SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,2,5-TRIMETHYL-4-N-ARYLIMINO(AMINO)- AND 4-(N-ARYL-N-ETHOXYCARBONYL)-AMINOPIPERIDINES

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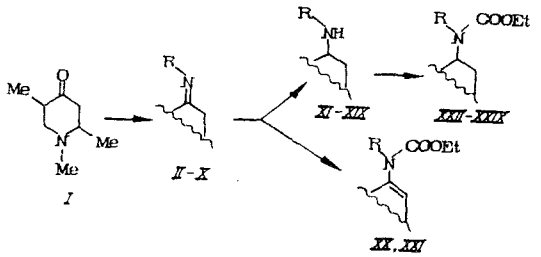
UDC 615.28:547.821.43].012.1+615.28:547.821.43].036.8

The synthesis and examination of the spatial structure and biological activity of γ-imino- (and amino-) piperidines has formed the subject of numerous reports [1, 5, 9, 15, 17]. This is largely due to the identification of highly active analgesics, namely 4-propionylanilidopiperidines (fentanyl, fenadrin, and their analogs), which are derived from N-substituted piperidine-4-ones [4, 6, 19]. The search for novel biologically active piperidines, obtainable by simple and accessible means, remains a topical task. The development of a new method of preparation of 1,2,5-trimethylpiperidin-4-one (I) [11], the starting material for the analgesic promedol, has resulted in broadening of studies on the synthesis and examination of 4-imino(amino)piperidines, which show a wide spectrum of physiological activity [5]. Effective pesticides have been obtained from the ketone (I) [2, 3].

Urethanes are used extensively as drugs and pesticides, but such compounds with N-γ-piperidyl substituents have not been reported. In order to obtain and examine the biological activity of urethanes of this type, we have employed 1,2,5-trimethyl-4-N-phenyl- (II), -o-methoxyphenyl- (III), -p-methoxyphenyl- (IV), -o-bromophenyl- (V), -3,4-dichlorophenyl- (VI), -benzyl- (VII), -cyclohexyl- (VIII), -2-thiazolyl- (IX), -2-pyridyl- (X) iminopiperidines, and their reduction products, 1,2,5-trimethyl-4-N-phenyl-(XI), -o-methoxyphenyl- (XII), -p-methoxyphenyl- (XIII), -o-bromophenyl- (XIV), -3,4-dichlorophenyl- (XV), -benzyl- (XVI), -cyclohexyl- (XVII), -2-thiazolyl- (XVIII), and -2-pyridyl-(XIX) aminopiperidines respectively [9, 10, 14].



The imine (VI), and the amines (XV) and (XVIII) are novel. Ethoxycarbonylation of the imines (II) and (VII) and of amines (XI), (XII), and (XIV-XIX) was effected with ClCOOEt in dry ether in the presence of Et_3N, as described in [20]. From the imines (II) and (VII) there were obtained 1,2,5-trimethyl-1,2,5,6-tetrahydro-4-[N-phenyl)- (XX) and -(benzyl) (XXI)-N-ethoxycarbonyl]aminopyridines. The IR spectra of these compounds showed strong absorption for C=O stretching at 1700-1705 cm^{-1} characteristic of urethanes. The PMR spectra indicated the presence of isomers of these urethanes, as observed in the acylation of γ-iminopiperidines [18].

Ethoxycarbonylation of the amines (XI), (XII), and (XIV-XIX) afforded 1,2,5-trimethyl-4-[N-phenyl- (XXII), -o-methoxyphenyl- (XXIII), -o-bromophenyl-(XXIV), -3,4-dichlorophenyl- (XXV), -benzyl- (XXVI), -cyclohexyl- (XXVII), -2-thiazolyl- (XXVIII), and -2-pyridyl (XXIX)]-N-ethoxycarbonyl]aminopiperidines respectively.

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0091-150X/91/2506-037712.50

TABLE 1. Physicochemical Data for Urethanes (XX-XXIX)

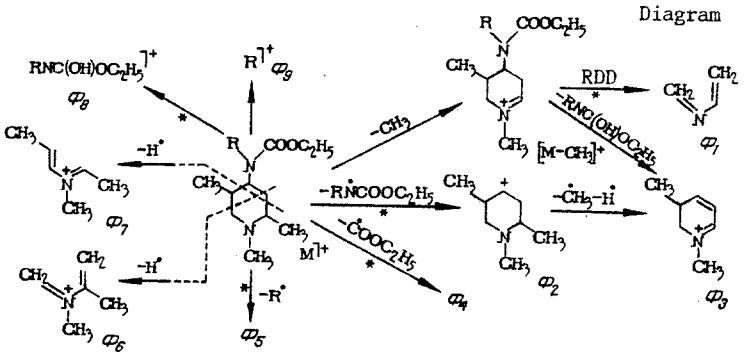
Compound	Yield, %	Empirical formula	IR spectrum, ν_{max}, cm^{-1}, CO	PMR spectrum, chemical shifts, δ, ppm: 2- and 5-CH_3 (m, 6H)	NCH_3 (s, 3H)	$COOCH_2$ (m, 2H)	other signals
XX	50	$C_{17}H_{24}N_2O_2$	1700	0.82—1.20	2.25 2.30	3.90—4.15	4.8 (3-H, d, 1H), 6.80—7.30 (arom. H, m, 5H)
XXI	48	$C_{18}H_{26}N_2O_2$	1700	0.95—1.30	2.24 2.37	3.80—4.10	4.22—4.60 (NCH_2, m, 2H), 5.00 (3-H, d 1H), 7.0—7.5 (arom. H, m, 5H)
XXII	57	$C_{17}H_{26}N_2O_2$	1713	0.90—1.22	2.03 2.15	3.80—4.20	6.9—7.3 (arom. H, m, 5H)
XXIII	45	$C_{18}H_{28}N_2O_3$	1708	0.85—1.17	2.10 2.13	3.75—4.18	6.75—7.1 (arom. H, m, 4H) 3.75 (OCH_3, s 3H)
XXIV	43	$C_{17}H_{25}BrN_2O_2$	1706	0.88—1.19	2.15 2.18	3.81—4.09	6.65—7.12 (arom. H, m, 4H)
XXV	58	$C_{17}H_{24}Cl_2N_2O_2$	1703	0.90—1.25	2.15 2.17	3.95—4.20	7.05—7.4 (arom H, m 3H)
XXVI	48	$C_{18}H_{28}N_2O_2$	1705	0.83—1.18	2.10 2.17	3.90—4.40	6.9—7.3 (arom H, m, 5H)
XXVII	60	$C_{17}H_{30}N_2O_2$	1700	0.93—1.13	2.18 2.22	2.60—2.87	1.22—1.31 (cyclohex H, m, 10H)
XXVIII	57	$C_{14}H_{23}N_3O_2S$	1700	0.90—1.20	2.15 2.17	4.05—4.42	6.35—6.47 and 6.85—7.05 (thiazol H, m, 3H)
XXIX	45	$C_{16}H_{25}N_3O_2$	1705	0.75—1.12	2.11 2.13	3.82—4.10	7.2—7.8 (arom H, m 3H), 8.30 (H_α pyridine m 1H)

TABLE 2. Characteristic Ions in the Masss Spectra of Urethanes (XX-XXII), (XXVI), and (XXVIII)

Compound	m/z Values (intensity, %): M^+	$(M-CH_3)^+$	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9
XX	288 (13)	273 (25)	—	124 (30)	—	215 (16)	—	84 (6)	98 (4)	165 (100)	77 (25)
XXI	302 (19)	287 (28)	—	124 (27)	—	229 (19)	211 (27)	84 (7)	98 (5)	179 (100)	91 (52)
XXII	290 (10)	275 (15)	70 (33)	126 (29)	110 (100)	217 (5)	—	84 (17)	98 (12)	165 (16)	77 (17)
XXVI	304 (16)	289 (12)	70 (15)	126 (28)	110 (100)	231 (6)	213 (13)	84 (14)	98 (15)	179 (35)	91 (41)
XXVIII	297 (3)	284 (2)	70 (10)	126 (28)	110 (65)	226 (25)	—	84 (9)	98 (5)	172 (46)	84 (9)

Their structures were confirmed by their IR and PMR spectra (Table 1). The starting amines (XI-XIX) used consisted of mixtures of stereoisomeric mixtures (according to TLC and the PMR spectra). The mass spectra of the urethanes (XXII-XXIX) showed medium-intensity molecular ion peaks $M^{1+\cdot}$ (Table 2). The presence of the ethyl-N-aryl(or hetaryl)-carbamate grouping in these compounds was confirmed by the occurrence in their mass spectra of the characteristic fragments $(M-COOC_2H_5)^+$, $(M-R)^+$, and R^+, together with the $RNHCOOC_2H_5$ ion (Table 2 and Diagram). These ions are formed as a result of localization of positive charge at the exocyclic nitrogen.

Diagram



The formation of fragments Φ_6 and Φ_7 is due to the cleavage of the ring characteristic of piperidines [7], while Φ_1 is a product of the dissociative ionization of the fragment $(M-CH_3)^+$ by retrodiene breakdown [16]. In order to examine their bactericidal, fungicidal, and herbicidal activity, a range of quaternary salts of the imines and amines was obtained (methiodides, hydrochlorides, and citrates). Their activity was compared with that of the urethanes obtained from these imines and amines. The pesticidal activity of twenty of these compounds was examined (Table 3).

The test compounds showed slight to moderate bactericidal, fungicidal, and herbicidal activity. Bactericidal and fungicidal activity was examined using pure cultures of the bacterium Xanthomonas malvacearum and the fungi Fusarium moniliforme and Rhizoctonia solanis, using standard methods [12]. The activities of the compounds were expressed as the percentage inhibition of the growth of the microorganisms. Most of the compounds were found to be inactive as bactericides, exceptions being the γ-iminopiperidine methiodides (V) (38%), (VI) (23%), and (VIII) (53%), and the amino-compound (XIX) (46%). The fungicidal activity in vitro using

TABLE 3. Pesticidal Activity of Compounds Obtained

Type of activity of compound (test organism)	Compound																				
	imines						amines						urethanes								
	IIIc	Vc	VIc	VIIc	VIIIc	IXc	XIIc	XIIId	XVd	XVIc	XVIIIe	XIX	XXI	XXIId	XXIIe	XXIIId	XXIVd	XXVd	XXId	XXVIId	XXVIIIe
Bactericidal[a] (Xanthomonas malvacearum)	0	38	23	0	53	17	27	17	0	5	25	46	28	0	20	0	0	0	0	0	0
Fungicidal[a] (Fusarium moniliforme)	0	51	62	0	57	17[f]	0[f]	0[f]	10	5	48[f]	0		0	62	0	0	0	0	30	32[f]
(Rhizoctonia solanis)	50	40	0	0	33	0	32	50	0	5	62	60	0	0	30	0	0	0	0	40	32
Cucumber powdery mildew	61	52	65	73	52	27	–	–	70	62	0	52	83	42	53	40	40	56	55	44	0
Tomato phytophthora	32	28	47	0	57	0	–	–	56	10	0	28	0	82	0	80	55	85	10	57	0
Bean gray mold	28	0	0	16	0	29	–	–	40	12	0	28	0	61	72	62	41	50	79	45	14
Herbicidal[b] (radish)	–	–	–	40	–	40	40	60	40	–	20	–	40	0	60	40	40	40	40	40	0

[a]Percentage inhibition of development of bacteria and fungal mycelia or mold as compared with controls.
[b]Percentage death of plant shoots in vegetative stage.
[c]Methiodides.
[d]Hydrochlorides.
[e]Citrates.
[f]In Fusarium graminiarum culture.

these two test organisms was also poor with the exception of the imines (III), (V), (VI), and (VIII) and the amines (XVIII) and (XIX) (50-62% reduction in infection).

The fungicidal activity of the compounds was also examined in green plants grown to the 6-8 leaf stage, these being sprayed with 0.1% spore suspensions (50-200 thousand/ml) of tomato phytophthora, cucumber powdery mildew, and bean gray mold. The imines (III) and (V-VIII) showed high activity (52-73%) against cucumber powdery mildew. This high activity was maintained when the imines were converted into the amines (XV), (XVI), and (XIX). The urethanes (XXII)-(XXVIII) were less active against cucumber powdery mildew, but they were more active (61-85%) against tomato phytophthora and bean gray mold.

Herbicidal activity was assessed using the method described in [13]. The rates of application of the compounds and the standards (Basagran, Dual, and Merpelan) were 5 kg of active ingredient per hectare. Herbicidal activity was expressed as the relative percentage control fifteen days after treatment of the green plants. Both the amines and the urethanes derived therefrom were found to show weak selective phytotoxicity against radish (20-60%).

Some of the compounds obtained were also tested for pharmacological activity. The urethanes (XXII) and (XXVII) showed moderately high stimulant activity on the CNS. Urethanes (XXI-XXVIII) failed to show analgesic activity (hot plate test). Weak H_1-histamine blocking activity was found in the carbamate (XXVIII), while the carbamate (XXI) showed slight antiulcer activity.

EXPERIMENTAL

The mass spectra of the products were obtained on an MX-1303 standard model equipped for direct introduction of the sample into the ion source, ionizing voltage 70 eV, inlet temperature 50-70°C. IR spectra were recorded on a Specord IR-75 instrument (in films). PMR spectra were obtained on Tesla BS-478c (60 MHz) and Tesla BS-497 (100 MHz) instruments ($CDCl_3$, internal standard TMS). The purities of the products were checked by TLC on Alufol plates. The elemental analyses were in agreement with the calculated values.

N-(1,2,5-Trimethyl-4-piperidylidene)-3,4-dichloroaniline (VI). A mixture of 19.5 g (0.14 mole) of 1,2,5-trimethylpiperidin-4-one, 20.0 g (0.12 mole) of 3,4-dichloroaniline, and 150 ml of toluene was boiled in a Dean and Stark apparatus in the presence of 0.5 ml of glacial acetic acid for eight hours, to give 14.0 g (40%) of the imine (VI), $C_{14}H_{18}Cl_2N_2$, as a yellow, glassy solid, bp 165-167°C/3 mm Hg. IR spectrum: 1650 cm^{-1} ($\nu C{=}N$). Picrate, mp 168-175°C.

1,2,5-Trimethyl-4-N-(3,4-dichlorophenyl)aminopiperidine (XV). To a suspension of 4.4 g (0.12 mole) of $NaBH_4$ in 50 ml of 2-propanol was added a solution of 3.45 g (0.012 mole) of the imine (VI) in 20 ml of 2-propanol at 20°C. The mixture was heated at 60°C for 3 h, then 40 ml of water was added and heating continued for 2 h. The alcohol was removed, and the reaction products extracted with ether and dried over $MgSO_4$. The residue after removal of the ether was distilled in vacuo to give 1.62 g (46%) of the amine (XV), $C_{14}H_{20}Cl_2N_2$ as a viscous, glassy yellow mass, bp 165-167°C/1 mm Hg, n_D^{20} 1.5710. IR spectrum: 3300 cm^{-1} (νNH).

1,2,5-Trimethyl-4-N-(2-thiazolyl)aminopiperidine (XVIII). Similarly, from 4.94 g of the imine (IX) [8] there was obtained 1.7 g (34%) of the amine (XVIII), $C_{11}H_{19}N_3S$, as a yellow, viscous, glassy mass, bp 152-155°C/6 mm Hg. IR spectrum: 3330 cm^{-1} (νNH). PMR spectrum, δ, ppm: 0.90-1.11 (2- and 5-CH_3, m, 6H), 2.15 and 2.20 (N-CH_3, s, each 3H), 3.57 (NH, br. s, 1H); 6.37 and 7.02 (thiazole ring protons, d, 1H each).

Ethoxycarbonylation of Imines (II) and (VII), and Amines (XII) and (XIV-XIX). To a solution of 0.01 mole of the imine or amine in 50 ml of dry ether containing 0.01 mole of Et_3N was added dropwise with cooling at 0-5°C a solution of 0.02 mole of ClCOOEt in 10 ml of dry ether. The mixture was stirred for 10-12 h at 20°C, and the $Et_3N{\cdot}HCl$ which separated was filtered off. The ether solution was washed successively with water (2 × 10 ml), 10% $NaHCO_3$ solution (2 × 10 ml), and water (2 × 10 ml), dried over $MgSO_4$, then passed through a layer of alumina. Removal of the solvent gave the urethanes (XX-XXIX), the physicochemical data for which are given in Tables 1 and 2.

Methiodides of γ-Iminopiperidines (II), (V-IX), and Amine (XVII). These were obtained by mixing ether solutions of the imine or amine with MeI, in quantitative yields. The mp's were respectively 144-146, 128-130, 145-150, 162-165, 104-107, 106-109 and 153-155°C.

Hydrochlorides of Amines (XII), (XIII), and (XV), and of Urethanes (XXII-XXVII). These were obtained by passing dry gaseous HCl into ether solutions of the compounds until no more

HCl was taken up. The mp's were respectively 112-115, 158-161, 113-116, 122-125, 128-131, 112-116, 150-154 and 176-180°C.

(XVII) and (XXVIII) Citrates were obtained by mixing ether solutions of the free bases of these compounds with saturated ethereal citric acid. The mp's were 82-85 and 127-130°C respectively.

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