Synthesis of Oximes, Aziridines, and Allyl Alcohols Derived from Substituted 1-Phenyl-1-nonen-3-ones as Potential Cytotoxic and Antitumor Agents

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Abstract □ A number of nuclear-substituted 1-phenyl-1-nonen-3-one oximes were synthesized. Reduction of several of these compounds with lithium aluminum hydride yielded the corresponding 1-phenyl-2,3-epiminononanes, shown by 100-MHz NMR spectroscopy to be the *cis*-geometrical isomers. When several ring-substituted 4-dimethylaminomethyl-1-phenyl-1-nonen-3-ones were treated with hydroxylamine hydrochloride under forcing conditions, the product isolated was the corresponding oxime. Reaction under mild conditions led only to the isolation of the Michael addition product of the oxime in low yield. Reduction of some nuclear-substituted 4-dimethylaminomethyl-1-phenyl-1-nonen-3-ones with sodium borohydride led to the formation of the corresponding allyl alcohols, and the products were shown by ^{1}H- and ^{13}C-NMR spectroscopy to be the *threo*-isomers or, alternatively, a mixture of *erythro*- and *threo*-isomers. Reaction of phosphoric acid with one of the substituted allyl alcohols led to a diolefin, shown by NMR spectroscopy to be a mixture of (*E*, *E*)- and (*E*, *Z*)-isomers in a ratio of 65:35.

Keyphrases □ 1-Phenyl-1-nonen-3-one derivatives, various—synthesized □ Oximes—various 1-phenyl-1-nonen-3-one derivatives synthesized □ Aziridines—various 1-phenyl-1-nonen-3-one derivatives synthesized □ Allyl alcohols—various 1-phenyl-1-nonen-3-one derivatives synthesized

Drugs classified as alkylating agents are used extensively in cancer chemotherapy. While a number of these compounds are clinically available, additional alkylating agents are needed (1, 2). A group of novel alkylating agents that have received some attention are acyclic α,β-unsaturated ketones, some of which show antineoplastic activity (3–5). While the substituted styryl ketones I [$R_1 = R_2 = H$, Cl, or $N(CH_3)_2$] were virtually devoid of bioactivity (5), conversion to the corresponding Mannich bases led to compounds with promising antitumor and cytotoxic activities shown to be due, in part at least, to interference with mitochondrial function (6). It was decided, therefore, to prepare further analogs of I such as the oximes (II*a*–II*f*) and the Mannich bases of the oximes (V*a*–V*d*) (Scheme I).

A group of alkylating agents with marked antineoplastic activity are aziridines, including triethylenemelamine, which is used clinically (7). In addition, allyl alcohols have alkylating properties due to the stability of the carbonium ion. In the aryl-substituted allyl alcohols VI*a*–VI*d*, the carbonium ion would be expected to be further stabilized by delocalization of the positive charge on the ring. To this end, therefore, the preparation of the aziridines III*a*–III*d* and allyl alcohols was undertaken (Scheme I).

DISCUSSION

The ketones I were converted into the corresponding oximes (II*a*–II*f*) in yields ranging from 5 to 76%. 2-Benzylidenecyclohexanone oximes can be reduced with lithium aluminum hydride to give the corresponding 1-benzyl-1,2-epiminocyclohexanes in good yield (8). Reaction of the oximes with this reagent afforded the aziridines III*a*–III*d* in yields of approximately 20%.

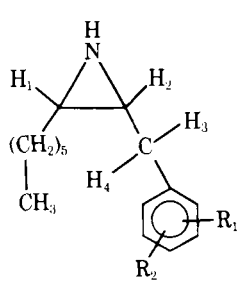
Since steric factors in the reaction of aziridines with biological macromolecules are important (9), the configuration of the aziridines was determined using ^{1}H-NMR spectroscopy. The 100-MHz spectra of III*a*, III*c*, and III*d* were similar, with resonances at δ 2.6 (H_3 and H_4), 2.2 (H_2), and 2.0 (H_1) ppm (see Structure A). The resonance of H_1 was broadened because of coupling with the aliphatic side chain, so attention was focused on the coupling of protons 1 and 2 by examination of the H_2 resonance, which appeared as a quartet with J = 6.0 Hz. Decoupling of H_{3-4} changed the pattern to a doublet with $J_{1,2}$ = 6.0 Hz. The quartet at 2.2 ppm resulted from the combined effect of $H_{3,4}$ on H_2 with $J_{2-3,4}$ = 6.0 Hz and H_1 on H_2 with $J_{1,2}$ = 6.0 Hz, giving a doublet of triplets whose two inner lines coincided.

When an *ortho*-substituent was present on the phenyl ring (III*b*), a complex pattern for $H_{3,4}$ resulted since H_3 and H_4 were no longer magnetically equivalent. Decoupling H_3 and H_4 separately showed that $J_{2-3} = J_{2,4}$ = 6.0 Hz, with the coupling J_{1-2} being 6.0 Hz. Since the coupling between protons 1 and 2 was shown to be 6.0 Hz, the *cis*-configuration was attributed to the aziridines III*a*–III*d*. Several workers (10–12) reported the coupling of adjacent protons of *cis*-aziridines to be approximately 6 Hz while the coupling is approximately 3 Hz in the *trans*-isomers.

Oxime formation proceeded with difficulty in the attempted synthesis of V*a*–V*d*, and only V*b* and V*d* were obtained as crystalline solids in low yields. In an attempt to reduce by-product formation through lengthy heating conditions, IV*a* (as the free base) was reacted with hydroxylamine hydrochloride for a short time in methanol. From the reaction mixture, a low yield of colorless crystals was obtained and shown by ^{1}H-NMR spectroscopy, mass spectrometry, and elemental analysis to be the Michael addition product of the oxime of the Mannich base (VII).

The Mannich bases IV*b*, IV*d*, and IV*e* were reduced with sodium borohydride to give the allyl alcohols VI*a*–VI*c*, which allowed the possibility of a mixture of diastereoisomers. Examination of the ^{1}H-NMR spectrum of VI*b* gave an unresolved spectrum for which unequivocal assignments could not be made. The ^{13}C-NMR spectrum showed absorptions at 69.85, 59.05, and 39.64 ppm attributable to C-3 and C-4 as well as to the methylene carbon adjacent to the quadrivalent nitrogen atom. Off-resonance decoupling showed the peak at 59.05 ppm to be a triplet and was assigned to the methylene carbon atom. Since C-3 was situated at a position with increased deshielding relative to C-4, the peaks at 69.85 and 39.64 ppm were assigned to C-3 and C-4, respectively, with off-resonance decoupling indicating doublets centered at 69.85 and 39.64 ppm.

The ^{13}C-NMR spectra of VI*b* and the *threo*-isomer of VI*a* (13) were virtually superimposable. For VI*a*, the absorptions of C-3 and C-4 were at 70.04 and 39.76 ppm, respectively. ^{13}C-NMR spectroscopy of VI*c* showed absorptions at 69.48 and 39.83 ppm, which were assigned to C-3 and C-4, respectively, of the *threo*-isomer and at 76.41 and 40.32 ppm for the *erythro*-isomer. The ratio of the intensities of the *threo*- to the *erythro*-isomers was 40:60.



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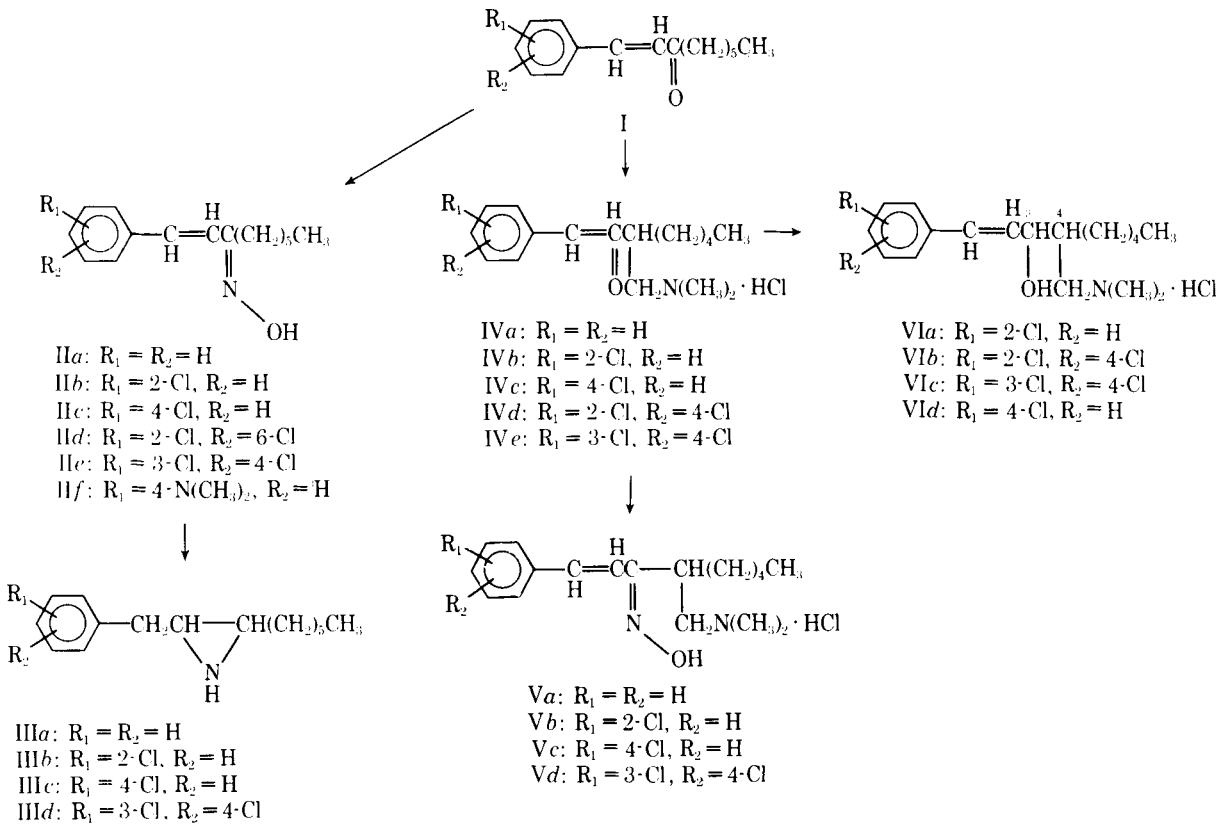
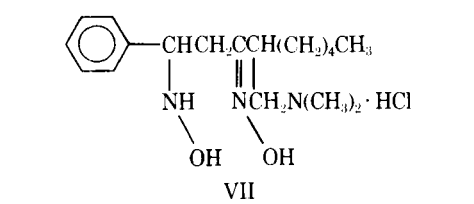


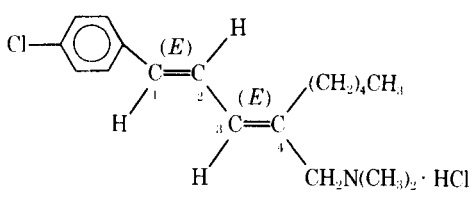
Scheme I

Reduction of IV*c* gave VI*d*, possessing the *threo*-configuration (13). This compound was treated with phosphoric acid in an attempt to prepare the phosphate ester as a candidate antineoplastic drug since certain cancerous tissue has a higher phosphatase content than other tissues (14). The product obtained was shown to be the corresponding diolefin. While the olefinic C-1 and C-2 atoms were seen from ^{1}H-NMR spectroscopy to have the (*E*)-configuration, the possibility exists of the product being a mixture of VIII*a* and VIII*b* because of variation in the spatial arrangements of the groups at C-3 and C-4.

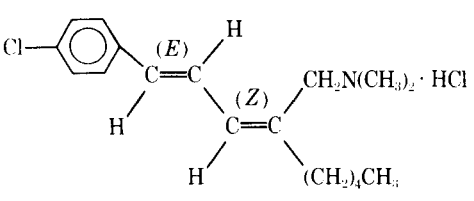
In VIII*b*, the methylene group adjacent to the nitrogen is subject to steric impedance because the neighboring styryl group forces the electrons of the methylene protons toward the nitrogen atom, thereby causing a greater deshielding than in VIII*a*. ^{1}H-NMR spectroscopy indicated two *AB* quartets centered at 3.90 and 3.62 ppm, assigned to the methylene group adjacent to the nitrogen for VIII*b* and VIII*a*, respectively, in a ratio of 35:65.



VII



VIII*a*



VIII*b*

EXPERIMENTAL[1]

Melting points are uncorrected. Organic extracts were washed with water and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed *in vacuo*, using a water aspirator. NMR spectra[2] were carried out in deuterochloroform. GLC[3] was undertaken using a 3% methyl silicone gum rubber column[4] (1.524 m × 0.635 cm) unless otherwise stated.

1-Phenyl-1-nonen-3-one Oximes—1-Phenyl-1-nonen-3-one (15) (10.0 g, 0.046 mole) in ethanol (30 ml) was added to a stirring solution of hydroxylamine hydrochloride (3.6 g, 0.051 mole) and potassium acetate (5.0 g, 0.051 mole) in water (10 ml), and the mixture was heated to 60° for 1 hr. On cooling, the reaction mixture was extracted with ether to give a pale-yellow oil; its IR spectra showed the presence of unreacted ketone.

The oil was placed in sodium bisulfite solution (16) (200 ml), stirred for 1 hr, and extracted with ether, producing a colorless oil that solidified on cooling. Recrystallization from petroleum ether (bp 30–60°) gave 1-

[1] Elemental analyses were carried out by Mr. R. G. Teed of the Department of Chemistry and Chemical Engineering, University of Saskatchewan. Mass spectra (AE1 MS-12 mass spectrometer, Picker X-Ray Engineering Ltd., Montreal 304, Quebec, Canada) were determined at 70 ev by Mr. D. R. Bain, Department of Chemistry and Chemical Engineering, University of Saskatchewan. IR spectra (Beckman IR 8 spectrophotometer, Beckman Instruments Inc., Edmonton, Alberta, Canada) were determined as Nujol mulls with sodium chloride disks unless otherwise stated.

[2] For 60-MHz spectra: Bruker WP60 spectrophotometer, Brucker Spectrospin (Canada) Ltd., Mississauga, Ontario, L5L 1J9, Canada, and Varian T60 spectrophotometer, Varian Associates of Canada Ltd., Georgetown, Ontario, L7G 2J4, Canada. For 100-MHz spectra: Varian HA 100-12 spectrophotometer, Varian Associates of Canada Ltd., Georgetown, Ontario, L7G 2J4, Canada.

[3] Varian Aerograph model 90-P, Varian Associates of Canada Ltd., Georgetown, Ontario, L7G 2J4, Canada.

[4] All GLC columns were obtained from Varian Associates of Canada Ltd., Edmonton, Alberta, Canada.

Table I—Substituted 1-Phenyl-1-nonen-3-one Oximes

Compound	Yield, %	Melting Point	Molecular Formula	Analysis, % Calc.	Found
II*b*	39	74–75°	$C_{15}H_{20}ClNO$	C 67.80	67.84
				H 7.53	7.32
				N 5.27	5.30
II*c*	66	90–91°	$C_{15}H_{20}ClNO$	C 67.80	68.00
				H 7.53	7.67
				N 5.27	5.29
II*d*	5	56.5–57°	$C_{15}H_{19}Cl_2NO$	C 60.00	60.29
				H 6.33	6.38
				N 4.67	4.54
II*e*	76	101–102°	$C_{15}H_{19}Cl_2NO$	C 60.00	60.38
				H 6.33	6.40
				N 4.67	4.60
II*f*	30	88–89°	$C_{17}H_{26}NO$	C 74.45	74.37
				H 9.49	9.62
				N 10.22	10.25

Table II—Substituted 1-Phenyl-2,3-epiminononanes [a]

Compound	Yield, %	Boiling Point (°/mm)	Molecular Formula	Analysis, % Calc.	Found
III*a*	13	127°/0.05	$C_{15}H_{23}N$	C 82.95	83.15
				H 10.60	10.84
				N 6.45	6.37
III*b*	12	124°/0.07	$C_{15}H_{22}ClN$	C 71.57	71.45
				H 8.75	9.03
				N 5.57	5.50
III*c*	26	128°/0.05	$C_{15}H_{22}ClN$	C 71.57	71.63
				H 8.75	9.11
				N 5.57	5.44
III*d*	24	147°/0.06	$C_{15}H_{21}Cl_2N$	C 62.94	63.04
				H 7.34	7.53
				N 4.90	4.81

[a] The value of J_{2-3} was 6.0 Hz for each compound.

phenyl-1-nonen-3-one oxime (30% yield), mp 72–73°, as colorless needles; IR: 3220 (br) (OH), 1635 (w) (C=N), 1620 (w) (C=C), 965 (w) (HC=CH), and 950 (w) (NO) cm^{-1}; ^{1}H-NMR: δ 9.35 (broad, 1, NOH), 7.0–7.5 (m, 5, C_6H_5), 6.6 (s, 2, C_1H and C_2H), 2.2–2.85 (m, 2, C_4H_2), 1.1–2.0 [m, 8, $(CH_2)_4$], and 0.7–1.15 (m, 3, C_9H_3) ppm.

Anal.—Calc. for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.87; H, 9.24; N, 6.06.

Compounds II*b*, II*c*, II*e*, and II*f* were prepared similarly from the corresponding substituted 1-phenyl-1-nonen-3-ones (15), except that the use of sodium bisulfite solution was unnecessary and II*f* was recrystallized from petroleum ether (bp 100–120°). The oximes, except II*f*, appeared as colorless needles; II*f* appeared as yellow prisms.

In preparing II*d* from 1-(2,6-dichlorophenyl)-1-nonen-3-one (15), equimolar amounts of reactants were heated at 60° for 36 hr. The crude product was treated exhaustively with sodium bisulfite solution until no more unreacted ketone was present (IR evidence). The resultant oil was dissolved in petroleum ether (bp 30–60°), and flocculent colorless crystals of II*d* deposited after storage at −10° for 3 weeks. The structures of the oximes II*b*–II*f* were confirmed by IR and NMR spectroscopy, and some of the physical data are summarized in Table I.

1-Phenyl-2,3-epiminononanes (III)—A solution of 1-phenyl-1-nonen-3-one oxime (25.2 g, 0.109 mole) in dry ether (200 ml) was added dropwise to a stirring suspension of lithium aluminum hydride (6.6 g, 0.17 mole) in dry ether (120 ml), and the resultant mixture was heated under reflux for 24 hr. On cooling, the reaction complex was decomposed by the dropwise addition of methanol and subsequently water. After filtration, the ethereal extract was washed with water (3 × 100 ml) and dried.

Evaporation of the solvent gave a pale-yellow oil (7.5 g), showed by GLC to consist of two components in the ratio of 90:10. Fractional distillation gave 1-phenyl-2,3-epiminononane (5.4 g, 13% yield), bp 127°/0.05 mm, as a colorless oil, shown by GLC to be one component; IR (neat): 3225 (br) (NH) cm^{-1}; ^{1}H-NMR: δ 7.25 (s, 5, C_6H_5), 2.75 (d, 2, C_1H), 1.9–2.5 (br, 3, C_2H, C_3H, NH), 1.1–1.8 [m, 10, $(CH_2)_5$], and 0.65–1.1 (m, 3, C_9H_3) ppm.

Attempts to separate completely the two components of the crude reaction mixture by preparative GLC were unsuccessful. A 3% methyl silicone gum rubber column[5] (1.524 m × 0.635 cm) was best; columns (6.096 m × 0.953 cm) containing polyethylene glycol[6], methyl phenyl silicone[7], free fatty acid phase modified polyethylene glycol[8], octylphenoxyethanol[9], liquid methyl silicone[10], poly(*m*-phenyl) ether[11], and diethylene glycol succinate[12] gave only poor resolution. An oil containing the minor component of the crude reaction product as the principal product (60%) was obtained by preparative GLC, using a methyl silicone gum rubber column[5] (1.524 m × 0.635 cm), and examined by mass spectrometry. The parent ion, *m/e* 219, and a prominent peak at *m/e* 114, due probably to an α-cleavage fragment ion, suggested that the minor component in the crude reaction mixture was 3-amino-1-phenylnonane.

When the reaction between 1-phenyl-1-nonen-3-one oxime and lithium aluminum hydride was carried out in the presence of dry tetrahydrofuran in place of ether, the major product (85%) was 1-phenyl-2,3-epiminononane with the saturated amine as the minor product (15%).

Reaction of oximes II*b*, II*c*, and II*e* with lithium aluminum hydride in dry ether gave reaction products consisting of two components; these components could not be separated by preparative GLC. Purification of the crude mixtures by fractional distillation afforded 1-(2-chlorophenyl)-2,3-epiminononane (III*b*), 1-(4-chlorophenyl)-2,3-epiminononane (III*c*), and 1-(3,4-dichlorophenyl)-2,3-epiminononane (III*d*) (Table II).

Oximes V*a*–V*d* and VII—The free Mannich base (4.5 g, 0.015 mole), obtained from the hydrochloride salt IV*b* (17) by basifying with aqueous sodium hydroxide solution at 0° and extracting with ether, was heated with hydroxylamine hydrochloride (1.4 g, 0.02 mole) in methanol (10 ml) for 48 hr. Removal of the solvent gave a viscous yellow oil, which gave a semisolid on trituration with ether. The semisolid was boiled with acetone for 1 min, producing a finely divided powder (0.8 g). This powder was recrystallized from acetone–methanol to give V*b* as colorless prisms (0.53 g, 10% yield), mp 175°; IR: 3120 (br) (OH), 2650 (br) $[CN^+H(CH_3)_2]$, 1610 (w) (C=N), 1590 (w) (CH=CH), 960 (m) (CH=CH), and 930 (m) (NO) cm^{-1}; mass spectrum: *m/e* 322 (M^+ − HCl) (0.16%) and 58 (100).

Anal.—Calc. for $C_{18}H_{28}Cl_2N_2O$: C, 60.17; H, 7.80; N, 7.80. Found: C, 60.11; H, 7.27; N, 7.77.

The 3,4-dichloro derivative V*d* was prepared similarly as colorless prisms (13%), mp 192°; IR: 3120 (br) (OH), 2660 (br) $[CN^+H(CH_3)_2]$, 1620 (w) (C=N), 1590 (w) (CH=CH), 960 (m) (CH=CH), and 940 (m) (NO) cm^{-1}; mass spectrum: *m/e* 356 (M^+ − HCl) (0.01%) and 58 (100).

Anal.—Calc. for $C_{18}H_{27}Cl_3N_2O$: C, 54.89; H, 6.86; N, 7.12. Found: C, 54.65; H, 6.83; N, 7.04.

Attempts to form V*a* and V*c* gave only viscous oils from which no crystalline material could be obtained.

4-Dimethylaminomethyl-1-phenyl-1-nonen-3-one (50.0 g, 0.18 mole), obtained by neutralization of IV*a* (*vide supra*), was added to hydroxylamine hydrochloride (27.8 g, 0.4 mole) in methanol (100 ml) at 0°. The resultant mixture was heated under reflux for 2 hr. The solvent was removed partially, and ether was added. Upon refrigeration at −10°, colorless plates of 4-dimethylaminomethyl-1-hydroxyamino-1-phenylnonan-3-one oxime hydrochloride (VII) (3.2 g, 5% yield), mp 177–178°, were obtained; IR: 3220 and 3260 (br) (OH), 2680 (br) $[CN^+(CH_3)_2]$, 1640 (w) (C=N), and 935 (w) (NO) cm^{-1}; mass spectrum: *m/e* 321 (M^+ − HCl) (0.4%), 58 (100), and 44 (20.1).

Anal.—Calc. for $C_{18}H_{32}ClN_3O_2$: C, 60.42; H, 8.95; N, 11.75. Found: C, 59.21; H, 8.45; N, 11.28.

Allyl Alcohols VI—To a solution of 1-(3,4-dichlorophenyl)-4-dimethylaminomethyl-1-nonen-3-one (15.6 g, 0.045 mole), obtained by basification of IV*e* (*vide supra*) in methanol (90 ml) cooled at 0°, was added sodium borohydride (15.1 g, 0.04 mole) in water (150 ml, pH adjusted to 9 with aqueous sodium hydroxide). This solution was stirred at 5–8° for 1 hr and then heated under reflux for 3 hr. On cooling, aqueous hydrochloric acid was added to adjust the pH to 5. Evaporation of the solvent gave a white semisolid, which was dissolved in water and extracted with ether.

The aqueous extracts were basified with aqueous sodium hydroxide and extracted with ether. Evaporation of the ether gave a pale-yellow oil (10 g). On treatment with ethanolic hydrochloric acid (10% w/v), the oil deposited a colorless solid, which was recrystallized from dry acetone, yielding (*E*)-1-(3,4-dichlorophenyl)-4-dimethylaminomethyl-1-nonen-3-ol (VI*c*) (5.5 g, 32%), mp 139.5°, as colorless needles; IR: 3320 (br) (OH), 2670 (br) $[CN^+H(CH_3)_2]$, 1570 (w) (CH=CH), and 960 (m) (CH=CH)

[5] SE-30
[6] Carbowax 20M column (20%).
[7] OV-17 column (20%).
[8] FFAP column (20%).
[9] Triton X-100 column (20%).
[10] OV-101 column (3%).
[11] PMPE column (20%).
[12] DEGS column (30%).

cm^{-1}; mass spectrum: *m/e* 343 (M^+ − HCl) (1.8%), 345 (0.9), and 58 (100); ^{1}H-NMR: δ 7.67–6.07 (m, 5, C_6H_3, C_1H and C_2H), 4.9 (ragged t, 1, C_3H), 4.27–2.50 [m, 8, $CH_2N(CH_3)_2$], 2.50–1.77 (broad s, 1, C_4H), 1.28 [s, 8, $(CH_2)_4$], and 0.83 (t, 3, CH_3) ppm.

Anal.—Calc. for $C_{18}H_{28}Cl_3NO$: C, 56.76; H, 7.36; N, 3.68. Found: C, 56.82; H, 7.42; N, 3.67.

The 2,4-dichloro analog VI*b*, prepared in a similar manner in 38% yield, was recrystallized from dry acetone as colorless needles, mp 142.5°; IR: 3320 (br) (OH), 2680 (br) [$NH^+(CH_3)_2$], 1580 (w) (CH=CH), and 955 (m) (CH=CH); mass spectrum: *m/e* 343 (M^+ − HCl) (0.9%), 345 (0.6), and 58 (100); ^{1}H-NMR ($CDCl_3$): δ 7.56–6.70 (m, 4, C_6H_3 and C_1H), 6.50–5.96 (dd, 1, C_2H), 4.83 (ragged t, 1, C_3H), 4.08–2.53 [m, 8, $CH_2N(CH_3)_2$], 2.53–1.90 (broad s, 1, C_4H), 1.30 [s, 8, $(CH_2)_4$], and 0.87 (t, 3, CH_3) ppm.

Anal.—Calc. for $C_{18}H_{28}Cl_3NO$: C, 56.76; H, 7.36; N, 3.68. Found: C, 57.03; H, 7.14; N, 3.69.

1-(*p*-Chlorophenyl) - 4-dimethylaminomethyl - 1,3-nonadiene Hydrochloride—*threo*-(*E*)-1-(*p*-Chlorophenyl) - 4-dimethylaminomethyl-1-nonen-3-ol (10 g, 0.029 mole), mp 157° [lit. (13) mp 151–152°], prepared by the published procedure (13), was added to phosphoric acid (85% v/v). The solution was stirred at room temperature for 24 hr. The reaction mixture, on extraction with ether, gave a yellow oil (3.2 g). This oil was treated with ethanolic hydrochloric acid (10% w/v) to give a colorless solid.

Recrystallization of the precipitate from ether–ethanol gave 1-(*p*-chlorophenyl)-4-dimethylaminomethyl-1,3-nonadiene hydrochloride (1.4 g, 15%), mp 203°, as colorless plates; IR (free base, neat): 3020 (w) (CH=CH), 2760, 2800 (m) (NCH_3), 1625 (w) (CH=CH), and 945 (s) (CH=CH); mass spectrum: *m/e*: 291 (M^+ − HCl) (21%), 220 (35), and 58 (100); ^{1}H-NMR ($CDCl_3$): δ 7.30 (s, 4, C_6H_4), 7.27–6.17 (m, 3, C_1H, C_2H, C_3H), 4.10–2.30 [m, 8, $CH_2N(CH_3)_2$], 1.40 [s, 8, $(CH_2)_4$], and 0.83 (t, 3, CH_3) ppm.

Anal.—Calc. for $C_{18}H_{27}Cl_2N$: C, 74.10; H, 8.92; N, 4.80. Found: C, 74.73; H, 8.56; N, 4.80.

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Effect of Antineoplastic and Cytotoxic Mannich Bases Derived from Conjugated Styryl Ketones on Mitochondrial Respiration in Rat Liver Cells

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Abstract □ Five cytotoxic Mannich bases (5-dimethylamino-1-substituted phenyl-1-penten-3-ones), three having antineoplastic activity, were evaluated for respiratory-inhibiting properties in rat liver mitochondria in the presence of four substrates: succinate, glutamate, 3-hydroxybutyrate, and palmitylcarnitine. Four compounds (I*b*–I*e*) showed significant inhibiting properties which, on occasion, were reversed partially by coenzyme Q_{10}. Evaluation of the spectra of the mitochondrial cytochromes indicated that I*b*–I*e* blocked the electron transport chain prior to the sequence of cytochromes. Since inhibition occurred when different substrates were used, a common site of action for I*b*–I*e* is likely; competition of I*b*–I*e* with coenzyme Q_{10} probably occurs. Compounds I*a*–I*e* inhibited RNA polymerase from Swiss mouse kidney cells but were virtually bereft of activity *versus* RNA polymerase from L-1210 leukemia cells. Polarography of the Mannich bases and the related styryl ketones showed that antineoplastic activity was associated with higher half-wave potentials.

Keyphrases □ 1-Phenyl-1-penten-3-one derivatives—effect on enzyme activity in rat liver mitochondria, various substrates □ Enzyme activity—effect of 1-phenyl-1-penten-3-one derivatives in rat liver mitochondria □ Structure–activity relationships—1-phenyl-1-penten-3-one derivatives evaluated for effect on enzyme activity in rat liver mitochondria

Mannich bases have a wide range of biological activities including antimicrobial effects (1–3), analgesic activity (4), local anesthetic properties (5, 6), and psychotropic effects (7). Recently, a number of Mannich bases and related compounds including 5-dimethylamino-1-substituted phenyl-1-penten-3-ones I*a*–I*e* were shown to have cyto-

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