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RING-CHAIN TAUTOMERISM OF 1,3-OXAZOLIDINES PREPARED FROM NOREPHEDRINE AND NORPSEUDOEPHEDRINE

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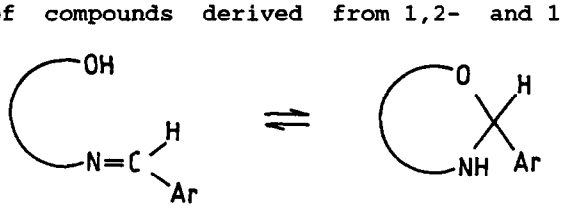
Abstract: The reactions of norephedrine and norpseudoephedrine with eleven different aromatic aldehydes led, in each case, to tautomeric equilibria consisting of two ring and one open-chain forms and obeying the equation: $\log K_X = \rho\sigma^+ + c$, where $\rho = 0.54\pm0.02$ and 0.53 ± 0.02 and $c = -0.36\pm0.02$ and $+0.34\pm0.02$, respectively. A connection was also found between the stereoselectivity of the ring-closures and the Hammett σ^+ constants.

Although condensations of ephedrine and pseudoephedrine with oxo compounds have been thoroughly investigated[2,3] relatively little attention has been paid to those of the nor-derivatives.[4-8] In the latter studies the ring-chain tautomerism has been mentioned only sporadically. The important role of this tautomerism in explaining the reactivity[9] and stereochemistry of these condensation reactions[10] and in their use as "prodrugs"[11] motivated a study on the 1,3-oxazolidines derived from norephedrine and norpseudoephedrine. At the same time the present work continues our systematic investigations[12-14] on the ring-chain tautomerism of compounds derived from 1,2- and 1,3-aminoalcohols and aldehydes:

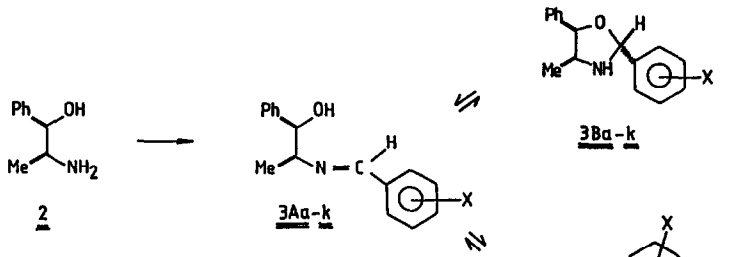


1A ⇌ 1B

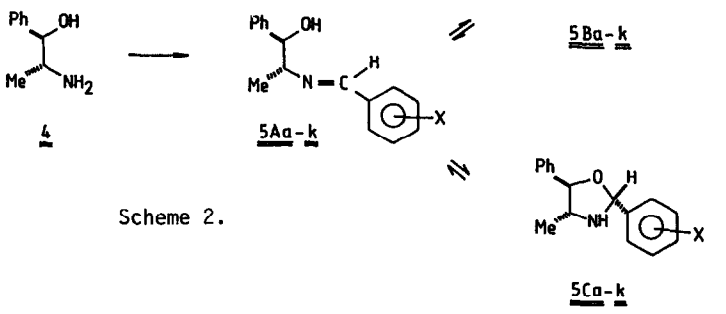
SYNTHESIS AND RESULTS

(±)-Norephedrine (**2**; Scheme 1) and (1R,2R)-norpseudoephedrine (**4**; Scheme 2) were allowed to react with aromatic aldehydes under very mild conditions; in Scheme 1 the reactions starting from (±)-norephedrine are shown only for the

(1R,2S)-enantiomer. The reactions took place quantitatively at ambient temperature.



Scheme 1.



Scheme 2.

A time-dependent ^1H NMR spectroscopic study on the product formation in $CDCl_3$ at 400 MHz unequivocally showed that a three-component equilibrium was attained in every case (Figs. 1 and 2, Table 1). The relative amounts of the ring and chain tautomers were determined from the integrals of the acetal and methine signals, respectively. The relative configurations of the ring forms of compounds **3** and **5** were confirmed by 2DNOE measurements.[15]

For tetrahydro-1,3-oxazines[12,13] and 1,3-oxazolidines[14], we recently established that the ring-chain tautomerism for their 2-aryl-substituted derivatives can be described by Equation (1):

$$\log K_X = \rho\sigma^+ + c \qquad (1)$$

where K_X = [ring]/[chain], σ^+ is the Hammett constant[16], and c is a constant characteristic of the ring system and the solvent used. Constant ρ does not depend on substitution of the hetero ring.[12-14] The solvent-dependence of ρ is not very strong, yet significant; at the same time, the value of the intercept c depends greatly on the nature of the solvent.[14] In

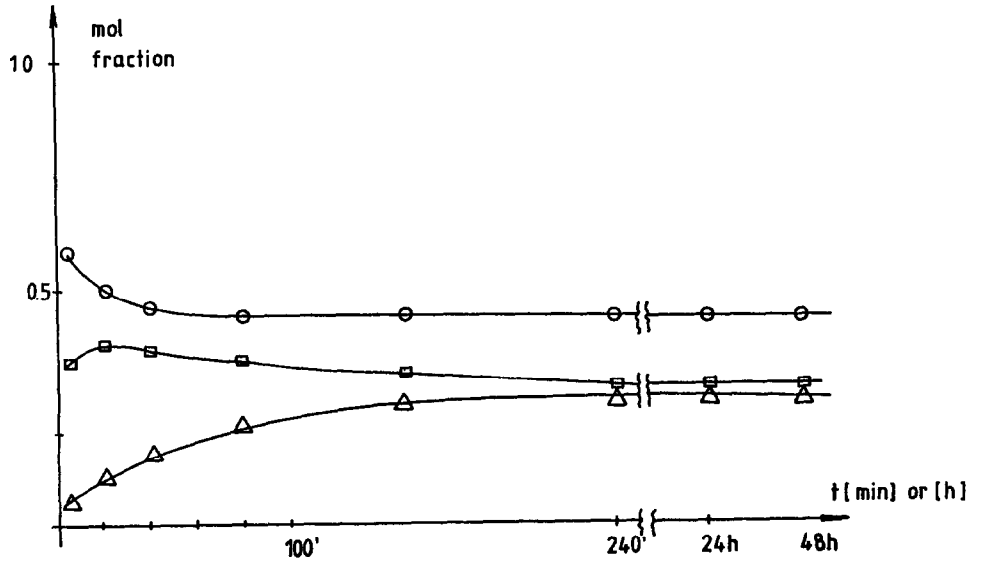


Figure 1. Time-dependent tautomerisation of compound 3a.

(o: 3Aa; □: 3Ba; Δ: 3Ca)

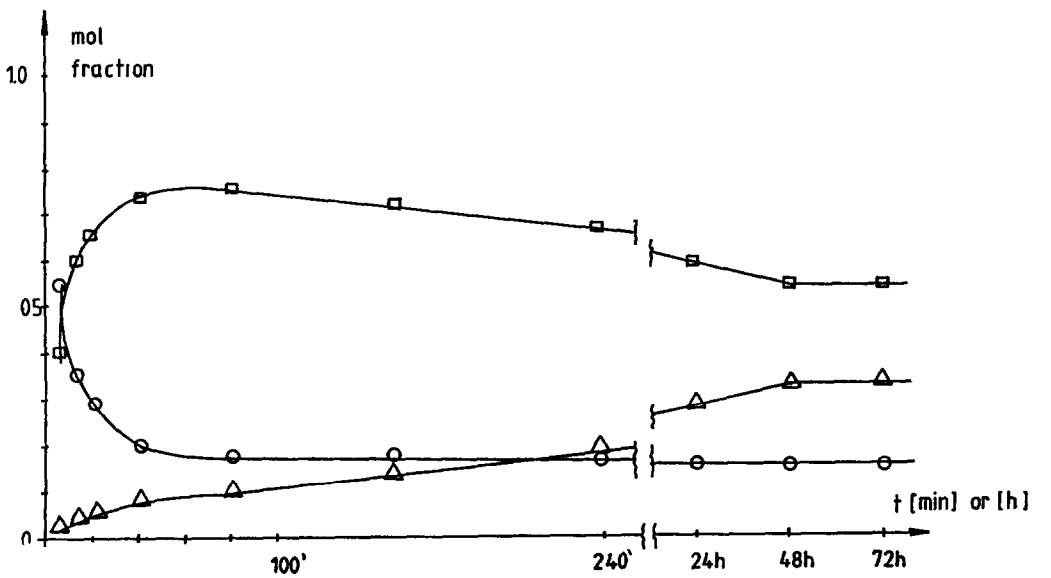


Figure 2. Time-dependent tautomerisation of compound 5a.

(o: 5Aa; □: 5Ba; Δ: 5Ca)

Table 1. Selected chemical shifts (ppm) and coupling constants (Hz) for compounds 3g and 5g[a]

No.	H-2	H-4	H-5	Me	$J_{4,5}$	$J_{4,4Me}$
3A	8.28	3.64	4.84	1.11	4.3	6.7
3B	5.63 (5.56)	3.65 (3.60)	5.13 (5.07)	0.78 (0.71)	7.9 (6.6)	6.7 (6.5)
3C	6.08	3.82	5.13	0.79	6.1	6.4
5A	8.30	3.52	4.68	1.14	6.7	6.4
5B	5.89 (5.87)	3.26 (3.23)	4.38 (4.35)	1.31 (1.27)	8.2 (8.0)	6.1 (6.1)
5C	5.76	3.22	4.46	1.32	6.4	6.4

[a]All chemical shifts and couplings are within 0.02 ppm and 0.2 Hz, respectively. Literature data[7] at 100 MHz shown in parentheses.

$CDCl_3$ ρ is 0.76±0.04 for tetrahydro-1,3-oxazines[12,13] and 0.57±0.03 for 1,3-oxazolidines.[14] Constant c, the intercept, is illustrative of the degree of ring-closure. A negative value for c indicates destabilization and a positive value stabilization of the ring form.[12]

In this work, the three-component tautomeric equilibria for the two sets (3 and 5) of seven p- and four m-substituted derivatives (Schemes 1 and 2, respectively) could also be characterized by Equation (1) [Fig. 1 and Tables 2 and 3]. From a comparison of the intercepts c for 3 and 5 it is obvious that the ring forms of 5 (derivatives of the erythro aminoalcohol) are considerably more stable than those of compounds 3 (Δc = 0.70, Tables 2 and 3).

Two-component ring-chain tautomeric equilibria are often attained very rapidly, within a few seconds.[14,17] In the present case, however, the equilibria were established relatively slowly and were also considerably dependent on the substituents.

The time-dependent formation of the equilibrium products was examined for four compounds (**3a**, **3k**, **5a**, and **5k**) in $CDCl_3$ solution. The equilibrium was established extremely fast for the (p-dimethylamino)phenyl-substituted derivatives **3k** and **5k**. The isomer and tautomer ratios determined immediately after dissolution were the same as those found after 24 hours. The formation

Table 2. Melting points and tautomer ratios for compounds 3a-k

No	X	M.p(°C) Solvent	Formula	σ^+	3A(%)	3B(%)	3C(%)	$\log \frac{[3B]+[3C]}{[3A]}$	$\frac{[B]}{[C]}$
3a	p-NO_2	100-101 hexane	$C_{16}H_{16}N_2O_3$	0.79	44.0	29.1	26.9	0.105	1.08
3b	p-CN	104-105 hexane	$C_{17}H_{16}N_2O$	0.659	45.7	28.5	25.8	0.075	1.10
3c	m-CF_3	oil	$C_{17}H_{16}I_3NO$	0.52	58.6	22.9	18.5	-0.151	1.24
3d	m-Br	oil	$C_{16}H_{16}BrNO$	0.405	62.1	21.4	16.5	-0.215	1.30
3e	m-Cl	oil	$C_{16}H_{16}ClNO$	0.399	60.9	22.6	16.5	-0.193	1.37
3f	p-Cl	83-84 hexane	$C_{16}H_{16}ClNO$	0.114	64.6	22.2	13.2	-0.261	1.68
3g	H	85-86 hexane	$C_{16}H_{17}NO$	0	67.3	21.5	11.2	-0.314	1.92
3h	m-CH_3	oil	$C_{17}H_{19}NO$	-0.066	73.7	17.3	9.0	-0.448	1.93
3i	p-CH_3	56-57 hexane	$C_{17}H_{19}NO$	-0.311	75.5	16.9	7.6	-0.489	2.22
3j	p-OCH_3	oil	$C_{17}H_{19}NO_2$	-0.778	85.0	10.5	4.5	-0.753	2.33
3k	p-$N(CH_3)_2$	135-137 hexane	$C_{18}H_{22}N_2O$	-1.7	95.1	3.6	1.3	-1.288	2.77

$\log K_X = (0.54\pm0.02)\ \sigma^+ - (0.36\pm0.02)$

Table 3. Melting points and tautomer ratios for compounds 5a-k

No.		M.p. (°C) Solvent	Formula	σ^+	5A(%)	5B(%)	5C(%)	log $\frac{[5B]+[5C]}{[5A]}$	$\frac{[B]}{[C]}$
5a	p-NO_2	103-104 hexane	$C_{16}H_{16}N_2O_3$	0.79	14.2	53.6	32.2	0.781	1.66
5b	p-CN	99-100 hexane	$C_{17}H_{16}N_2O$	0.659	15.0	52.7	32.3	0.753	1.63
5c	m-CF_3	oil	$C_{17}H_{16}F_3NO$	0.52	21.8	53.6	24.6	0.555	2.18
5d	m-Br	oil	$C_{16}H_{16}BrNO$	0.405	24.9	52.9	22.2	0.479	2.38
5e	m-Cl	oil	$C_{16}H_{16}ClNO$	0.399	23.1	53.5	23.4	0.522	2.29
5f	p-Cl	126-127 hexane	$C_{16}H_{16}ClNO$	0.114	26.8	50.8	22.4	0.436	2.27
5g	H	106-107 hexane	$C_{16}H_{17}NO$	0	30.2	50.8	19.0	0.364	2.67
5h	m-CH_3	oil	$C_{17}H_{19}NO$	-0.066	35.3	48.6	16.1	0.263	3.02
5i	p-CH_3	98-99 hexane	$C_{17}H_{19}NO$	-0.311	39.3	44.4	16.3	0.189	2.72
5j	p-OCH_3	157-159 ethanol	$C_{17}H_{19}NO_2$	-0.778	52.0	35.0	13.0	-0.035	2.69
5k	p-$N(CH_3)_2$	160-161 ethanol	$C_{18}H_{22}N_2O$	-1.7	78.9	16.0	5.1	-0.573	3.13

$\log K_X = (0.53\pm0.02)\ \sigma^+ + (0.34\pm0.02)$

of the equilibrium mixture was much slower for the 2-(p-nitrophenyl) derivatives **3a** and **5a**. A constant tautomer ratio for the erythro derivative **3a** was attained in about 4 hours (Fig. 1). In the case of the threo counterpart **5a** the tautomeric equilibrium was established in about 48 hours at ambient temperature (Fig. 2).

Spassov et al.[18] studied the tautomerism of a mixture of oxazolidine Schiff bases prepared from erythro- and threo-2-(furyl)serine methyl ester and furfural. In contrast with the observations described in this work, they reported the formation of a two-component tautomeric mixture for the erythro isomer, whereas the threo isomer gave, similarly as in our results, two cyclic C-2 epimers in equilibrium with the open-chain form. They stated that the establishment of the tautomeric equilibria required about 4 hours in $CDCl_3$ at room temperature. Therefore the 2-furyl-substituted derivatives of norephedrine and norpseudoephedrine were synthesized and three-component tautomeric equilibria were found in both cases: **3A:3B:3C** = 84:10:6 and **5A:5B:5C** = 63:24:14.

The relative amounts of the cyclic form, i.e. the stereoselectivity of the ring closure reactions of **3** and **5**, showed interesting trends in both cases. In the erythro series the ratio [B]/[C] (Table 3) is just above 1 for the p-nitrophenyl and 2.77 for the (p-dimethylamino)phenyl substitution. In other words, this ratio depends almost linearly on the Hammett σ^+ constants (r = -0.962). The threo series behaved similarly (Table 3; r = -0.812).

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Jeol GX-400 FT NMR spectrometer in $CDCl_3$. The experimental details were given earlier.[12] Melting points (Tables 2 and 3) are uncorrected. All compounds prepared gave correct elemental analyses (within ±0.4% C,H,N).

Reactions of norephedrine and norpseudoephedrine with aromatic aldehydes. The aminoalcohol, **2** or **4** (151 mg; 1 mmol), was dissolved in ethanol (10 ml) and an appropriate aromatic aldehyde (1 mmol) was added. After standing for 2-3 h at room temperature, the solvent was evaporated off and the products were crystallized. The derivatives of m-substituted aldehydes were oils, which, after being dried for 2 h in a vacuum desiccator, gave correct analytical data.

Reactions of norephedrine and norpseudoephedrine with furfurol. The reactions

were performed as above. Mp's (after crystallization from hexane) were 100-101 and 67-68 °C, respectively.

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