Comparison of Antimicrobial Activity of Nuclear-Substituted Aromatic Esters of 5-Dimethylamino-1-phenyl-3-pentanol and 3-Dimethylamino-1-phenyl-1-propanol with Related Cyclic Analogs

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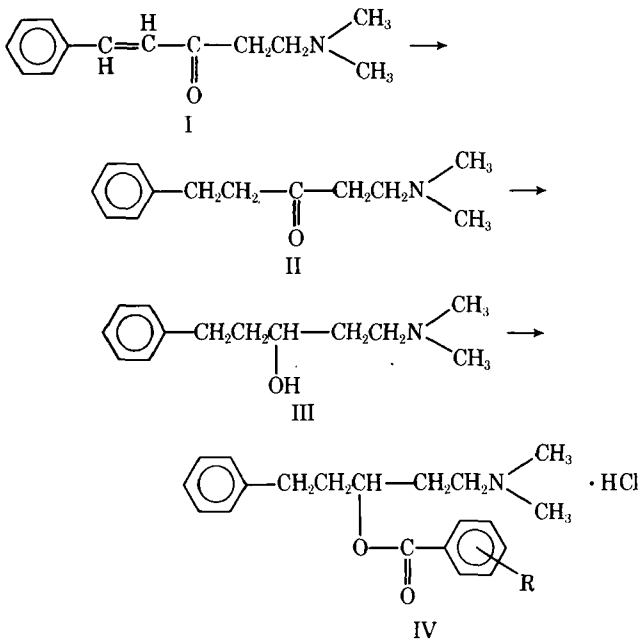
Abstract □ A series of six aromatic esters of both 5-dimethylamino-1-phenyl-3-pentanol and 3-dimethylamino-1-(2-phenylcyclohexyl)-1-propanol was prepared. Antimicrobial evaluation showed that the cyclic analogs had approximately twice the activity of the open chain series; in particular, the *o*-chlorophenyl ester showed pronounced activity against three pathogenic fungi at approximately 10 ppm. Aromatic esters of 3-dimethylamino-1-phenyl-1-propanol were prepared and demonstrated lower activity than two esters of 2-dimethylamino-1-phenylcyclohexanol. The screening results showed that the best activity was found when a dimethylene chain was present between the phenyl ring and the carbon atom bearing the acyloxy function and that the cyclic derivatives were more active than their more flexible counterparts.

Keyphrases □ Esters, aromatic—nuclear substituted, preparation, IR, NMR, and mass spectra, comparison of antimicrobial activity with related cyclic analogs □ Antimicrobial evaluation—series of nuclear-substituted aromatic esters, compared with cyclic analogs

Various Mannich bases have antimicrobial activity (1–6), and reduction of the ketone group of Mannich bases has led to compounds with increased pharmacological activity (7). The activity of the alcohols possibly may be improved by esterification, thereby masking the polar hydroxyl group and facilitating transportation to a site of action. The hydrolysis of a series of benzoate esters derived from a precursor alcohol would be influenced by the Hammett and Taft values of the nuclear substituents, and a correlation between the rate of hydrolysis and the antimicrobial activity of the esters may emerge.

Recently, cyclic analogs of some pharmacologically active compounds, such as dopamine (8, 9), amphetamine (10), psychotropic drugs (11–13), antihistaminics (14), and acetylcholine (15–18) were prepared and screened. Some literature references described rigid analogs having enhanced potency over their more flexible counterparts (19, 20), while in other cases a comparison of flexible and rigid derivatives indicated higher bioactivity in the flexible compounds (21–23).

The preparation of the acyclic substituted pentanes (II–IV) (Scheme I) and the substituted propanes (IX and X), in addition to the corresponding rigid analogs [VI–VIII (Scheme II), XI, and XII], was planned so that their antimicrobial potency could be evaluated.



IV*a*: R = H IV*d*: R = 4-Cl
IV*b*: R = 2-Cl IV*e*: R = 4-CH_3
IV*c*: R = 3-Cl IV*f*: R = 4-NO_2

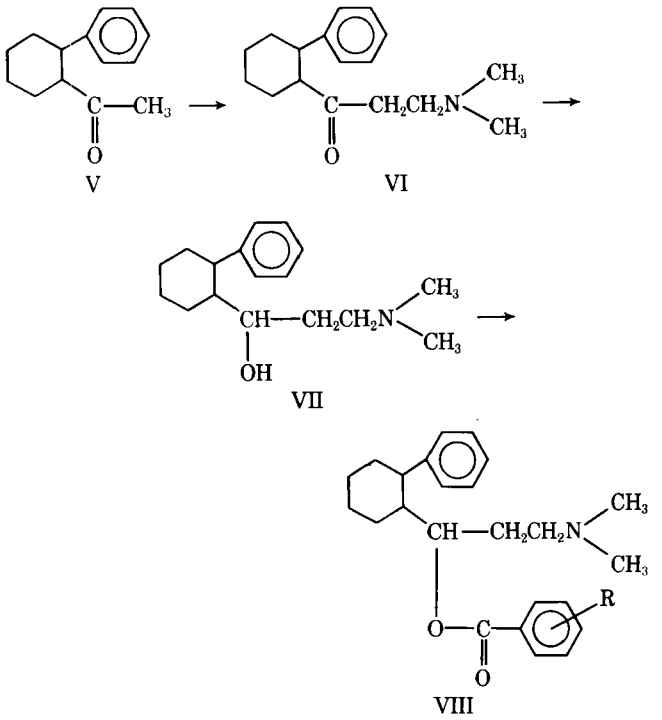
Scheme I

RESULTS AND DISCUSSION

The substituted pentane derivatives were prepared from the Mannich base (I) as shown in Scheme I. The cyclic series of derivatives shown in Scheme II required the synthesis of 1-acetyl-2-phenylcyclohexane (V). Reaction of butadiene with 1-phenyl-1-buten-3-one gave the required Diels–Alder adduct (22%) which, on reduction with Raney nickel, gave V in 92% yield; V was shown previously to have the *trans*-configuration (24).

A Mannich reaction between V, formaldehyde, and dimethylamine hydrochloride gave a product with the correct elemental analysis and molecular weight for VI. However, the possibility exists of a reaction occurring at the acetyl methyl or cyclohexyl methine group of V to give either VI or XIII (Scheme III). PMR evidence confirmed the identity of the product as VI. Furthermore, mass spectrometry of V showed a prominent M − 43 peak (26% relative abundance) due to the loss of the acetyl group, but no such loss was observed in the mass spectrum of the Mannich base obtained, supporting the structure assigned to VI. Reduction of VI gave the required alcohol (VII), acylation of which gave the corresponding esters in yields ranging from 30 to 50%.

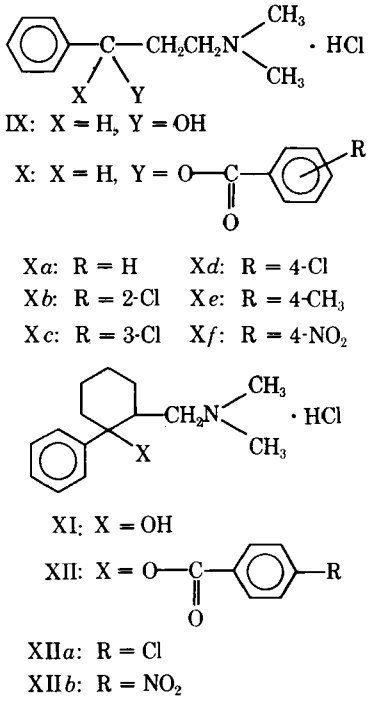
Esterification of the acyclic alcohol (IX) gave the desired products (X) in 54–70% yields. The cyclic alcohol (XI), prepared by reaction between phenylmagnesium bromide and 2-dimethylaminomethylcyclohexanone, showed only one peak when examined by GLC, suggesting isomeric purity. Kinetic and thermodynamic consideration would predict that the product formed would have the



V VI VII VIII

VIII*a*: R = H VIII*d*: R = 4-Cl
VIII*b*: R = 2-Cl VIII*e*: R = 4-CH_3
VIII*c*: R = 3-Cl VIII*f*: R = 4-NO_2

Scheme II



IX: X = H, Y = OH

X: X = H, Y = O—C(=O)—R

X*a*: R = H X*d*: R = 4-Cl
X*b*: R = 2-Cl X*e*: R = 4-CH_3
X*c*: R = 3-Cl X*f*: R = 4-NO_2

XI: X = OH

XII: X = O—C(=O)—R

XII*a*: R = Cl
XII*b*: R = NO_2

trans-N,N-dimethylbenzylamine configuration.

Attempted preparation of the esters under similar reaction conditions to those used with the previous series of compounds yielded only the *p*-chloro and *p*-nitro esters (XII*a* and XII*b*, respectively). In other cases, unreacted XI was obtained. More vigorous reaction conditions such as heating the reactants under reflux in ether or acetone for 6 hr or forming the lithium complex of X prior to treatment with an acyl chloride, followed by heating the mixture under reflux in ether for 8 hr, were unsuccessful in producing the desired esters.

After some compounds had been evaluated for antimicrobial activity (Table I), the screen became unavailable and the assessment of bioactivity was completed elsewhere (Table II). Since different microorganisms were used (Tables I and II), the average antimicrobial potency was evaluated for each compound so that activity correlations could be made.

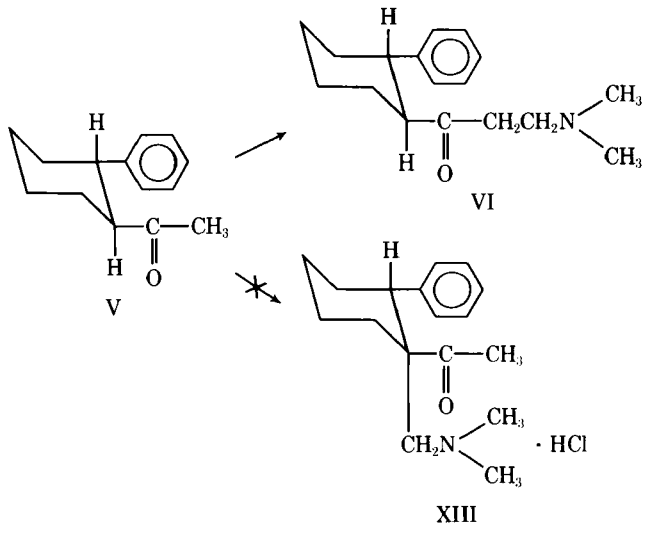
Compound I is an α,β-unsaturated ketone, a class of compounds with demonstrated antibacterial effectiveness (25), but showed only marginal antimicrobial activity. If the alcohol III was an active antimicrobial agent, then the rate of hydrolysis to III would depend on the nuclear substituents on the ester aromatic ring in IV if base-catalyzed hydrolysis (ρ:2.460) took priority over acid-catalyzed hydrolysis (ρ:−0.144). The unsubstituted ester IV*a* showed a low level of activity. Use of the Hammett equation predicted that the base-catalyzed hydrolysis rate of IV*e* should be approximately half that of IV*a*, but IV*e* demonstrated approximately a threefold increase in antimicrobial potency. However, a predicted increase in hydrolysis of the esters in the case of the nuclear chlorinated derivatives (IV*b*–IV*d*) also brought about an increase in activity, suggesting that a correlation between the rate of hydrolysis of esters and antimicrobial activity did not exist.

In the case of the *p*-nitro ester, which would be expected to hydrolyze more quickly than the other esters, no activity at the highest dose level tested was observed. The nature of the substituents seemed more important than the rate of hydrolysis, and antimicrobial activity possibly was due to the ester *per se*.

Models suggest that the cyclic esters (VIII) would be less easily hydrolyzed than the acyclic compounds (IV) due to steric reasons. Thus, if hydrolysis to the precursor alcohol was responsible for biological activity, a decrease in activity would be predicted. The average antimicrobial activity was 190 in IV but 391 in the related cyclic esters. This twofold increase in activity further substantiated the view that the esters themselves are active. Furthermore, the general trend in activity was similar to that of the open chain analogs, *i.e.*, an increase in activity of the *p*-methyl and chlorinated esters (VIII*b*–VIII*e*) over the unsubstituted compound (VIII*a*), with the *p*-nitro ester showing the least activity. The high potency of VIII*b* against three pathogenic fungi is noteworthy.

While the acyclic alcohol (IX) was devoid of antimicrobial activity, esters X*a*–X*e* showed a low level of activity. In general, the results parallel those found with the previous series of esters, although these compounds were less active; *i.e.*, the average antimicrobial activity was 36, or less than one-fifth of the activity of the related *n*-pentane derivatives (IV). The cyclic alcohol (XI) was devoid of activity, like its acyclic relative IX, but the two esters obtained (XII*a* and XII*b*) had an antimicrobial activity of 73, higher than that for the open chain analogs (X*d* and X*f*).

The screening results may be summarized as follows. First, a dimethylene chain between the aromatic ring and the acyloxy function in the series of esters IV and VIII gave higher activity than esters X and XII, where the aromatic ring was attached to the same carbon atom as the acyloxy function. This result could be due to IV and VIII having preferred spatial arrangements at a possible re-



V VI XIII

Scheme III

Table I—Screening[a] of Esters of 1-Phenyl-5-dimethylamino-3-pentanols and 1-Phenyl-3-dimethylamino-1-propanols and Related Derivatives against Various Microorganisms[b]

Microorganism[c]	I	IVa	IVb	IVc	IVd	IVe	IVf	IX	Xb	Xc	Xd	Xe	Xf	XI	XIIa	XIIb
Streptococcus faecalis	> 200	200	200	50	50	200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	200	200
Staphylococcus aureus (R)[d]	> 200	> 200	200	200	200	200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	200	> 200
Staphylococcus aureus (S)[e]	> > 200	> > 200	200	200	200	200	> 200	> > 200	> > 200	> > 200	> > 200	> > 200	> > 200	> > 200	200	> > 200
Klebsiella pneumoniae	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Pseudomonas aeruginosa	> 200	> > 200	> 200	> > 200	> > 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> > 200	> > 200
Escherichia coli	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Salmonella typhimurium	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> > 200	> > 200	> > 200	> 200	> > 200	> > 200	> > 200	> > 200
Trichophyton mentagrophytes	50	200	200	50	50	200	200	> 200	> 200	200	200	> 200	> > 200	> > 200	50	200
Mycobacterium smegmatis	200	200	200	50	50	200	> 200	> 200	> 200	> 200	> 200	> 200	> > 200	> > 200	200	200
Candida albicans	> 200	200	200	50	50	50	> 200	> 200	> 200	200	200	> 200	> > 200	> > 200	200	> 200
Bacillus subtilis	200	200	200	50	50	50	200	> 200	> > 200	200	200	> 200	> > 200	> > 200	200	> 200
Fusarium oxysporum	200	200	200	50	50	50	200	> 200	> > 200	200	200	200	> > 200	> > 200	200	> > 200
Penicillium citrinum	200	200	200	50	50	50	200	> 200	> > 200	200	200	200	> > 200	> > 200	200	> > 200
Aspergillus niger	200	200	200	50	50	50	200	> 200	> > 200	200	200	200	> > 200	> > 200	200	> 200
Cryptococcus neoformans	200	200	200	50	50	50	200	> 200	> > 200	200	200	200	> > 200	> > 200	200	> 200
Blastomyces dermatitidis	200	200	200	50	50	200	200	> 200	> > 200	200	200	> 200	> > 200	> > 200	200	> > 200
Xanthomonas vesicatoria	200	200	200	50	50	200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	50	200
Streptococcus pyogenes	> 200	50	50	< 12	50	50	200	> 200	200	200	200	200	> 200	> 200	200	200
Sarcina lutea	> 200	200	200	< 12	50	50	200	> 200	> 200	200	200	200	> 200	> 200	200	200
Average antimicrobial activity[f]	63	84	95	410	284	221	47	0	10	53	53	47	0	0	110	36

[a] Conducted by Dr. J. F. Pagono and staff, Smith Kline and French Laboratories, Philadelphia, Pa. [b] Figures in table are the minimum inhibitory concentrations of the compounds in micrograms per milliliter. [c] The strains of microorganisms in this table are identified by the following numbers: ATCC 9790, SK&F 24390, SK&F 23390, SK&F 4200, SK&F 11320, SK&F 12140, SK&F 11350, SK&F 17410, ATCC 101, SK&F 3470, ATCC 6633, ATCC 9848, ATCC 16040, SK&F 330, EK1, EK2, ATCC 11551, ATCC 8668, and ATCC 9341, respectively. [d] Strain resistant to penicillin G. [e] Strain sensitive to penicillin G. [f] Figures were evaluated from the following expression: (combined antimicrobial activity × 100)/number of microorganisms in screen. The combined antimicrobial activity was determined by giving the following scores at the highest potency of the compound against the microorganism: 200 μg = 1, 50 μg = 4, and 12.5 μg = 16.

ceptor site or be associated with lipoid solubility factors.

Second, in comparing the screening results of the cyclic with the analogous acyclic series, the cyclic compounds had higher antimicrobial potency. A degree of rigidity between functional groups favors activity.

Third, the evidence suggests that the esters are active and that hydrolysis to the corresponding alcohols is an insignificant factor in evaluating the activities of these compounds.

EXPERIMENTAL[1]

5-Dimethylamino-1-phenyl-1-penten-3-one Hydrochloride (I)—The literature method (26) was followed, except that the time of heating under reflux was 24 hr, to give I in 22% yield as colorless crystals from acetone, mp 157–157.5° [lit. (26) mp 157°]; IR (potassium bromide): 1675 (w) shoulder (C=O) and 1665 (s) (C=O) cm^{-1}; mass spectrum: *m/e* 203 (parent peak); NMR (deuterochloroform): δ 7.8 (d, 1, $J_{1,2}$ = 16.5 Hz, C_1H) and 6.8 (d, 1H, $J_{2,1}$ = 16.5 Hz, C_2H) ppm.

Anal.—Calc. for $C_{17}H_{18}ClNO$: C, 65.12; H, 7.56. Found: C, 64.60; H, 7.80.

5-Dimethylamino-1-phenylpentan-3-one (II)—5-Dimethylamino-1-phenyl-1-penten-3-one (23 g, 0.113 mole) in ethanol was hydrogenated in a Paar apparatus with Raney nickel [approximately 10% (w/v)]. The solution was filtered through diatomaceous earth[2], and removal of the ethanol afforded a very pale-yellow oil (19.5 g); IR (smear): 1715 (s) (C=O) cm^{-1}. Attempts to form a crystalline hydrochloride failed, but a small quantity of the oil was converted to a picrate, mp 90–91° [lit. (27) mp 90–92°].

5-Dimethylamino-1-phenylpentan-3-ol (III)—A solution of II (18.5 g, 0.090 mole) in dry ether (100 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.63 g, 0.043 mole) in dry ether (100 ml). The reaction mixture was heated under reflux for 24 hr and, on cooling, was decomposed by the dropwise addition of water (8 ml). Removal of the solvent gave a colorless oil (16.0 g); IR (smear): 3400 (s) (OH) and 1715 (s) (C=O absent) cm^{-1}. Attempts to form a crystalline hydrochloride failed, and the structure of the alcohol was confirmed by conversion to various substituted benzoates.

Preparation of Benzoate Esters of 5-Dimethylamino-1-phenylpentan-3-ol Hydrochloride (IV)—The benzoate esters were prepared by the following general method. A solution of the acid chloride (0.0096 mole) in dry ether (30 ml) was added dropwise to a stirred solution of III (2 g, 0.0096 mole) in dry ether (30 ml). The temperature of the reaction was maintained at 0–10° during the addition process, and then the mixture was stirred at room temperature for 24 hr. Removal of the solvent afforded colorless to pale-yellow solids, which were recrystallized from ether–ethanol to give colorless crystals, except for the nitro ester which was pale yellow in color. The esters gave a parent ion corresponding to the molecular weight of the free base. The results are summarized in Table III.

3-Dimethylamino-1-(2-phenylcyclohexyl)-1-propanone Hydrochloride (VI)—A stirred mixture of *trans*-1-acetyl-2-phenylcyclohexane (3.4 g, 0.01 mole) (24), dimethylamine hydrochloride (1.4 g, 0.02 mole), paraformaldehyde (0.5 g, 0.01 mole), hydrochloric acid (0.5 ml), and isopentyl alcohol (15 ml) was heated under reflux for 48 hr. The reaction mixture was concentrated and, on scratching the side of the flask, a light-brown material deposited. On trituration with ether, a fawn solid (3.0 g) resulted. Recrystallization of the solid from ether–ethanol gave VI as colorless crystals

[1] Boiling points and melting points are uncorrected. IR spectra were determined on a Unicam SP200G spectrophotometer previously calibrated with polystyrene. Band intensities are designated as s (strong) and w (weak). Mass spectra were determined at 70 ev on an AE1 MS-12 single-focusing mass spectrometer, operated by Mr. D. Bain of the Department of Chemistry and Chemical Engineering, University of Saskatchewan. NMR spectra were determined using a Varian A60 instrument operating at 44°, with tetramethylsilane as the internal standard. Elemental analyses were carried out on a Coleman model 33 carbon–hydrogen analyzer by Mr. R. E. Teed of the Department of Chemistry and Chemical Engineering, University of Saskatchewan, and Mr. R. M. Smith of the College of Pharmacy, University of Saskatchewan. Hydrogenations were undertaken using a Paar series 3910 shaker apparatus at 27.2 kg (60 lb) of pressure. GLC was carried out using a MT model 220 gas chromatograph, equipped with flame-ionization detector and 1.8-m × 0.47-cm (6-ft × 0.18-in.) glass columns packed with 3% SE-52 adsorbed onto silanized Chromosorb W (70–80 mesh), and a Varian 90-P gas chromatograph employing different columns.

[2] Celite.

Table II—Screening[a] of 3-Dimethylamino-1-(2-phenylcyclohexyl)-1-propanone and Related Esters against Various Microorganisms[b]

Microorganism[c]	VI	VIIIa	VIIIb	VIIIc	VIIId	VIIIe	VIIIf	Xa
Staphylococcus pyogenes (S)[d]	100	100	50	25	25	50	100	>100
Staphylococcus pyogenes (R)[e]	100	100	50	25	25	50	100	>100
Streptococcus faecalis	100	100	50	25	25	50	100	>100
Escherichia coli	100	100	50	50	50	50	100	>100
Aerobacter aerogenes	100	50	100	100	100	100	100	>100
Salmonella pullorum	100	50	100	100	100	100	100	>100
Pseudomonas aeruginosa	100	50	100	100	100	100	100	>100
Proteus mirabilis	100	50	100	100	100	100	100	>100
Proteus vulgaris	100	100	100	100	50	100	100	>100
Klebsiella pneumoniae	100	50	100	12.5	25	50	100	100
Serratia marcescens	100	50	100	50	50	100	100	100
Candida albicans		100	12.5	100	100	100	100	100
Microsporum gypseum		50	6.25	50	50	50	50	>100
Trichophyton granulosum		100	12.5	50	100	100	100	>100
Trichomonas vaginalis		>100	50	50	50	50	100	
Trichomonas foetus	100							100
Average antimicrobial activity[f]	200	280	653	480	427	293	213	53

[a] Conducted by Ayerst Laboratories, Montreal, Quebec, Canada. [b] Figures in table are the minimum inhibitory concentrations of compounds in micrograms per milliliter. [c] The strains of microorganisms in this table are identified by the following numbers: AY-B-352, AY-B-353, AY-B-355, ATCC 11229, AY-B-357, AY-B-358, AY-B-359, AY-B-360, AY-B-361, ATCC 10081, ATCC 9103, AY-F-598, AY-F-605, AY-F-604, ATCC 30001, and ATCC 30003, respectively. [d] Strain sensitive to penicillin G potassium. [e] Strain resistant to penicillin G potassium. [f] Figures were evaluated from the following expression: (combined antimicrobial activity X 100)/number of microorganisms in screen. The combined antimicrobial activity was determined by giving the following scores at the highest potency of the compound against the microorganism: 100 μg = 2, 50 μg = 4, 25 μg = 8, 12.5 μg = 16, and 6.25 μg = 32.

Table III—Benzoate Esters of 5-Dimethylamino-1-phenylpentan-3-ol Hydrochloride (IV)

Compound	Yield, %	Melting Point	Molecular Formula	Analysis, % Calc.	Analysis, % Found	IR Spectra, cm^{-1} (C=O)
IV*a*	50	120–121°	$C_{20}H_{26}ClNO_2$	C 68.76 H 7.53	68.50 7.59	1710 (s)
IV*b*	43	101–101.5°	$C_{20}H_{25}Cl_2NO_2$	C 62.83 H 6.59	62.65 6.71	1710 (s)
IV*c*	45	103.5–105°	$C_{20}H_{25}Cl_2NO_2$	C 62.83 H 6.59	62.75 6.58	1710 (s)
IV*d*	36	122–123.5°	$C_{20}H_{25}Cl_2NO_2$	C 62.83 H 6.59	62.80 6.65	1710 (s)
IV*e*	60	133–134.5°	$C_{21}H_{28}ClNO_2$	C 69.69 H 7.78	70.10 8.18	1705 (s)
IV*f*	36	145–146°	$C_{20}H_{25}ClN_2O_4$	C 61.12 H 6.41	61.10 6.53	1720 (s)

(1.0 g, 20%), mp 177.5–178.0°; IR (mineral oil mull): 1710 (s) (C=O) cm^{-1}; mass spectrum: *m/e* 259 (M^+, 5), 91 (9), 73 (5), 72 (7), 59 (4), 58 (100), 57 (3), 45 (5), 44 (5), 42 (3), and 36 (8); NMR (deuterochloroform): δ 7.18 (m, 5H, C_6H_5), 3.0–1.2 (m, 14H, CH_2 and CH protons), 2.28, and 2.60 [m, 6H, $^+N(CH_3)_2$].

Anal.—Calc. for $C_{17}H_{26}ClNO$: C, 69.03; H, 8.76; N, 4.74. Found: C, 69.11; H, 9.17; N, 4.94.

From the mother liquors, a small quantity of a beige solid was obtained. This solid was recrystallized from ether–ethanol to give colorless crystals (0.3 g), mp 154–155°, considered to be VI contaminated with dimethylamine hydrochloride; IR (mineral oil mull): 1685 (s) and 1700 (s) (C=O) cm^{-1}; mass spectrum: *m/e* 259 (M^+, 4), 91 (9), 58 (75), 46 (18), 45 (58), 44 (100), 43 (38), 42 (45), 41 (35), 40 (37), 39 (14), 38 (76), 37 (30), 36 (78), 35 (86), 30 (37), and 27 (23); PMR (deuterochloroform): δ 7.3 (m, 5H, C_6H_5), 2.7 [s, 6H, $^+N(CH_3)_2$], and 2.2–1.0 (m, 22H, CH_3, CH_2, and CH protons).

Anal.—Found: C, 53.32; H, 9,69; N, 9.62.

The ether washings from the trituration were concentrated to give a fawn solid (3.0 g) which, on GLC analysis[3], had the same retention time as V.

In a previous experiment, 0.002-mole quantities of *trans*-1-acetyl-2-phenylcyclohexane, dimethylamine hydrochloride, and paraformaldehyde in ethanol (5 ml) containing hydrochloric acid (0.1 ml) were heated under reflux for 24 hr. On cooling and scratching the sides of the flask, a brown solid (0.3 g) deposited. Recrystallization from *n*-hexane showed this solid to be unreacted *trans*-1-acetyl-2-phenylcyclohexane (melting point and IR evidence).

3-Dimethylamino-1-(2-phenylcyclohexyl)propan-1-ol (VII)—A solution of VI (14.0 g, 0.054 mole) in dry ether (100 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.02 g, 0.027 mole) in dry ether (100 ml). The reaction mixture was then heated under reflux for 24 hr and cooled, and water (6 ml) was added dropwise. Evaporation of the solvent gave a colorless oil[4] (11.5 g); IR (smear): 3400 (s) (OH) and 1710 (s) (C=O absent) cm^{-1}. All attempts to form a crystalline hydrochloride failed, and the alcohol was characterized by the formation of benzoate esters (Table IV).

Preparation of Benzoate Esters of 3-Dimethylamino-1-(2-phenylcyclohexyl)propan-1-ol Hydrochloride (VIII)—The method used was the same as for the preparation of IV, except that 0.0038-mole quantities of VII and the acid chloride were employed. The esters gave a parent ion corresponding to the molecular weight of the free base. The results are summarized in Table IV.

Preparation of 3-Dimethylamino-1-phenylpropan-1-ol Hydrochloride (IX)—3-Dimethylamino-1-phenylpropan-1-one, prepared in 50% yield according to a literature method (28), mp 155° [lit. (28) mp 155–156°], crystallized from acetone–ethanol (95% v/v) as colorless crystals. Reduction of the ketone with lithium aluminum hydride, using a published procedure (29), gave IX as a colorless oil in 70% yield, bp 90° (0.6 mm) [lit. (30) bp 70–72° (0.3 mm)]; IR (smear): 3400–3100 broad (OH) and 1670 (s) (C=O absent) cm^{-1}. The free base was converted to the hydrochloride salt, mp 131–133° [lit. (31) mp 132–133°]; mass spectrum: *m/e* 179 (parent peak).

[3] FFAP column, 3.66 m × 0.31 cm (12 ft × 0.125 in.), 218°, flow rate of 115 ml/min.

[4] Analyzed by GLC on SE-30 column, 1.8 m × 0.31 cm (6 ft × 0.125 in.), 175°, flow rate of 120 ml/min.

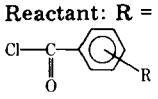
Table IV—Benzoate Esters of 3-Dimethylamino-1-(2-phenylcyclohexyl)propan-1-ol Hydrochloride (VIII)

Compound	Yield, %	Melting Point	Molecular Formula	Analysis, % Calc.	Analysis, % Found	IR Spectra, cm^{-1} (C=O)
VIII*a*	50	168–170°	$C_{24}H_{32}ClNO_2$	C 71.70 H 8.02	70.90 8.04	1715 (s)
VIII*b*	40	142–144°	$C_{24}H_{31}Cl_2NO_2$	C 66.04 H 7.15	65.40 7.18	1730 (s)
VIII*c*	30	152–154°	$C_{24}H_{31}Cl_2NO_2$	C 66.04 H 7.15	65.95 7.53	1725 (s)
VIII*d*	39	148–150°	$C_{24}H_{31}Cl_2NO_2$	C 66.04 H 7.15	65.15 7.32	1710 (s)
VIII*e*	40	128–130°	$C_{25}H_{34}ClNO_2$	C 72.17 H 8.23	70.90 8.64	1715 (s)
VIII*f*	40	108–110°	$C_{24}H_{31}ClN_2O_4$	C 64.58 H 6.95	64.85 7.52	1720 (s)

Table V—Benzoate Esters of 3-Dimethylamino-1-phenylpropan-1-ol Hydrochloride (X)

Compound	Yield, %	Melting Point	Molecular Formula	Analysis, % Calc.	Analysis, % Found	IR Spectra, cm^{-1} (C=O)
X*a*	55	166–167°	$C_{18}H_{22}ClNO_2$	C 67.59 H 6.93	66.75 6.76	1710 (s)
X*b*	54	126–127.5°	$C_{18}H_{21}Cl_2NO_2$	C 61.02 H 5.98	60.90 6.33	1730 (s)
X*c*	54	130.5–131°	$C_{18}H_{21}Cl_2NO_2$	C 61.02 H 5.98	61.13 6.15	1720 (s)
X*d*	68	148–149.5°	$C_{18}H_{21}Cl_2NO_2$	C 61.02 H 5.98	61.10 6.11	1710 (s)
X*e*	61	142–143°	$C_{19}H_{24}ClNO_2$	C 68.35 H 7.24	68.13 7.47	1715 (s)
X*f*	70	168–169°	$C_{18}H_{21}ClN_2O_4$	C 59.25 H 5.80	59.39 6.00	1730 (s)

Table VI—Reaction of 2-Dimethylaminomethyl-1-phenylcyclohexanol with Substituted Benzoyl Chlorides

Reactant: R = 	Product Isolated	Yield, %	Melting Point	Molecular Formula[a]	Analysis, % Calc.[a]	Analysis, % Found	IR Spectra, cm^{-1} (C=O)	Mass Spectrum P Calc.	Mass Spectrum P Found
H	XI	74[b]	162–164°	$C_{15}H_{24}ClNO$	C 70.66 H 7.54	66.63[c] 9.37[c]	Absent	337	233[d]
2-Cl	XI	71[b]	161–163°	$C_{15}H_{24}ClNO$	C 64.70 H 6.67	66.93[c] 9.19[c]	Absent	—	—
3-Cl	XI	71[b]	163–164°	$C_{15}H_{24}ClNO$	C 64.70 H 6.67	66.17[c] 9.21[c]	Absent	—	—
4-Cl	XII*a*	40[a]	190–192°	$C_{22}H_{27}Cl_2NO_2$	C 64.70 H 6.67	64.65 7.47	1725 (s)	371	371[d]
4-CH_3	XI	63[b]	163–164.5°	$C_{15}H_{24}ClNO$	C 71.21 H 7.79	65.82[c] 9.11[c]	Absent	—	—
4-NO_2	XII*b*	40[a]	189–191°	$C_{22}H_{27}ClN_2O_4$	C 63.07 H 6.50	62.85 6.39	1725 (s)	382	382[d]

[a] Calculated for benzoate esters. [b] This figure indicates the percentage recovery of unreacted alcohol. [c] Calculated analytical figures for 2-dimethylaminomethyl-1-phenylcyclohexanol hydrochloride: C, 66.72; H, 8.96. [d] Parent peak (P) represents the free base.

Anal.—Calc. for $C_{11}H_{18}ClNO$: C, 61.24; H, 8.40. Found: C, 61.30; H, 8.66.

Preparation of Benzoate Esters of IX (X)—A solution of the acyl chloride (0.0112 mole) in dry benzene (10 ml) was added slowly to a stirred solution of IX (2.0 g, 0.0112 mole) in dry benzene (10 ml) at 0–10°. The reaction mixture was stirred at room temperature for 2 hr, and evaporation of the solvent gave colorless to pale-yellow solids. Recrystallization of these solids from ether–ethanol gave colorless crystals, except in the case of the 4-nitro ester which was pale yellow in color. The esters gave a parent ion corresponding to the molecular weight of the free base. The results are summarized in Table V.

2-Dimethylaminomethyl-1-phenylcyclohexanol Hydrochloride (XI)—2-Dimethylaminomethylcyclohexanone was prepared in 17% yield using a literature procedure (32), bp 60–75° (1.0 mm) [lit. (33) bp 60° (1.0 mm)]; IR (smear): 1700 (s) (C=O) cm^{-1}. Reaction of XI with phenylmagnesium bromide, using a literature method (33), gave 2-dimethylaminomethyl-1-phenylcyclohexanol in 55% yield, bp 120–140° (1.0 mm) [lit. (33) bp 111–116° (0.20 mm)]. GLC[5] showed one component only; IR (smear): 3400–3020 (broad OH) and 1700 (s) (C=O absent) cm^{-1}. The alcohol was converted to the hydrochloride salt, mp 168.5–170°; mass spectrum: *m/e* 233 (parent peak).

Anal.—Calc. for $C_{15}H_{24}ClNO$: C, 66.72; H, 8.96. Found: C, 66.70; H, 9.26.

Attempted Preparation of Benzoate Esters of XI (XII)—The method employed was identical to that used in the preparation of the benzoate esters of IX, except that 0.0042-mole quantities of reactants were used and the reaction mixture was stirred at room temperature for 4 hr. The solids obtained were recrystallized from ether–ethanol to give colorless crystals, except in the case of the 4-nitro ester which was pale yellow in color. The results are given in Table VI.

[5] Microtek.

Screening of Compounds—The compounds in Table I were evaluated using an agar dilution method. In each case a stock solution of the compound was prepared by dissolving 20 mg of the sample in 1 ml of dimethyl sulfoxide, followed by the addition of 3 ml of water. Aliquots of the stock solution were pipetted into melted trypticase soy agar[6] to give final concentrations of the compound of 200, 50, 12.5, and 3.1 μg/ml. After hardening, the agar surface was inoculated with appropriately diluted suspensions of the test organisms using a Steers' multiple-inocula replicating device. The seeded plates were incubated (18 hr at 30° followed by 18 hr at 37°), and the plates were then observed for microbial growth.

The screening techniques for the compounds evaluated in Table II are as follows. In the antibacterial screen, 1 ml of stock solution (1000 μg/ml) was added to 9 ml of nutrient broth to give an initial concentration of 100 μg/ml; halving dilutions were then carried out in nutrient broth. All tubes were inoculated with 0.1 ml of a 1:10 dilution of an 18-hr culture of the test organism. All tubes were incubated for 24 hr at 37° and then examined for growth.

The antifungal screen involved the addition of 1 ml of the stock solution (1000 μg/ml), which was added to 9 ml of Sabouraud broth to give an initial concentration of 100 μg/ml; halving dilutions were carried out in Sabouraud broth. A spore suspension (0.1 ml) of *Trichophyton granulosum* and *Microsporum gypseum* and 0.1 ml of a 1:100 dilution of a broth culture of *Candida albicans* was added to the test tubes containing the various concentrations of the test substances. Tubes containing *C. albicans* were incubated at 37°, and tubes containing *M. gypseum* and *Tr. granulosum* were incubated at 28°. Tubes were examined for growth after 4 and 9 days of incubation.

In the antitrichomonal screen, 1 ml of the stock solution (1000 μg/ml) was added to 9 ml of Diamond medium to give an initial concentration of 100 μg/ml; halving dilutions were then carried out. Tubes were inoculated with approximately 2.5×10^5 organisms/ml and examined microscopically for growth after 48 hr of incubation.

[6] BBL.

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