Synthesis and Evaluation of 1-(Hydroxyphenyl)-1-nonen-3-ones and Related Compounds for Antineoplastic and Antimicrobial Activities

J. R. DIMMOCK *x, C. B. NYATHI ‡, and P. J. SMITH ‡

Received November 28, 1977, from the *College of Pharmacy and the ‡Department of Chemistry and Chemical Engineering, University of Saskatchewan, Saskatoon, Saskatchewan, S7N 0W0, Canada. Accepted for publication March 7, 1978.

Abstract □ Some 1-(hydroxyphenyl)-1-nonen-3-ones, the corresponding Mannich bases, and *O*-benzoyl esters were synthesized. Evaluation of these derivatives against murine P-388 lymphocytic leukemia indicated that, while the hydroxyphenyl styryl ketones and related esters were devoid of significant anticancer activities, etherification of the nuclear hydroxyl group gave compounds with a discernible increase in mean survival time. The hydroxyphenyl styryl ketones showed marked potencies against two pathogenic fungi and one yeast, while the corresponding ethers had diminished activities and the related esters were virtually devoid of antimicrobial activities. Two Mannich bases showed similar spectra of antimicrobial activities as the phenols and, in particular, were active against *Trichophyton mentagrophytes* and *Saccharomyces uvarum*.

Keyphrases □ 1-Phenyl-1-nonen-3-one derivatives—synthesized, evaluated for antineoplastic and antimicrobial activities □ Antineoplastic activity—various 1-phenyl-1-nonen-3-one derivatives evaluated in mice □ Antimicrobial activity—various 1-phenyl-1-nonen-3-one derivatives evaluated *in vitro* □ Structure–activity relationships—various 1-phenyl-1-nonen-3-one derivatives evaluated for antineoplastic activity in mice and antimicrobial activity *in vitro*

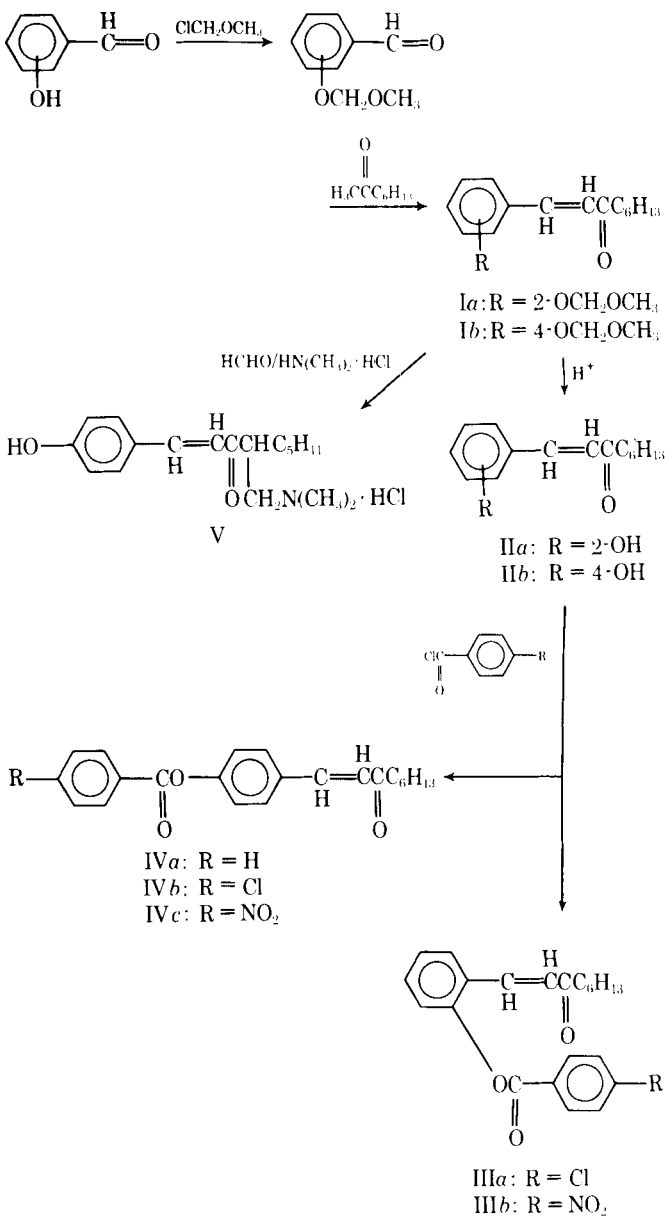
Recently (1, 2), some styryl ketones containing nuclear halogen and dimethylamino substituents and the related Mannich bases were examined for cytotoxic and antineoplastic activities. Metabolism of the cytotoxic (*E*)-2-benzylidenecyclohexanone was shown to proceed, in part at least, by nuclear hydroxylation (3). A convenient synthetic route to nuclear hydroxystyryl alkyl ketones would assist in identifying the structures of the metabolites; available methodology for the synthesis of these compounds indicates various problems such as dimer formation (4). Furthermore, certain nuclear hydroxy chalcones have tumor-inhibiting properties (5), and a number of cytotoxic sesquiterpenoid lactones have hydroxyl groups in close proximity to α,β-unsaturated keto functions (6).

A synthesis of hydroxystyryl alkyl ketones was initiated to evaluate them for antineoplastic activity. It was also considered that phenolic derivatives could be metabolized rapidly by conjugation (7) and that, by reacting the nuclear hydroxyl group with various benzoyl chlorides, esters could be produced which, on hydrolysis, would allow the gradual release of the parent phenol at a rate dependent on the Hammett value of the nuclear benzoyl substituent.

The interference of microsomal mixed function oxidase systems by methylenedioxyphenyl derivatives (8) suggested the synthesis of 1-(3,4-methylenedioxyphenyl)-1-nonen-3-one and the related Mannich base. Furthermore, as a continuing interest in the antimicrobial activities of Mannich bases and related compounds (9–11), it was proposed to examine the new derivatives for both antibacterial and antifungal activities.

DISCUSSION

An initial attempt to prepare 1-(hydroxyphenyl)-1-nonen-3-ones, utilizing the Claisen–Schmidt method (12), gave only a viscous oil and recovery of the starting material. This reaction depends on the formation of an intermediate aldol, produced by attack of the anion from the dialkyl ketone on the carbon atom of the aromatic aldehyde (13). In the presence of aqueous alkali, the phenoxide ion from the hydroxybenzaldehyde diminishes or abolishes the fractional positive charge on the carbonyl carbon atom of the benzaldehyde, thus inhibiting or preventing the synthesis of the intermediate aldol. Therefore, it was decided to protect the phenolic group by chemical modification prior to the condensation reaction. Since alkyloxymethyl ethers have been used previously for this purpose (14), the reaction sequence for the formation of I shown in Scheme I was followed successfully.



Scheme I

0022-3549/78/1100-1543$01.00/0

Table I—Antineoplastic Evaluation of Substituted 1-(Hydroxyphenyl)-1-nonen-3-ones and Related Compounds against P-388 Lymphocytic Leukemia in Mice

Compound	Maximum Increase in Mean Survival Time (Dose in mg/kg)[a]
I*a*	116 (200)
I*b*	121 (100)[b]
II*a*	112 (200)
II*b*	105 (200)
III*a*	94 (200)
III*b*	99 (100)[c]
IV*a*	110 (200)
IV*b*	97 (6.25)
IV*c*	105 (12.5)
V	113 (100)[d]
VI*a*	102 (100)
VI*b*	123 (50)[e]

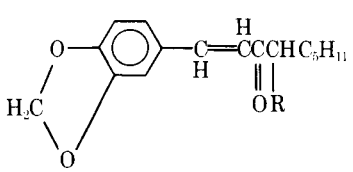
[a] The figures are the ratios of the survival time of treated animals to control animals expressed as a percentage. [b] On Day 5, there were 5/6 survivors at 200 and 100 mg/kg. [c] On Day 5, there were 5/6 survivors at 100 mg/kg and 6/6 survivors at 50 mg/kg. [d] On Day 5, there were 1/6 survivors at 200 mg/kg and 6/6 survivors at 100 mg/kg. [e] On Day 5, there were no survivors at 200 mg/kg and 6/6 survivors at 100 mg/kg.

Initial attempts to cleave the ethers I*a* and I*b* to the desired phenols II*a* and II*b* using hydrogen chloride, hydrogen bromide, acetic acid, sulfuric acid, and trifluoroacetic acid were unsuccessful. Aqueous formic acid led to the required compounds from which the corresponding *O*-benzoate esters III*a*, III*b*, and IV*a*–IV*c* were produced. It was decided that subjecting the phenols to the Mannich reaction might lead to ring aminomethylation (15) and that reaction of I*a* and I*b* under the Mannich conditions followed by cleavage of the protecting group would be feasible. However, reaction of I*b* with formaldehyde and dimethylamine hydrochloride led to the Mannich base V in 37% yield; *i.e.*, cleavage of the ether group occurred under the reaction conditions. Subsequently, it was shown that aminomethylation of II*b* gave V in 16% yield. The piperonylidene derivative VI*a* was prepared using the Claisen–Schmidt condensation and underwent the Mannich reaction to yield VI*b*.

The screening results of all compounds against P-388 lymphocytic leukemia in mice are summarized in Table I. Eight of the 12 compounds were nontoxic at the highest dose level examined (200 mg/kg); I*b* and III*b* had only marginal toxicity. With V and VI*b*, murine toxicity was noted at 200 mg/kg but was absent at 100 mg/kg. In compounds structurally related to these two Mannich bases, toxicity has been associated, in part at least, to impairment of mitochondrial function (16). The phenolic derivatives II*a* and II*b* gave small increases of approximately 9% in the mean survival time.

While the benzoate esters III*a*, III*b*, and IV*a*–IV*c* had lower antineoplastic activities than the precursor phenols, the corresponding ethers I*a* and I*b* increased the mean survival time by 19% on the average. This perceptible beneficial response could be due to preferential hydrolysis of the ether to the phenol in the tumorous cell since the claim has been made that the interstitial fluid surrounding certain cancers is more acidic than the plasma of blood afferent to the tumors (17). Alternatively, the diminished aqueous solubilities of the benzoate esters in comparison to the ethers may have retarded benzoate transport to the sites of action and, hence, diminished their anticancer potencies. Conversion of the styryl ketones II*b* and VI*a* to the corresponding Mannich bases V and VI*b* increased the antineoplastic activities in both cases.

Table II illustrates the evaluation of the 1-(hydroxyphenyl)-1-nonen-3-ones and related compounds for antimicrobial activities. The high potencies of the phenolic ketones II*a* and II*b* against the pathogenic fungi *Trichophyton mentagrophytes* and *Microsporum gypseum*, as well as the yeast *Saccharomyces uvarum*, are particularly noteworthy. The related ethers I*a* and I*b*, as well as the diether VI*a*, showed similar spectra of activities, but potencies were reduced and conversion of the phenols to the esters III*a*, III*b*, and IV*a*–IV*c* produced derivatives that were either bereft of activities at the higher concentrations tested (500 μg/ml) or showed very low levels of potencies. The Mannich bases V and VI*b* showed similar spectra of activities to the phenols and approached these derivatives in demonstrated bioactivities. With the exception of *Bacillus subtilis*, the compounds appeared to be virtually devoid of antibacterial activities.



VI*a*: R = H
VI*b*: R = $CH_2N(CH_3)_2 \cdot HCl$

EXPERIMENTAL[1]

Melting points and boiling points are uncorrected. Organic extracts were washed several times with water and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed *in vacuo*, using a water aspirator.

(*E*)-1-(Methoxymethoxyphenyl)-1-nonen-3-ones (I*a* and I*b*)—The methoxymethoxybenzaldehydes were prepared by the literature method (14), except that the sodium hydride dispersion was added in one operation rather than intermittently and the reaction mixture was stirred for 1 hr after sodium hydride addition. *o*-Methoxymethoxybenzaldehyde, bp 102°/0.55 mm [lit. (18) bp 100–102°/2.5 mm], was prepared as a colorless oil in 68% yield. The corresponding *para*-derivative, bp 113°/0.2 mm [lit. (19) bp 122°/2 mm], was prepared as a colorless oil in 74% yield. NMR spectroscopy and mass spectrometry were in accord with the proposed structures.

A mixture of *o*-methoxymethoxybenzaldehyde (83.1 g, 0.5 mole), 2-octanone (76.9 g, 0.6 mole), and sodium hydroxide (10 g, 0.25 mole) in water (300 ml) was heated under reflux for 18 hr. On cooling, the two phases were separated. The aqueous layer was extracted with benzene, and the organic extracts were combined with the original organic layer. Removal of both the benzene and excess 2-octanone gave a viscous brown oil, which was distilled to give (*E*)-1-(*o*-methoxymethoxyphenyl)-1-nonen-3-one (I*a*) in 59% yield, bp 178°/0.5 mm, as a yellow viscous oil; mass spectrum: *m/e* 276 ($M^{\cdot+}$, 2%) and 45 (100).

Anal.—Calc. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 72.80; H, 8.78.

The corresponding *para*-isomer, I*b*, was prepared in a similar manner as a yellow viscous oil, bp 191°/0.7 mm, in 42% yield. On standing, the oil solidified to a very pale-yellow waxy solid; mass spectrum: *m/e* 276 ($M^{\cdot+}$, 11%) and 45 (100).

Anal.—Calc. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.51; H, 8.43.

(*E*)-1-(Hydroxyphenyl)-1-nonen-3-ones (II*a* and II*b*)—A solution of (*E*)-1-(*o*-methoxymethoxyphenyl)-1-nonen-3-one (10 g, 0.036 mole) and aqueous formic acid (85% v/v, 15 ml, 0.338 mole) in petroleum ether (bp 100–120°, 250 ml) was heated under reflux for 20 min. On cooling, the layers were separated. The petroleum ether layer was concentrated to 50 ml and placed in a refrigerator (5°) to yield the desired ketone, II*a* (5.8 g), mp 98–100°. The aqueous phase, on refrigeration, deposited a further quantity of the required compound (0.41 g), mp 92–94°. Repeated recrystallization of the crude product from petroleum ether (bp 100–120°) afforded (*E*)-1-(*o*-hydroxyphenyl)-1-nonen-3-one (II*a*) (67% yield) as pale-yellow granular crystals, mp 101–102°; NMR ($CDCl_3$): δ 8.48 (s, 1, OH), 8.02 (d, 1, C_1H, $J_{1,2}$ = 16.2), 7.67–6.58 (m, 4, aromatic H), 6.97 (d, 1, C_2H, $J_{1,2}$ = 16.2), 2.70 (t, 2, C_4H), and 2.00–0.58 [m, 11, $(CH_2)_4CH_3$] ppm; mass spectrum: *m/e* 232 ($M^{\cdot+}$, 5%) and 147 (100).

Anal.—Calc. for $C_{15}H_{20}O_2$: C, 77.54; H, 8.68. Found: C, 78.03; H, 8.62.

The corresponding *para*-compound, II*b*, was prepared in an analogous manner, except that petroleum ether was not added to the reaction mixture. It crystallized from petroleum ether (bp 100–120°) as pale-yellow granular crystals (71% yield), mp 76–77°; mass spectrum: *m/e* 232 ($M^{\cdot+}$, 12%) and 147 (100).

Anal.—Calc. for $C_{15}H_{20}O_2$: C, 77.54; H, 8.68. Found: C, 77.89; H, 8.42.

Other attempts at cleaving I*b* to the desired hydroxy ketones II*a* and II*b* gave either viscous oils or a mixture of products. When hydrogen chloride or hydrogen bromide was bubbled through an ethereal solution of I*b* at room temperature for 1.5 hr, only brown viscous oils were formed. A solution of I*b* in ether and a twice molar ratio of acetic acid were stirred

[1] Elemental analyses were carried out by Mr. R. G. Teed of the Department of Chemistry and Chemical Engineering, University of Saskatchewan. Mass spectra (AEI 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. The 60-MHz NMR spectra (Varian T60 spectrophotometer, Varian Associates of Canada Ltd., Georgetown, Ontario, L7G 2J4, Canada) were carried out in deuterochloroform.

Table II—Antimicrobial Evaluation of Substituted 1-(Hydroxyphenyl)-1-nonen-3-ones and Related Compounds [a]

Microorganism	Ia	Ib	IIa	IIb	IIIa	IIIb	IVa	IVb	IVc	V	VIa	VIb
Escherichia coli (ATCC 8739)	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500
Pseudomonas aeruginosa (ATCC 10145)	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500
Klebsiella pneumoniae (ATCC 4352)	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>100
Salmonella typhimurium (G 46)	>500	>500	>100	>500	>500	>500	>500	>500	>500	>500	>500	>500
Bordetella bronchiseptica (ATCC 4617)	>500	>500	>500	>500	>500	>500	>500	>500	>500	>100	>500	>500
Staphylococcus aureus (ATCC 6538)	>500	>500	<100	<100	>500	>500	>500	>500	>500	>100	>500	>100
Streptococcus faecalis (ATCC 8030)	>500	>500	>500	>500	>500	>500	>500	>500	>500	>100	>500	>100
Bacillus subtilis (ATCC 6633)	<100	<100	<100	<100	>500	<100	>500	>500	<100	<100	<100	<100
Trichophyton mentagrophytes (ATCC 9533)	>250	<100	<10	<10	>500	>500	>100	>500	>250	<10	<100	<10
Microsporum gypseum (ATCC 14683)	<100	>100	<10	<10	>500	>500	>100	>500	>250	<100	>100	<100
Aspergillus niger (ATCC 10535)	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>100
Candida albicans (ATCC 10231)	>250	>500	<100	>500	>500	>500	>500	>500	>500	>100	>500	>100
Saccharomyces uvarum (ATCC 9080)	>500	>100	<10	<10	>500	>500	>500	>500	>500	<10	>500	<10
Average antimicrobial activity [b]	92	115	712	654	0	39	39	0	54	539	96	558

[a] The figures are the minimum inhibitory concentrations of the compounds in micrograms per milliliter. [b] Figures were calculated from the following expression: (combined antimicrobial activity × 100)/number of microorganisms in the screen. The combined antimicrobial activity was determined by giving the following scores at the highest potency of the compound against the microorganism: >250, 1; >100, 2.5; <100, 5; and <10, 25.

at room temperature for 2 hr, but only a quantitative recovery of I*b* was obtained. A solution of I*b* in benzene and acetic acid (5:1 v/v) was brought to reflux, 5 drops of sulfuric acid were added, and the resultant mixture was heated under reflux for 5 min. The product obtained was a mixture of I*b* and II*b* (PMR and mass spectral evidence). When a solution of I*b* in a mixture of equal parts of benzene and trifluoroacetic acid was heated under reflux for 48 hr, a mixture of I*b* and II*b* was obtained (PMR and mass spectral evidence).

An initial attempt to prepare II*a* and II*b* by the conventional Claisen–Schmidt reaction (12) from the appropriate hydroxybenzaldehyde, 2-octanone, and aqueous sodium hydroxide (3% w/v) produced only brown tars and unreacted hydroxybenzaldehyde (33%).

(*E*)-1-(Benzoyloxyphenyl)-1-nonen-3-ones (III*a*, III*b*, and IV*a*–IV*c*)—The esters III*a*, III*b*, and IV*a*–IV*c* were prepared by the following general method. The appropriate benzoyl chloride (0.025 mole) was added to a solution of either II*a* or II*b* (0.022 mole) in dry pyridine (20 ml), and the mixture was heated on a steam bath for 10 min and then stirred at room temperature for 24 hr. The solution was then poured onto crushed ice (20 g). After the ice melted, the crude reaction product was extracted with ether and purified by recrystallization.

(*E*)-1-[*o*-(*p*-Chlorobenzoyloxy)phenyl]-1-nonen-3-one (III*a*) crystallized from methanol as colorless needles in a 68% yield, mp 47–48.5°.

Anal.—Calc. for $C_{22}H_{23}ClO_3$: C, 71.23; H, 6.26. Found: C, 71.43; H, 6.23.

The corresponding *p*-nitro ester, III*b*, crystallized from methanol as pale-yellow needles in a 59% yield, mp 62–63.5°.

Anal.—Calc. for $C_{22}H_{23}NO_5$: C, 69.26; H, 6.08; N, 3.67. Found: C, 69.81; H, 6.18; N, 3.62.

(*E*)-1-[*p*-(Benzoyloxy)phenyl]-1-nonen-3-one (IV*a*) crystallized from ether as colorless flakes in an 83% yield, mp 85–86°.

Anal.—Calc. for $C_{22}H_{24}O_3$: C, 78.57; H, 7.20. Found: C, 79.11; H, 7.03.

The corresponding *p*-chloro ester, IV*b*, crystallized from ether as colorless flakes in an 85% yield, mp 115–116°.

Anal.—Calc. for $C_{22}H_{23}ClO_3$: C, 71.23; H, 6.26. Found: C, 71.62; H, 6.13.

The corresponding *p*-nitro ester, IV*c*, crystallized from ether as cream flakes in a 65% yield, mp 99–101°.

Anal.—Calc. for $C_{22}H_{23}NO_5$: C, 69.26; H, 6.08; N, 3.68. Found: C, 67.45; H, 5.94; N, 3.52.

PMR and mass spectral studies also confirmed the structures.

The crude reaction product from II*a* and benzoyl chloride was distilled to give an orange oil, bp 198–206°/0.2 mm. TLC of the distillate, using silica gel and a solvent mixture of chloroform–ethyl acetate–diethylamine (92:5:3), indicated the presence of unreacted ketone II*a*, which was not separated from the desired ester by a chromatography column packed with silica gel and eluted with the solvent mixture used for TLC. Attempted redistillation of the oil led only to the formation of a yellowish-brown viscous mass.

(*E*)-4-Dimethylaminomethyl-1-(*p*-hydroxyphenyl)-1-nonen-3-one Hydrochloride (V)—A mixture of (*E*)-I*b* (15 g, 0.054 mole), dimethylamine hydrochloride (4.4 g, 0.054 mole), and paraformaldehyde (4.9 g, 0.054 mole) in ethanol (100 ml) containing hydrochloric acid (0.5–2.0%) was heated under reflux for 24 hr. On cooling, the alcohol was removed *in vacuo;* the residue was suspended in water and extracted with ether. Separation of the organic phase, followed by removal of ether, afforded (*E*)-II*b* (2.1 g, 17% yield). The aqueous layer was cooled with ice water and basified to pH 9 with aqueous sodium hydroxide (0.1 *M*).

The liberated oil was extracted with ether, and the organic extract was washed with water, dried, and then acidified with ethanolic hydrochloric acid (20% w/v). The solution was concentrated and placed in a refrigerator, and the colorless solid that deposited was recrystallized from acetone to give V (6.5 g, 37% yield) as a colorless powder, mp 174–176°; NMR: δ 10.56 (s, 1, N^+H), 10.22 (s, 1, OH), 7.72 (d, l, C_1H, $J_{1,2}$ = 16.0), 7.64 (d, 2, aromatic H, $J_{2',3'}$ = 8.7), 6.90 (d, 2, aromatic H, $J_{5',6'}$ = 8.7), 6.90 (d, l, C_2H, $J_{1,2}$ = 16.0), 3.80–3.00 (m, 3, C_4H, CH_2), 2.72 [s, 6, $N(CH_3)_2$], and 1.90–0.57 [m, 11, $(CH_2)_4CH_3$] ppm; mass spectrum: *m/e* 289 (M^+ − HCl, 2%) and 58 (100).

Anal.—Calc. for $C_{18}H_{28}ClNO_2$: C, 66.34; H, 8.66; N, 4.30. Found: C, 62.03; H, 8.71; N, 4.08.

(*E*)-1-(3,4-Methylenedioxyphenyl)-1-nonen-3-one (VI*a*) and the Related Mannich Base (VI*b*)—A mixture of 3,4-methylenedioxybenzaldehyde (24.0 g, 0.16 mole), 2-octanone (23.1 g, 0.18 mole), and sodium hydroxide (4 g, 0.1 mole) in water (100 ml) was heated under reflux for 23 hr. On cooling, the reaction mixture was extracted with benzene. Evaporation of the solvent produced a yellow solid, which was recrystallized from petroleum ether (bp 100–120°) to give VI*a* (16.4 g, 39% yield) as colorless needles, mp 56.5–58° [lit. (20) mp 61°]; mass spectrum: *m/e* 260 ($M^{\cdot+}$, 22%) and 175 (100).

Anal.—Calc. for $C_{16}H_{20}O_3$: C, 73.81; H, 7.75. Found: C, 73.92; H, 7.95.

A solution of hydrochloric acid (10 ml) in ethanol (250 ml) was added to a mixture of VI*a* (41.2 g, 0.16 mole), dimethylamine hydrochloride (12.9

g, 0.16 mole), and paraformaldehyde (4.8 g, 0.16 mole) in methanol (12.5 ml), and the resultant mixture was heated under reflux for 1 hr. On cooling, a colorless solid deposited, which was recrystallized from acetone to give (*E*)-4-dimethylamino-1-(3,4-methylenedioxyphenyl)-1-nonen-3-one hydrochloride (VI*b*) (18.3 g, 32% yield) as colorless needles, mp 149–150°; mass spectrum: *m/e* 317 (M^+ − HCl, 2%) and 58 (100).

Anal.—Calc. for $C_{19}H_{28}ClNO_3$: C, 64.47; H, 7.98; N, 3.96. Found: C, 64.78; H, 8.07; N, 3.81.

Screening—For anticancer screening[2], the compounds were administered in saline (II*a*, IV*a*–IV*c*, and V), saline with polysorbate 80 (II*b*, III*a*, III*b*, VI*a*, and VI*b*), saline with alcohol (I*b*), and hydroxypropylcellulose (I*a*) intraperitoneally to CD_2F_1 mice. Injections were made daily for 9 consecutive days.

For the antimicrobial screen[3], the compounds were dissolved in water or dimethyl sulfoxide and diluted serially to various concentrations. The concentrations of stock solutions were prepared in such a way that when 0.5 ml was added to 15 ml of agar medium, the desired final concentrations were obtained. Trypticase soy agar medium was employed for the bacteria, and modified Sabouraud agar was used for the fungi and yeasts. The test organisms were grown previously for 2 days at 35° for bacteria and yeasts and 1 week for fungi at 24° on slants of the same medium.

The agar plates were streaked with a loopful of cell suspension that had been washed off from the slants and diluted to approximately 10^5 organisms/ml. The plates were incubated for 2–14 days at 24° for fungi and at 35° for bacteria. The bacteria were assessed at 500 and 100 μg/ml; therefore, >100 indicates a compound showing inhibition of growth at 100, but not 500, μg/ml. The fungal growth was measured at concentrations of 500, 250, 100, and 10 μg/ml; >100 indicates, for example, that growth was inhibited at 100, but not 250, μg/ml.

REFERENCES

(1) J. R. Dimmock and W. G. Taylor, *J. Pharm. Sci.*, **64,** 241 (1975).

(2) J. R. Dimmock, G. B. Baker, and R. G. Sutherland, *Can. J. Pharm. Sci.*, **10,** 53 (1975).

(3) J. R. Dimmock, N. W. Hamon, K. W. Hindmarsh, A. P. Sellar, W. A. Turner, G. H. Rank, and A. J. Robertson, *J. Pharm. Sci.*, **65,** 538 (1976).

(4) I. M. Heilbron and F. Irving, *J. Chem. Soc.*, **1929,** 934.

(5) O. K. Kabiev and S. M. Vermenichev, *Izv. Akad. Nauk Kaz. SSR, Ser. Biol.*, **9,** 72 (1971); through *Chem. Abstr.*, **75,** 47091u (1971).

(6) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14,** 1147 (1971).

(7) A. Goldstein, L. Aronow, and S. M. Kalman, "Principles of Drug Action: The Basis of Pharmacology," 2nd ed., Wiley, Toronto, Canada, 1974, p. 258.

(8) E. Hodgson and J. E. Casida, *Biochem. Pharmacol.*, **8,** 179 (1961).

(9) J. R. Dimmock, A. M. Qureshi, L. M. Noble, P. J. Smith, and H. A. Baker, *J. Pharm. Sci.*, **65,** 38 (1976).

(10) J. R. Dimmock, W. A. Turner, and H. A. Baker, *ibid.*, **64,** 995 (1975).

(11) J. R. Dimmock, D. K. Kowal, W. A. Turner, P. J. Smith, L. M. Noble, and W. J. Pannekoek, *ibid.*, **67,** 401 (1978).

(12) P. J. Smith, J. R. Dimmock, and W. G. Taylor, *Can. J. Chem.*, **50,** 871 (1972).

(13) J. Packer and J. Vaughan, "A Modern Approach to Organic Chemistry," Oxford University Press, London, England, 1958, p. 760.

(14) P. J. Nelson and A. F. A. Wallis, *Tappi*, **56,** 132 (1973).

(15) F. F. Blicke, in "Organic Reactions," vol. I, R. Adams, Ed., Wiley, New York, N.Y., 1942, p. 311.

(16) J. R. Dimmock, N. W. Hamon, K. W. Hindmarsh, D. G. Mills, L. E. Negrave, G. H. Rank, and A. J. Robertson, *J. Pharm. Sci.*, **65,** 482 (1976).

(17) P. M. Gullino, F. H. Crantham, S. H. Smith, and A. C. Haggerty, *J. Natl. Cancer Inst.*, **34,** 857 (1965).

(18) H. Bohnsack and W. Seibert, *Riechstoffe, Aromen, Koerperpflegemittel*, **15,** 407 (1965); through *Chem. Abstr.*, **64,** 17458f (1966).

(19) *Ibid.*, **15,** 321 (1965); through *Chem. Abstr.*, **64,** 17349g (1966).

(20) O. F. Hedenburg and H. Wachs, *J. Am. Chem. Soc.*, **70,** 2216 (1948).

(21) R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3,* **3** (Sept. 1972).

[2] Carried out by the Drug Research and Development Division, National Cancer Institute, Bethesda, Md., using their protocols (21).

[3] Bio-Research Laboratories Ltd., Montreal, Quebec, Canada.

ACKNOWLEDGMENTS

The authors thank the Medical Research Council of Canada for the award of an operating grant (MA 5538) to J. R. Dimmock. They also thank Connlab Holdings Ltd. for financial assistance. The United Nations provided a stipend to C. B. Nyathi, which is gratefully acknowledged.