Hydride Reductions of 1-Phenyl-1-nonen-3-one: Mass Spectrometry of 1-Phenyl-1-nonen-3-ols and Relative Stereochemistry of the Diastereoisomeric 4-Dimethylaminomethyl-1-Phenyl-1-nonen-3-ols[1]

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WESLEY GORDON TAYLOR and JONATHAN RICHARD DIMMOCK. Can. J. Chem. **52**, 2522 (1974).

The metal hydride reduction products of some styryl ketones and dimethylaminomethyl Mannich bases have been investigated. Sodium borohydride selectively attacked the carbonyl carbon atom to give the desired allylic alcohols. Reduction of 1-phenyl-1-nonen-3-one with lithium aluminum hydride gave 1-phenyl-3-nonanol which represents the conjugate addition product. Fragmentations of 1-phenyl-1-nonen-3-ol were compared to the modes of mass spectral breakdown of 4-phenyl-3-buten-2-ol, an allylic alcohol which is known to behave like a saturated ketone on electron bombardment. Peaks corresponding to the McLafferty ion and the loss of a methyl radical from this rearrangement product were observed. Certain Mannich bases were reduced to diastereoisomeric allylic amino alcohols. The separation, ^{1}H n.m.r. spectroscopy, and relative stereochemistry of the diastereoisomers are discussed.

WESLEY GORDON TAYLOR et JONATHAN RICHARD DIMMOCK. Can. J. Chem. **52**, 2522 (1974).

On a examiné les produits de la réduction par les hydrures métalliques de quelques styryles cétones et de leurs bases de Mannich diméthylaminométhylées. Le borohydrure de sodium attaque d'une façon sélective le groupement carbonyle et conduit aux alcools allyliques désirés. La réduction de la phényl-1 nonèn-1 one-3 par l'hydrure double de lithium et d'aluminium conduit aux phényl-1 nonanol-1; ceci correspond au produit d'addition conjugué. On a comparé les modes de fragmentations du phényl-1 nonèn-1 ol-3 avec les modes de coupures en spectrométrie de masse du phényl-4 buten-3 ol-2, un alcool allylique connu pour réagir comme une cétone saturée lors du bombardement électronique. On a pu observer les pics correspondants à l'ion de McLafferty et à celui correspondant à la perte d'un radical méthyle provenant du produit de réarrangement. Certaines bases de Mannich se réduisent en aminoalcools allyliques diastéréoisomères. On discute de la séparation, de la r.m.n. du proton et de la stéréochimie relative des diastéréoisomères. [Traduit par le journal]

Introduction

The synthesis and mass spectral characteristics of the α, β-ethylenic ketones **1** required for this work have been reported (1). Nuclear substituted dimethylaminomethyl Mannich bases **2** were prepared (2) and these water-soluble styryl ketones have been evaluated for *in vitro* and *in vivo* anticancer activity by established procedures (3). In attempts to alter the polarized olefinic system in the conjugated ketones while maintaining the rigid stereochemistry of the ethylenic bond, the allylic alcohols **3** and allylic amino alcohols **4** were prepared (Scheme 1) for testing in experimental tumor screens.[4]

Current interest in unsaturated alcohols as possible anticancer agents has stemmed from the requirements for an allylic ester functional group in tumor-inhibitory members of the pyrrolizidine alkaloids (4). These allylic aminoesters are thought to function as biological alkylating agents by a mechanism involving alkyl oxygen ester fission to give stable carbonium ions (5). More recently, Willette and Driscoll (6) have studied synthetic allylic esters as acyclic model compounds of the pyrrolizidine alkaloids. For the same reason, we have prepared and tested[4] a series of substituted allylic esters, two of which (**3***b*-*p*-nitrobenzoate and **4***a*-*p*-nitrobenzoate) are described herein.

Based on early literature reports, the choice of metal hydride reducing agent for synthesizing unsaturated alcohols from cinnamyl derivatives is sodium borohydride (7) because lithium aluminum hydride may lead to reduction of the ethylenic bond (8). Conjugate addition by sodium

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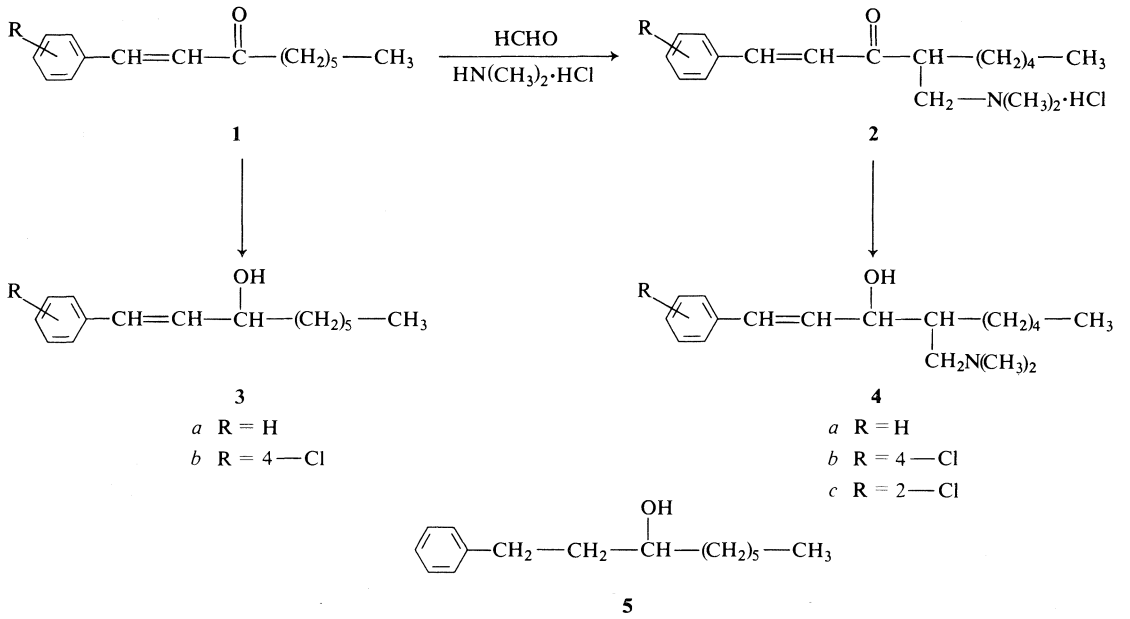
[4]The antineoplastic activity and other pharmacological activities of these alcohols will be reported elsewhere.



SCHEME 1

borohydride to give saturated alcohols, however, represented a substantial competing process in a more recent study of the metal hydride reductions of β-alkyl-α,β-unsaturated ketones (9). In fact, lithium aluminum hydride emerged as a better agent than sodium borohydride for preparing a series of allylic alcohols. To clarify the pattern of reduction with our olefinic ketones, and since the reduction of Mannich bases **2** is complicated by the formation of diastereoisomeric amino alcohols, we initially examined the styryl ketone **1***a* to determine a suitable reducing agent for preparing allylic alcohols from α,β-unsaturated ketones of these two particular types.

Results and Discussion

Reductions

Four metal hydrides were chosen for this study (Table 1) and they are listed in order of decreasing reducing power (10). Gas–liquid chromatography was employed in order to examine the ratio of carbonyl addition **3***a* to conjugate addition **5** products. It was found that lithium aluminum hydride reduction of the unsaturated ketone **1***a* gave the saturated alcohol **5** (>99%). As expected, olefinic proton signals were absent from the n.m.r. spectrum and i.r. spectroscopy revealed the absence of carbonyl stretching bands with hydroxyl stretching appearing at 3350 cm^{-1}.

As seen in Table 1, sodium borohydride proved to be the best reducing agent for synthesizing 1-phenyl-1-nonen-3-ol (**3***a*) from **1***a*. Reduction mixtures from the lithium borohydride and sodium trimethoxyborohydride experiments analyzed as multi-component mixtures although *ca.* 80% of **3***a* was detected by g.l.c. By avoiding reflux temperatures, sodium borohydride converted **1***a* to the allylic alcohol **3***a* (99%) whereas the saturated alcohol **5** represented 6% of the mixture when the methanol–water medium was heated under reflux prior to product isolation. Iqbal and Jackson (11) have likewise shown that the reductions of α,β-unsaturated ketone systems with sodium borohydride gave more of the allylic relative to the saturated alcohol when low reaction temperatures are employed. The aqueous methanol media is also desirable in order to prevent solvent addition to the β-carbon atom (9).

Sodium borohydride smoothly reduced the 4-chloro ketone **1***b* to the allylic alcohol **3***b* (Scheme 1). The crude reduction mixture showed 97% of one component (g.l.c.) with 3% representing unreduced ketone and less than 0.5% of an unidentified component.

Mass Spectrometry

The fragmentation in **3***a* and *b* were somewhat predictable by reference to reported work (12, 13)

TABLE 1. Reductions of 1-phenyl-1-nonen-3-one

Metal hydride	Reducing agent/1-phenyl-1-nonen-3-one (mol)	Conditions		Solvent	Product analysis (%)*		
		Initial	Final		**3***a*†	**5**‡	Yield§ (%)
$LiAlH_4$	0.02/0.02	0° 20 min	3 h reflux	Et_2O	1	99	71
$LiBH_4$	0.01/0.01	0° 20 min	3 h reflux	Et_2O	85‖	2.5	77
$NaBH(OCH_3)_3$	0.052/0.01	0° 20 min	3 h reflux	Et_2O	79¶	2	70
$NaBH_4$	0.02/0.02	0° 30 min	24 h room temperature	MeOH–H_2O	99	1	77
$NaBH_4$	0.02/0.02	0°, then 24 h room temperature	8 h reflux	MeOH–H_2O	94	6	66

*By g.l.c. on the crude reduction products.
†1-Phenyl-1-nonen-3-ol, retention time 8.4 min.
‡1-Phenyl-3-nonanol, retention time 4.7 min. Authentic mixtures (2.0 and 4.0%) of **5** in **3***a* analyzed within ±0.2% of the expected values assuming an equal detector response factor for the two alcohols.
§Reported yields are based on crude material.
‖The remainder was a component with retention time of 11.4 min (2%), unreduced ketone (2.5%), and other lower retention time peaks (8%).
¶Also detected was a component with a retention time of 11.4 min (6%), unreduced ketone (6%), and several lower retention time peaks (7%).

on the mass spectra of other allylic alcohols. In this context, the alcohols gave spectra (Figs. 1 and 2) which were characteristic of unsaturated alcohol and saturated ketone mixtures.

In the first case, an allylic bond cleavage product which represented the base peak was observed. This ion (*a*) subsequently lost water to give peaks at *m/e* 115 and 149 for **3***a* and **3***b*, respectively. The removal of an *ortho* hydrogen atom in the allylic ion (*a*) has been considered as one route to ($a - H_2O$) (Scheme 2). In contrast to the ion ($a - H_2O$) process, the emanation of 18 mass units from the allylic alcohol molecular ions was not a favorable fragmentation (<2%) but the saturated alcohol **5**, Fig. 3, gave the ($M - H_2O$) ion at *m/e* 202 (23%). The α-cleavage ion (*a*), *m/e* 135, from **5** also expelled water to give an important peak at *m/e* 117.[5]

The generation of a saturated ketone molecular ion from the allylic alcohol molecular ion followed by fragmentation accounted for most of the remaining products (Scheme 2). In the case of 4-phenyl-3-buten-2-ol (*m/e* 105 = 100%; *m/e* 115 = 35%; *m/e* 133 = 35%), the two rearranged hydrogen atoms originated from the secondary carbon atom and the hydroxyl group (12). Fragment ions from **3***a* and **3***b* included the acylium ion (a_r), isomeric with the base peak (*a*), in addition to the McLafferty ion (b_r). The latter ion decomposed either to ion (a_r) by an unusual loss of a methyl group (14, 15) or to a substituted tropylium ion (*c*). Prominent peaks for the loss of one and two hydrogen atoms from ion (*c*) were

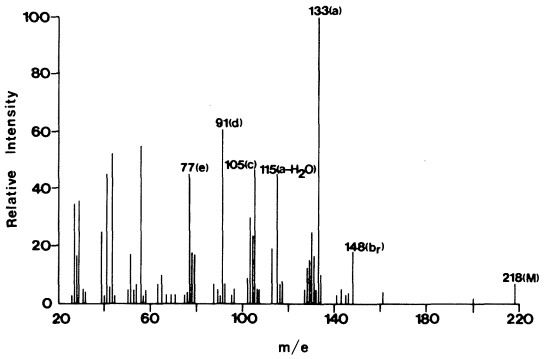


FIG. 1. Mass spectrum (70 eV) of **3***a*.

[5]Exact mass measurements and metastable transitions of the ions involved in the major fragmentation pathways of **3***a*, **3***b*, and **5** are available from the Depository of Unpublished Data, National Science Library, National Research Council of Canada, Ottawa, Canada K1A 0S2.

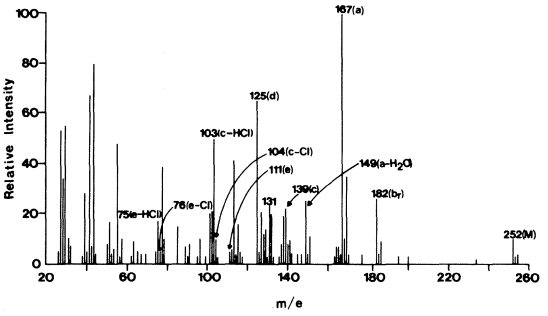


FIG. 2. Mass spectrum (70 eV) of **3***b*.

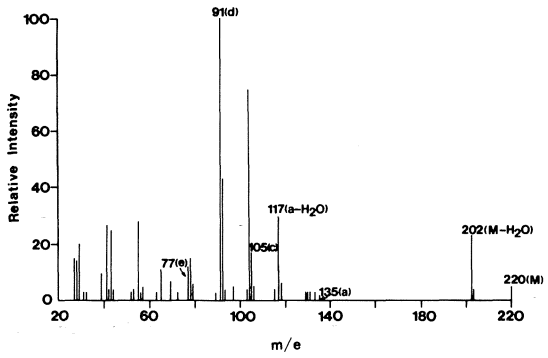


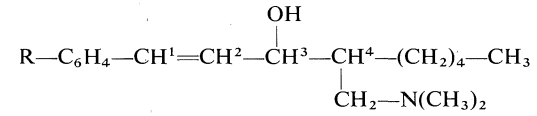
FIG. 3. Mass spectrum (70 eV) of **5**.

noted. With **3***b*, ion (*c*) and the phenyl cation (*e*) decomposed by losing a chlorine atom or hydrogen chloride. Peaks at *m/e* 131 and 132 may be due to the loss of hydrogen chloride or a chlorine atom from the McLafferty rearrangement product (1). Fragments in the region *m/e* 127 to 130 are unique to the allylic alcohols discussed since these ions were suppressed in the mass spectra of **5** (Fig. 3) and of 4-phenyl-2-butanone (12).

Stereochemistry

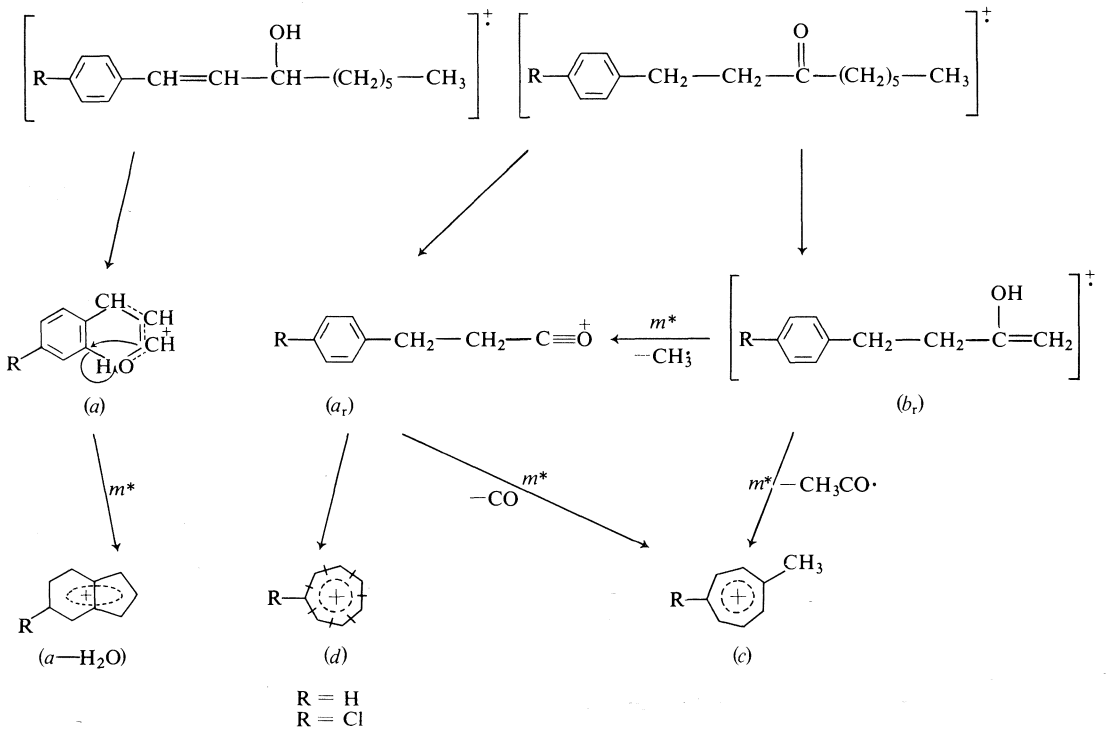
Since sodium borohydride selectivity reduced the carbonyl group of the ketones **1** and of related nonasymmetric α,β-unsaturated amino ketones (16, 17), this reagent was used to convert the available racemic Mannich bases **2** to the desired allylic amino alcohols **4** (Scheme 1). Reduction conditions were initially developed for **2***a* and, even after the required 3 h heating under reflux, there was obtained no evidence for sodium borohydride reduction of the ethylenic bond. The n.m.r. spectrum on crude **4***a* clearly revealed that diastereoisomeric allylic alcohols were present. In addition to the 10 lines evidenced from δ 5.85–6.87, the methine protons at C-3 appeared at δ 4.23 (ragged triplet) and at δ 3.98 (doublet of

TABLE 2. Nuclear magnetic resonance data for diastereoisomeric allylic amino alcohols



	Isomer	Ratio of isomers (%)	δ H^1	δ H^2	$J_{H}1_{H}2$	$J_{H}1_{H}3$	$J_{H}2_{H}3$	δ H^3	$W_{H}3$	$J_{H}3_{H}4$	Footnote reference
4*a*											
R = H	*threo*	67	6.63	6.08	15.5	1	4.5	4.23	9	3.5	*
			(6.77)	(6.20)	(15.5)	—	(4.5)	(4.77)	(10)	(4.5)	†
	erythro	33	6.52	6.02	15.5	—	6.5	3.98	16	8	*
			(6.60)	(6.15)	(15.5)	—	(7)	(4.17)	(18)	(9)	†
4*b*											
R = 4-Cl	*threo*	65	6.32	5.83	15	1	4.0	4.05	9	4	‡
			(6.80)	(6.27)	(16)	—	(4.5)	(4.87)	(11)	(6.5)	†
	erythro	35	6.15	5.73	15	—	6.0	3.78	16	7.5	‡
			(6.63)	(§)	(16)	—	(7.0)	(4.22)	(18)	(9)	†
4*c*											
R = 2-Cl	*threo*	70	‖	6.10	15.5	‖	4.5	4.28	10	3.5–5	‡
			‖	(6.15)	(15.5)	‖	(4.5)	(4.77)	(10)	(5.5)	†
	erythro	30	‖	6.00	15.5	‖	6.5	4.03	16	8	‡¶

*As 0.5 *M* solutions of the free base in carbon tetrachloride (D_2O added). The coupling constants and half-bandwidth measurements are expressed in Hz.
†In parentheses are given the corresponding values found in deuterochloroform for the hydrochloride salt (*threo* isomer) and the maleate salt (*erythro* isomer).
‡Data from the mixture of free bases.
§The lower field portion of this doublet of doublets was obscured by olefinic proton signal of maleic acid.
‖The H^1 signal appeared with the aromatic proton multiplet and hindered the observation of allylic coupling between H^1 and H^3. $J_{H}1_{H}3$ was identified in the other *threo* isomers by irradiating the H^3 signal.
¶An attempt at isolating the minor isomer as the maleate salt was unsuccessful. The n.m.r. data was then derived from the free base mixture.



SCHEME 2

doublets). On integration of H-3, the diastereoisomeric ratio of the amino alcohols was found to be 67:33.[6] Pertinent n.m.r. data for the three pairs of diastereoisomers are collected in Table 2.

Assignments of relative configurations to acyclic diastereoisomers (18, 19) has become possible from the Karplus (20) relationship between the magnitude of J and the dihedral angle separating vicinal protons. In the present work, assignments to **4** are made using i.r. and n.m.r. spectroscopy. Application is also made to the *RS* nomenclature wherein the **3***R*,**4***S*/**3***S*,**4***R* and **3***R*,**4***R*/**3***S*,**4***S* isomers implies, respectively, the *erythro* and *threo* configurations (21).

Because intramolecular hydrogen bonded conformational preferences of acyclic diastereoisomers may contribute more to conformational preferences which are constructed by considering nonbonded steric interactions of adjacent substituents (22, 23), it was important to confirm that the amino alcohols were internally hydrogen bonded. The i.r. spectra of both diastereoisomeric bases **4***a* revealed broad absorptions corresponding to the bonded hydroxyl stretching band.[7] Diluted solutions of the aminoalcohols showed a strong i.r. band at 3220 cm^{-1} (*threo* isomer) and at 3185 $\pm$ 5 cm^{-1} (*erythro* isomer) down to a concentration of 0.005 *M*. A weak free hydroxyl stretching band appeared near 3600 cm^{-1}. The bonded and free hydroxyl stretching bands did not change dramatically in intensity and in position with changes in concentration thus providing evidence[8] that the diastereoisomers were both

[6]The unsubstituted alcohols **4***a* were resolved on a Carbowax column (peak area ratio of 73:27) but identical retention times for the diastereoisomeric chlorinated alcohols **4***b* and **4***c* precluded the use of g.l.c. to estimate the isomer ratios. These ratios were determined by integrating the H-3 signals in the free base mixtures.

[7]The i.r. spectra in carbon tetrachloride were determined at the following molar concentrations (cell thickness in parentheses): 0.50 (0.1 mm); 0.10 (0.25 mm); 0.025 (1.0 mm); 0.010 (2.5 mm); 0.005 (5.0 mm).

[8]In the related 3-dimethylamino-2-methyl-1-phenyl-1-propanol system, Angiolini and Gottarelli (24) based their conformational analysis on the hydrogen bonded tetrahydro-1,3-oxazine-like ring system. Rather than making configurational assignments to **4** based on axial–equatorial relationships of H-3, and H-4, we have considered "pure" staggered rotomers depicting *trans* ($\Phi = 180°$) and *gauche* ($\Phi = 60°$) orientations of the carbon–hydrogen bonds at C-3 and C-4.

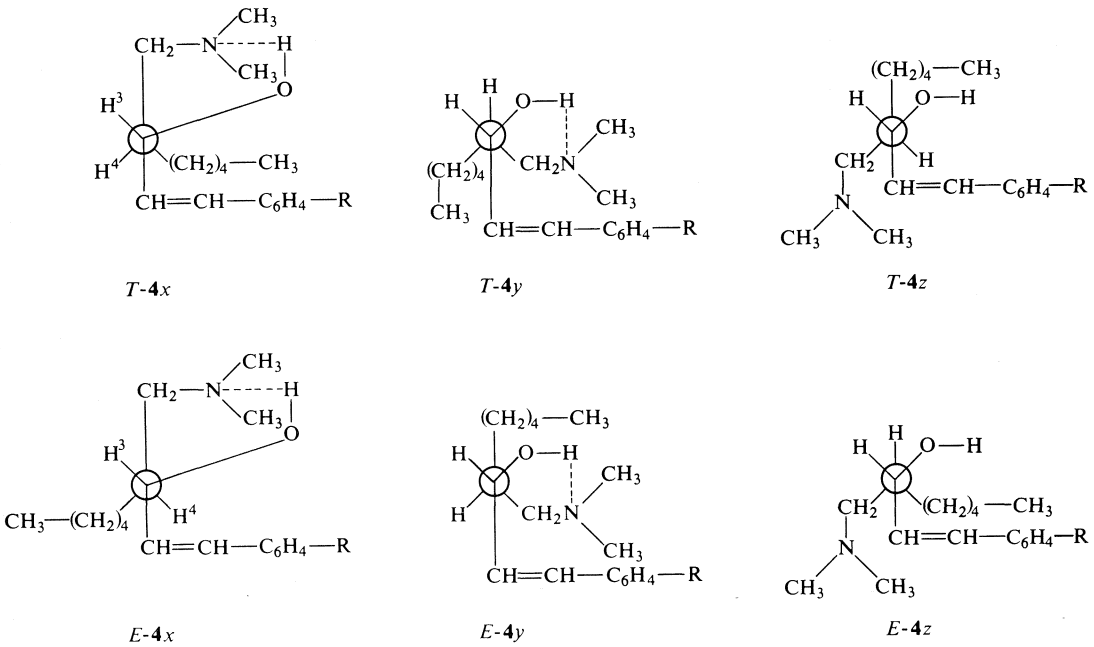


FIG. 4. Newman projections of (3*R*,4*R*)-4-dimethylaminomethyl-1-phenyl-1-nonen-3-ol (*T*-**4**) and (3*R*,4*S*)-4-dimethylaminomethyl-1-phenyl-1-nonen-3-ol (*E*-**4**).

intramolecular hydrogen bonded in the nonpolar solvent.

Derivation of $J_{H^3H^4}$ for the major isomers (*threo* in Table 2) was based on half-bandwidth measurements of the H-3 signal (9–10 Hz) minus the sum of the coupling to H-3 by H-1 (1 Hz) and H-2 (4–4.5 Hz). The 3.5–5 Hz coupling constants suggested a *gauche* orientation of the protons at C-3 and at C-4.

The rotomers *T*-**4***z* and *E*-**4***z* (Fig. 4) cannot assume a hydrogen-bonded conformation and they can be eliminated as preferred conformations of either diastereoisomer. Although rotomer *E*-**4***y* has the *gauche* relationship of H-3 and H-4, *E*-**4***y* is not as stable as *E*-**4***x* since the latter rotamer has bulky substituents flanked by hydrogen atoms. Therefore the major isomer, having as a preferred conformation rotamer *T*-**4***x* has the **3***R*,**4***R* (*threo*) configuration.

For the minor isomer, the n.m.r. data (Table 2) are in agreement with this diastereoisomer having the **3***R*,**4***S* (*erythro*) relative configuration. Since the H-3 signal gave four lines (J = 6.0–6.5 Hz; J = 7.5–8.0 Hz) and a $J_{H^2H^3}$ of 6.0–6.5 Hz was seen in the doublet of doublets of the H-2 signal, $J_{H^3H^4}$ was equal to 7.5–8.0 Hz. A *trans* relationship of H-3 and H-4 in a conformational preference of the diastereoisomer was suggested. This is shown in Fig. 4 as rotomer *E*-**4***x*.

Half-bandwidths of H-3 for the diastereoisomeric salts were consistently similar to the same signals for the free bases (Table 2). A much lesser degree of conformational homogeneity is indicated for *threo*-**4***a* methiodide (see Experimental) which gave a half-bandwidth of 14 Hz compared to half-bandwidths of 9 Hz for the corresponding tertiary amine and 10 Hz for the hydrochloride salt.

Experimental

Elemental analyses on the compounds reported in this work were performed by F. B. Strauss, Microanalytical Laboratories, Oxford, England. Melting points and boiling points are uncorrected. Nuclear magnetic resonance spectra were obtained with a Varian T-60 spectrometer. The spectra were run at room temperature with tetramethylsilane providing the internal standard. Infrared absorption spectra were recorded on a Unicam SP-200G spectrophotometer. Mass spectra were determined on an MS-12 spectrometer operated by Mr. D. Bain, Department of Chemistry, University of Saskatchewan, Saskatoon. Gas–liquid chromatography was performed on a Pye Series 104 chromatograph which was equipped with a flame ionization detector. The 5 ft × 0.25 in. o.d. glass column contained 4% Carbowax 20 M adsorbed onto Chromosorb G, 100–120 mesh. The carrier flow rate was 75 cm³/min (nitrogen) with the gas chromatograph operating at 220°.

Preparation of 1-Phenyl-3-nonanol (5)

Using the quantities and conditions given in Table 1, lithium aluminum hydride reduction of (*E*)-1-phenyl-1-

nonen-3-one gave, after adding water, filtering and evaporating *in vacuo* the dried ($MgSO_4$) ether extracts, a colorless oil which was distilled through an air condenser packed with 10 cm of Raschig rings: b.p. 136–138°/1.0 mm (lit. (25) b.p. for **5** is 95–97°/0.5 mm).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.44; H, 10.91.

Preparation of (E)-1-Phenyl-1-nonen-3-ols (3)

(*E*)-1-Phenyl-1-nonen-3-one (4.326 g, 0.02 mol) was dissolved in methanol (30 ml) and cooled to 0°. Sodium borohydride (0.757 g, 0.02 mol) in water (12 ml; adjusted to p*H* 8.5 with aqueous NaOH) was added dropwise with stirring for 30 min. The reaction was continued at 0° for 1 h, stirred at room temperature for 24 h, evaporated *in vacuo*, and the resulting semisolid was suspended in p*H* 4 water (75 ml). The solution was extracted with ether, washed with water, and dried ($MgSO_4$). Evaporation under reduced pressure gave an oil which was distilled *in vacuo* to give 2.37 g of **3***a*, b.p. 128° (0.80 mm) (lit. (26) b.p. 156–157°/2.0 mm). The distillates, which solidified on cooling, furnished an analytical sample, m.p. 28–29°, as a white solid (from hexane); n.m.r. (CCl_4) gave doublets (J = 16 Hz) at δ 6.45 and 6.02 for C(H)=C(H) with other signals as expected.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.10; H, 10.05.

(*E*)-1-(*p*-Chlorophenyl)-1-nonen-3-ol (**3***b*) was prepared by the above procedure from (*E*)-1-(*p*-chlorophenyl)-1-nonen-3-one (5.015 g, 0.02 mol) and sodium borohydride (0.76 g, 0.02 mol). The crude product was recrystallized from hexane to give **3***b* (2.89 g, 57%) as a white solid with m.p. 42–43°.

Anal. Calcd. for $C_{15}H_{21}ClO$: C, 71.27; H, 8.375. Found: C, 70.95; H, 8.16.

(*E*)-1-(*p*-Chlorophenyl)-1-nonen-3-ol *p*-nitrobenzoate was prepared from **3***b* (2.53 g, 0.01 mol, in 20 ml anhydrous pyridine) and *p*-nitrobenzoyl chloride (2.28 g, 0.012 mol) by stirring at 5° for 30 min then at 22° for 17 h. The reaction mixture was poured into ice and 5 ml of 10% hydrochloric acid was added. The aqueous suspension was extracted with ether. The ether extracts were washed successively with 5% hydrochloric acid, 10% sodium carbonate, then water, and dried ($MgSO_4$). Evaporation *in vacuo* gave a yellow syrup which crystallized on cooling. Three recrystallizations from petroleum ether (b.p. 60–80°) gave the desired ester (0.27 g, 6.7%) as a white powder: m.p. 58–59°; i.r. (KBr) 1715 (C=O) and 965 cm^{-1} (C(H)=C(H)); n.m.r. (CCl_4) δ 8.13 (s, 4, *p*-$NO_2C_6H_4$), 7.20 (s, 4, *p*-ClC_6H_4), 6.60 (d, 1, J = 15 Hz, C_1H), 6.08 (dd, 1, J = 15 Hz, J = 6.5 Hz, C_2H), 5.57 (q, 1, J = 6.5 Hz, C_3H), 2.10–1.10 (m, 10, $(CH_2)_5$), and 0.87 p.p.m. (m, 3, C_9H_3); mass spectrum *m/e* 401 (M^+).

Anal. Calcd. for $C_{22}H_{24}ClNO_4$: C, 65.75; H, 6.02; N, 3.49. Found: C, 66.00; H, 5.88; N, 3.53.

Preparation of 4-Dimethylaminomethyl-1-phenyl-1-nonen-3-ols (4) (Table 2)

A solution of (*E*)-4-dimethylaminomethyl-1-phenyl-1-nonen-3-one hydrochloride (30.99 g, 0.10 mol) in methanol (150 ml) was cooled at 0°. Sodium borohydride (3.785 g, 0.10 mol) in p*H* 8.5 water (60 ml) was added dropwise and, after stirring for 1 h at 5–8°, the mixture was heated under reflux for 3 h. The reaction vessel was cooled (ice bath) and the p*H* adjusted to 5 with ethanolic hydrochloric acid. Solvent evaporation *in vacuo* gave a white semisolid which, after dissolving in water (200 ml), was extracted with ether. The p*H* of the cold aqueous solution was adjusted to 10 by addition of aqueous sodium hydroxide solution. Following extraction of the free bases with ether, the ether extracts were washed with water and dried ($MgSO_4$). Evaporation of the ether under reduced pressure afforded a colorless oil (23.14 g, 84% yield of the mixture of diastereoisomers (**4***a*)).

Amino alcohols **4***b* were similarly prepared (12.40 g, 71%) by reducing (*E*)-1-(*p*-chlorophenyl)-4-dimethylaminomethyl-1-nonen-3-one hydrochloride (19.4 g, 0.0565 mol) with sodium borohydride (2.14 g, 0.0565 mol). As the free base, (*E*)-1-(*o*-chlorophenyl)-4-dimethylaminomethyl-1-nonen-3-one (9.50 g, 0.031 mol) gave the alcohols **4***c* (6.43 g, 67%) on reduction with sodium borohydride (1.46 g, 0.039 mol) in methanol.

(a) Derivatives of 4a

(*i*) The mixture of diastereoisomeric aminoalcohols (20.65 g) was stirred in ether (350 ml) and ethanolic hydrochloric acid was added until the p*H* was adjusted to 6. On cooling, a product precipitated which was recrystallized from acetone to furnish *threo*-**4***a* hydrochloride (9.03 g, 39%) as white crystals: m.p. 126°; i.r. (KBr) 3335 (OH) and 970 cm^{-1} (C(H)=C(H)); mass spectrum *m/e* 275 (M^+ − HCl).

Anal. Calcd. for $C_{18}H_{30}ClNO$: C, 69.31; H, 9.70; N, 4.49. Found: C, 69.50; H, 9.68; N, 4.55.

(*ii*) A mixture of diastereoisomeric alcohols (2.0 g, 0.0073 mol) was dissolved in absolute ethanol (2 ml) and methyl iodide (2.07 g, 0.015 mol) was added. The reaction mixture was heated under reflux for 1 h. Evaporation *in vacuo* gave a tan semisolid which crystallized on cooling. Recrystallization from absolute ethanol gave *threo*-**4***a* methiodide (0.91 g, 38%) as an off-white powder: m.p. 112.5–113.5°; i.r. (KBr) 3360 (OH) and 970 cm^{-1} (C(H)=C(H)).

Anal. Calcd. for $C_{19}H_{32}INO$: C, 54.67; H, 7.73; I, 30.41; N, 3.36. Found: C, 54.68; H, 7.71; I, 30.63; N, 3.40.

No attempt was made to isolate the *erythro* isomer of **4***a* as the methiodide.

(*iii*) The ether mother liquor from *i* was evaporated *in vacuo* to give a light yellow oil (9.46 g). From a 5.0 g portion of this oily mixture the free bases were liberated. The mixture (0.55 g, 0.002 mol) was stirred in ether (65 ml) and maleic acid (0.23 g, 0.002 mol) was added. On cooling, the deposited product (0.579 g, m.p. 83–90°) was recrystallized from acetone to give *erythro*-**4***a* maleate (0.30 g, 38%): m.p. 98°; i.r. (KBr) 3290 (OH) and 975 cm^{-1} (C(H)=C(H)); mass spectrum *m/e* 275 (M^+ − $C_4H_4O_4$).

Anal. Calcd. for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.45; H, 8.45; N, 3.56.

(*iv*) To a chilled (−5°) solution of *threo*-**4***a* free base (2.75 g, 0.010 mol) in 50 ml ether was added *p*-nitrobenzoyl chloride (2.23 g, 0.012 mol). After the addition

had been completed (30 min), the reaction mixture was stirred (ice bath) for 1 h and ether (50 ml) was added. Esterification was continued for 42 h. A product was collected, washed with ether, and recrystallized from acetone to give *threo*-**4***a* *p*-nitrobenzoate hydrochloride. On thin layer silica gel plates (*n*-butanol – glacial acetic acid – water 12:3:5 v/v/v) the compound migrated as one spot. Another recrystallization from acetone did not alter the m.p. of 136°; i.r. (KBr) 1725 (C=O) and 960 cm^{-1} (H)(C=C)(H); n.m.r. ($CDCl_3$) δ 12.50–11.67 (broad s, 1, $\overset{+}{N}H$, exchanged with D_2O), 8.27 (s, 4, *p*-$NO_2C_6H_4$), 7.33 (m, 5, phenyl *H*), 6.83 (d, 1, J = 14 Hz, C_1H), 6.57–5.90 (m, 2, C_2H and C_3H), 3.63–2.70 (m, 8, $CH_2\overset{+}{N}(CH_3)_2$), 2.70–2.20 (broad s, 1, C_4H), 1.97–1.10 (m, 8, $(CH_2)_4$), and 0.90 p.p.m. (m, 3, C_9H_3); mass spectrum *m/e* 424 (M^+ – HCl).

Anal. Calcd. for $C_{25}H_{33}ClN_2O_4$: C, 65.13; H, 7.21; N, 6.08. Found: C, 64.92; H, 7.18; N, 6.21.

(*b*) *Derivatives of* **4***b* *and* **4***c*

(*i*) A diastereoisomeric mixture of **4***b* (12.16 g) was stirred in ether and the p*H* was adjusted to 6 with ethanolic hydrochloric acid. A product was precipitated with ether, dried, and recrystallized from acetone to give *threo*-**4***b* hydrochloride (5.05 g, 37%): m.p. 151–152°; i.r. (KBr) 3315 (OH) and 975 cm^{-1} (H)(C=C)(H); mass spectrum *m/e* 309 (M^+ – HCl).

Anal. Calcd. for $C_{18}H_{29}Cl_2NO$: C, 62.42; H, 8.44; N, 4.04. Found: C, 62.58; H, 8.46; N, 4.04.

(*ii*) The ether mother liquor from *i* was evaporated *in vacuo* and the free bases liberated as previously described. To the mixture (2.33 g, 0.0075 mol) in ether (150 ml) was added maleic acid (0.87 g, 0.0075 mol). Crystals were precipitated by adding cold ether to give, after recrystallization from ethyl butyrate, *threo*-**4***b* maleate (1.48 g, 46%) melting at 103–105°. An analytical sample had m.p. 109–110°; i.r. (KBr) 3290 (OH) and 975 cm^{-1} (H)(C=C)(H); mass spectrum *m/e* 309 (M^+ – $C_4H_4O_4$).

Anal. Calcd. for $C_{22}H_{32}ClNO_5$: C, 62.03; H, 7.57; N, 3.29. Found: C, 62.20; H, 7.64; N, 3.22.

(*iii*) The hydrochloride salts of **4***c* were formed on 5.06 g of the free base mixture to give, after recrystallization from ethyl acetate, *threo*-**4***c* hydrochloride (2.07 g, 46.5%) as white crystals: m.p. 113–114°; i.r. (KBr) 3335 (OH) and 970 cm^{-1} (H)(C=C)(H); mass spectrum *m/e* 309 (M^+ – HCl).

Anal. Calcd. for $C_{18}H_{29}Cl_2NO$: C, 62.42; H, 8.44; N, 4.04. Found: C, 62.26; H, 8.43; N, 4.22.

(*iv*) Separation of *erythro*-**4***c* from the diastereoisomeric mixture was unsuccessful giving, after adding equimolar amounts of maleic acid to the mixture of free bases (2.77 g, 0.0089 mol) in ether, an insoluble oil which failed to crystallize by storage under vacuum in a desiccator.

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