohexene;[36] m.p. 208° from anhyd MeOH; IR 3030, 2990, 1655, 1450, 1050, 960, 918, 778, 705. (Found: C, 59·2; H, 6·6; Br, 22·2; N, 7·6. $C_{18}H_{25}BrN_2O$ requires: C, 59·2; H, 6·9; Br, 21·9; N, 7·7%).

(c) *With* 1-N-*pyrrolidinocycloheptene.* By the same procedure as under (a) IIIg was obtained in 47% yield from 18·0 g (0·082 mole) of 1-N-pyrrolidinocycloheptene;[37] m.p. 218° from anhyd MeOH; UV 250 (11660); IR 3090, 2980, 1655, 1450, 1430, 1380, 1290, 1000, 965, 942, 775, 760, 695; NMR (DMSO-D_6): 0·9–2·3 (12H,m's,8H of cycloheptane + 4H of pyrrolidine), 2·5–3·5 (m's overlapped with solvent signals), 3·6–4·2 (4H,m,CH_2—$\overset{+}{N}$—CH_2), 7·2–8·0 (5H,m,C_6H_5), 11·7 (1H,s,OH). (Found: C, 59·8; H, 7·0; Br, 21·3; N, 7·3. $C_{19}H_{27}BrN_2O$ requires: C, 60·1; H, 7·2; Br, 21·1; N, 7·4%).

Treatment of IIIf *with basic ion-exchange resin.* A cold soln of IIIf (0·8 g, 0·0022 mole) in anhyd MeOH (100 ml) was passed through an excess of Amberlite IR 45 (BDH) previously washed with anhyd MeOH. Evaporation of MeOH under reduced press afforded 0·6 g (96% yield) of IVf; m.p. 105° from hexane–benzene; UV (hexane) 251 (11900); IR 2920, 1460, 1445, 1375, 1205, 1150, 1110, 980, 920, 908, 885, 763, 694. (Found: C, 76·3; H, 8·5; N, 9·9. $C_{18}H_{24}N_2O$ requires: C, 76·0; H, 8·5; N, 9·8%).

2-*Phenacylcylopentanone mono oxime* Ve. A soln of 21 g (0·06 mole) of IIIe in 90% aqueous EtOH (100 ml) was heated on a water bath for 15 min. After elimination of the solvent under reduced press the crude mixture was chromatographed. Hexane–ether 83/17 gave 4·4 g (27% yield) of Ve, as a viscous oil which solidified on standing; m.p. 57–60°; UV 245 (9600); IR 3220, 3080, 2910, 1740, 1540, 1450, 1330, 1300, 1155, 950, 925, 835, 765, 695. (Found: C, 71·7; H, 6·9; N, 6·3. $C_{13}H_{15}NO_2$ requires: C, 71·9; H, 7·0; N, 6·4%).

3-*Phenyl-9-hydroxy-5,6,7,8,9,10-hexahydro-1,2,4H-benzoxazine* (VIf). IIIf (0·5 g, 0·0014 mole) dissolved in water (30 ml) was kept at room temp overnight, giving a ppt of almost pure VIf; IR 3330, 2995, 1615, 1565, 1495, 1450, 1265, 970, 920, 908, 760, 695; Mass: M^+ 231, (M^+-OH) 214 *m/e*.

VIf was also obtained by hydrolysis of IVf (30 mg, 0·1 mmole) in EtOH–water 80/20 (1 ml) at room temp; after two days the crystalline ppt (10 mg, 43% yield) was collected and identified by m.p. and IR comparison.

3-*Phenyl-5,6-pentamethylene-6-hydroxy-5,6-dihydro-1,2,4H-oxazine* (VIg). By a similar procedure (see under VIf) VIg was obtained from 0·1 g of IIIg after one min boiling in water (10 ml). VIg (0·05 g, 77% yield) was isolated by extracting with ether and $CHCl_3$; IR 3380, 2930, 1460, 1440, 1370, 1255, 1180, 1160, 1055, 980, 955, 920, 910, 895, 753, 693; Mass: M^+ 245, (M^+-OH) 228, (M^+-H_2O) 227 *m/e*.

6-hydroxy-5,6-dihydro-1,2,4H-oxazines from the reaction of ω-bromoacetophenone oxime

(a) *With 1-N-piperidinopropene.* To a soln of 1-N-piperidinopropene[38] (4·0 g, 0·032 mole) in dry benzene (20 ml) a soln of ω-bromoacetophenone oxime (6·8 g, 0·032 mole) in the same solvent (30 ml) was added under stirring at room temp. A light ppt was formed. After several hr the solvent was removed under reduced press and the residue was heated in 95% EtOH (30 ml) for 15 min in a water bath. Removal of the EtOH under reduced press gave a residue that was chromatographed. Hexane–ether 80/20 gave VIa; Fehling and Tollens tests were positive; IR 3180, 2900, 1460, 1445, 1165, 1015, 945, 918, 885, 870, 775, 763, 692; Mass: M^+ 191, (M^+-H_2O) 173 *m/e.*

Hexane–ether 70/30 gave 0·5 g (7·2% yield) of the N-phenacylpiperidine *syn*(phenyl) oxime, m.p. 139°, identified by comparison with the data from the literature;[39] IR 2920, 2840, 1480, 1460, 1440, 1375, 1310, 1105, 1080, 993, 980, 958, 923, 918, 865, 760, 735, 712; M^+ 218, (M^+-OH) 201 *m/e.*

By the same procedure as under (a) were obtained:

(b) *Compound* VIb, *from* 1-N-*pyrrolidino*-1-*butene*[40] (3·5 g, 0·028 mole). Fehling and Tollens tests were positive; IR 3190, 2910, 1450, 1350, 1295, 1165, 1045, 962, 945, 915, 868, 785, 768, 695; Mass: M^+ 205, (M^+-H_2O) 187 *m/e.*

(c) *Compound* VIc, *from* 1-N-*pyrrolidino-isobutene*[40] (8·5 g, 0·068 mole). Fehling and Tollens tests were positive; IR 3180, 2930, 1470, 1450, 1385, 1105, 1000, 905, 775, 765, 695; Mass: M^+ 205, (M^+-OH) 188 *m/e.*

(d) *Compound* VId, *from* 3-N-*morpholino*-2-*pentene*[41] (7·4 g, 0·048 mole). The product was eluted from the column with hexane–ether 90/10; IR 3280, 2920, 1455, 1150, 1045, 1010, 945, 918, 769, 695; Mass: M^+ 219, (M^+-H_2O) 201 *m/e.*

3-p-*Bromophenacyl*-5,5-*dimethyl*-6-*hydroxy*-5,6-*dihydro*-1,2,4H-*oxazine* (VIh). Obtained by the same procedure as for VIa starting from *p*-bromophenacyl bromide oxime[42] (1·2 g, 0·004 mole) and 1-N-pyrrolidino-isobutene (1·0 g, 0·008 mole). Eluted from the column with hexane–ether 85/15. Fehling and Tollens tests were positive; IR 3250, 2920, 1460, 1070, 1005, 957, 935, 915, 862, 820; Mass: M^+ 285 and 283, (M^+-OH) 268 and 266 *m/e.*

Acetylation of VIa. VIa (0·50 g, 0·0026 mole) in Ac_2O (6 ml) and pyridine (1 ml) was kept at room temp for 14 hr. After the usual work up the crude acetate was chromatographed (hexane–ether 90/10) affording a mixture of "*cis*" and "*trans*" acetates XIIIa (0·41 g, 66% yield), m.p. 52–54°, from benzene–hexane; UV 245 (11500); IR 2900, 1745, 1450, 1370, 1240, 1135, 1040, 1030, 945, 930, 920, 765, 700; Mass: M^+ 233, (M^+-CH_3COOH) 173 *m/e.* (Found: C, 67·3; H, 6·3; N, 5·9. $C_{13}H_{15}NO_3$ requires: C, 66·9; H, 6·5; N, 6·0%).

Methylation of VIa. A soln of VIa (3·0 g, 0·0156 mole) and conc H_2SO_4 (0·3 ml) in dry MeOH (50 ml) was refluxed for 15 min. After the usual work up the crude reaction mixture was chromatographed. An oily mixture of "*cis*" and "*trans*" methyl ethers XIIa (1·9 g, 59% yield) was obtained by eluting with hexane ether 98/2. Upon standing (~1 month) crystals separated from the oil, corresponding to one of the two isomers, m.p. 59° from hexane–benzene; UV 245 (11800); IR 2900, 1490, 1475, 1445, 1360, 1345, 1195, 1095, 1070, 1040, 995, 930, 918, 890, 865, 763, 696; Mass: M^+ 205, (M^+-CH_3OH) 173 *m/e.* (Found: C, 70·6; H, 7·1; N, 6·7. $C_{12}H_{15}NO_2$ requires: C, 70·2; H, 7·4; N, 6·8%).

The oily portion, examined on VPC,* gave a unique peak. The material collected by preparative VPC† showed the NMR signals of both epimers.

β-Benzohydroxamylisobutyraldehyde 2,4-dinitrophenylhydrazone XVa. 1·0 g (0·0052 mole) of VIa was boiled with a soln of 2,4-dinitrophenylhydrazine (1·03 g, 0·0052 mole) in 95% EtOH (70 ml) and 1 ml of conc HCl for 5 min. The soln was left standing for 2 hr in the cold. The yellow ppt (0·95 g, 51% yield) on crystallization from EtOH gave pure XVa, m.p. 203°; UV 224 (18700), 291 (17·600), 342 (19500); IR 3260, 3180, 2910, 2850, 1630, 1580, 1530, 1510, 1450, 1410, 1340, 1300, 1260, 1195, 1140, 1055, 935, 833, 763, 690; Mass: M^+ 371 (<1%), (M^+-18) 353 *m/e.* (Found: C, 54·4; H, 4·6; N, 18·7. $C_{17}H_{17}N_5O_5$ requires: C, 55·0; H, 4·6; N, 18·9%).

LAH *reduction of* VIa. A soln of VIa (1·1 g, 0·0057 mole) and LAH (0·4 g, 0·01 mole) in dry ether (60 ml) was refluxed for 3 hr. After the usual work up the crude reaction mixture was purified by chromatography (hexane–ether 80/20) yielding 0·4 g (36% yield) of XVIa, m.p. 101° from benzene; UV 245 (11100); IR 3200, 2900, 1640, 1460, 1380, 1050, 1025, 955, 920, 778, 765, 703; NMR (DMSO-d_6): 0·81 (3H, d, J = 6·5 c/s, Me).

* A Fractovap GV apparatus (C. Erba, Milano) was used, equipped with a 2m × 6mm Pyrex column packed with SE-30 1% on Gas-Chrom P, at 150° (He).

† A Varian-Aerograph 90 P-3 apparatus was used, equipped with a 5′ × ¼″ column packed with Chromosorb w 60–80 mesh, at 172° (He).

1·4–2·1 (1H,m,CH—Me), 2·72 (2H,d,J = 7·0 c/s, CH_2—C=N), 3·1–3·4 (2H,m, changing into a doublet at 3·29, J = 6·0 c/s by addn of D_2O, CH_2O), 4·47 (1H,t,J = 5·1 c/s, C—OH), 7·2–7·8 (5H,m,C_6H_5), 11·1 (1H,s,N—OH); Mass: M^+ 193, (M^+-H_2O) 175 *m/e*. (Found: C, 68·4; H, 7·9; N, 7·2. $C_{11}H_{15}NO_2$ requires: C, 68·4; H, 7·8; N, 7·2%).

$NaBH_4$ *reduction of* VIa. A soln of VIa (0·50 g, 0·0026 mole) and $NaBH_4$ (0·60 g, 0·016 mole) in 95% EtOH (20 ml) was kept at room temp for 14 hr. The soln diluted with water and extracted with ether gave 0·45 g (90% yield) of XVIa (identified by m.p. and IR comparison with the product from LAH reduction).

LAH *reduction of* VIc. By the same procedure as for VIa, from 0·6 g of VIc 0·4 g (66% yield) of XVIc was obtained, m.p. 123° from benzene–EtOH; UV 242 (8400); IR 3180, 2900, 1615, 1450, 1390, 1300, 1265, 1030, 1020, 950, 778, 752, 700; NMR (DMSO-d_6): 0·73 (6H,s,2Me), 2·78 (2H,s,CH_2—C=N), 3·06 (2H,d,J = 5·5 c/s, changing into a singlet by addn of D_2O, CH_2O), 4·42 (1H,t,J = 5·5 c/s, C—OH), 7·2–7·8 (5H,m,C_6H_5), 11·1 (1H,s,N—OH); Mass: M^+ 207, (M^+-OH) 190, (M^+-H_2O) 189 *m/e*. (Found: C, 69·7; H, 8·4; N, 6·8. $C_{13}H_{17}NO_2$ requires: C, 69·5; H, 8·3; N, 6·8%).

Oximation of 2-*phenacylcyclohexanone*. A soln of 2-phenacylcyclohexanone[43] (0·65 g, 0·003 mole) in 95% EtOH (10 ml) was added to a soln of $NaOAc.3H_2O$ (0·42 g, 0·003 mole) and $NH_2OH.HCl$ (0·21 g, 0·003 mole) in 95% EtOH (30 ml). After 1 hr reflux the soln was diluted with water and extracted with ether and $CHCl_3$. From the collected extracts 0·65 g of crude oil was obtained that was chromatographed. By elution with hexane–ether 88/12 the mono oxime Vi (0·24 g, 35% yield) was obtained m.p. 118° from hexane; UV 242 (12300); IR 3230, 2910, 1695, 1450, 1410, 1380, 1340, 1310, 1295, 1205, 1195, 1005, 938, 752, 690; Mass: (M^+-H_2O) 213, $C_6H_5CO^+$ 105 *m/e*. (Found: C, 72·8; H, 7·6; N, 6·1. $C_{14}H_{17}NO_2$ requires: C, 72·7; H, 7·4; N, 6·1%). By elution with hexane–ether 84/16 the dioxime X (0·13 g, 17% yield) was obtained, m.p. 169° from benzene–hexane; UV 245 (9010); IR 3230, 2900, 1460, 1440, 972, 958, 948, 761, 688; Mass: M^+ 246, (M^+-OH) 229 *m/e*. (Found: C, 67·8; H, 7·3; N, 11·2. $C_{14}H_{16}N_2O_4$ requires: C, 68·3; H, 7·4; N, 11·4%).

Beckmann fragmentation of VIg. A soln of VIg (0·24 g) in trifluoroacetic acid (2 ml) was kept at room temp for 20 min, diluted with water, neutralized with 10% soln of KOH and distilled till 10 ml of distillate was collected. The distillate was extracted with benzene; the extracts, dried over Na_2SO_4 and cautiously evaporated, gave a liquid residue (35 mg) whose IR (neat) showed the bands of benzonitrile (2230, 1480, 1450, 762, 680) and the bands of methylenecycloheptanone[44] (1699, 1615, 1330, 1190, 1140, 1105, 943). Mass/VPC experiments confirmed most of the liquid to be a mixture of benzonitrile [M^+ 103, (M^+-CN) 77 *m/e*] and α-methylenecycloheptanone [M^+ 124, (M^+-CO) 96 *m/e*].

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