SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF N-METHYL[BENZYL]-3-ALKYL-12b-METHYLOCTAHYDROINDOLO[2,3-a]QUINOLIZINES

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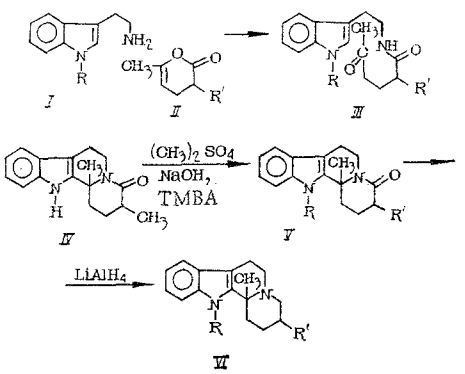
UDC 615.212/.214:547.834.2/.012.1

There are reports in the literature that some octahydroquinolizidines with an angular methyl group exhibit high psychotropic [1], antiinflammatory and analgesic activity [2]. It was therefore of interest to synthesize N-substituted 3-alkylindoloquinolizidine bases (VI) with an angular methyl group, and to study their pharmacological properties.

The bases (VIa-h) were obtained by the route depicted below. The starting N-methyl-(benzyl)tryptamines (Ia-b) and the δ-enol-lactones (IIa-d) were obtained by standard methods [1, 3, 4].



Ia: $R = CH_3$; Ib: $R = CH_2C_6H_5$,
IIa: $R' = CH_3$; IIb: $R' = C_2H_5$, IIc: $R' = C_3H_7$, IId: $R' = C_4H_9$,
III, V, VIa: $R = CH_3$, $R' = CH_3$; III, V, VIb: $R = CH_3$, $R' = C_2H_5$;
III, V, VIc: $R = CH_3$, $R' = C_3H_7$; III, V, VId: $R = CH_3$, $R' = C_4H_9$;
III, VI VIe: $R = CH_2C_6H_5$, $R' = CH_3$; III, V, VIf: $R = CH_2C_6H_5$, $R' = C_2H_5$,
III, V, VIg: $R = CH_2C_6H_5$, $R' = C_3H_7$; III, V, VIh: $R = CH_2C_6H_5$, $R' = C_4H_9$.

Condensation of (Ia-b) with the enol-lactones (IIa-d) to give the tryptamines (III) was carried out by boiling benzene solutions of equimolar amounts of the components. The structures of the tryptamides obtained were confirmed by their IR and PMR spectra, and by a positive Ehrlich color reaction, indicating the presence of a free 2-position in the indole ring. The IR spectrum contained a band at 1710 cm^{-1} typical of the ketonic carbonyl group, and absorption at 1670 cm^{-1} indicating the presence of an amide carbonyl group. Signals were observed in the PMR spectrum at 2.1 ppm, indicating the presence of the CH_3CO-group. Compounds (IIIa-h) cyclized to the lactams (Va-h) on boiling in methanolic solution in the presence of a small amount of hydrochloric acid.

Modification of literature methods [5, 6] enabled us to obtain (Va) by methylating (IV) with dimethyl sulfate in the presence of trimethylbenzylammonium chloride (TMBA) and alkali, whereas alkylation with benzyl chloride and alkyl halides under similar conditions was unsuccessful.

A negative Ehrlich color reaction, and the absence of ketonic carbonyl absorption in the IR spectra, confirmed the presence of the tetracyclic system in (V).

The lactams (Va-h) were reduced to the bases (VIa-h) by lithium aluminohydride in ether—tetrahydrofuran. The PMR spectra of these compounds showed a signal at 1.8 ppm indicative

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 5, pp. 556-560, May, 1982. Original article submitted September 28, 1981.

TABLE 1. α-Alkyl-γ-acetylbutyric Acid N-Methyl(benzyl)-tryptamides (IIIa-h)

Compound	Yield, %	Molecular formula	Found, %			Calculated, %			R_f
			C	H	N	C	H	N	
IIIa	84,7	$C_{18}H_{24}N_2O_2$	72,28	8,22	9,36	72,00	8,00	9,33	0,28
IIIb	70,3	$C_{19}H_{26}N_2O_2$	73,06	7,65	8,79	72,84	7,98	8,94	0,42
IIIc	60,4	$C_{20}H_{28}N_2O_2$	72,83	9,02	8,26	73,17	8,63	8,53	0,50
IIId	81,4	$C_{21}H_{30}N_2O_2$	73,26	9,03	8,36	73,62	8,77	8,18	0,52
IIIf	83,3	$C_{25}H_{30}N_2O_2$	76,80	7,38	7,48	76,92	7,69	7,17	0,46
IIIg	77,4	$C_{26}H_{32}N_2O_2$	77,31	8,10	6,57	77,22	9,92	6,93	0,46
IIIh	84,0	$C_{27}H_{34}N_2O_2$	77,88	8,20	7,02	77,51	8,13	6,69	0,50

of the presence of the $\geq C-CH_3$ group [7]. The oily compounds were characterized as their hydrochlorides. The lactams (V) and the bases (VI) contain two asymmetric centers (C-3 and C-12b), and are therefore capable of existing as diastereoisomeric pairs. TLC showed that all were in fact formed as the diastereoisomers, and in all cases, judging from the intensities of the spots, the stereoisomer with the greater R_f value predominated.

EXPERIMENTAL CHEMICAL PART

IR spectra were obtained on a UR-20 instrument (East Germany), all in vaseline oil, and PMR spectra were recorded on a T-60 radiospectrometer (USA), working frequency 60 MHz, δ scale. TLC was carried out on grade II alumina; the tryptamides (IIIa-h) and bases (VIa-h) in the solvent system chloroform–acetone–alcohol (10:1:0.25), and the lactams (Va-h) in the system benzene–alcohol (5:1). Development was effected with iodine vapor.

α-Alkyl-γ-acetylbutyric Acid N-Methyl(benzyl)tryptamides (IIIa-h). A solution of 0.04 mole of N-methyl(benzyl)tryptamine in 100-120 ml of dry benzene was boiled under a reflux condenser fitted to a water separator, until all moisture had been removed, then 0.04 mole of the enol-lactone was added and the mixture boiled for 20-22 h. The benzene was removed completely from the oily tryptamides, the residue dissolved in chloroform, the solution washed successively with dilute alkali, water, hydrochloric acid, and again with water, dried, concentrated to a small volume, and passed through a column containing alumina. After removal of the solvent, the lactams were obtained as viscous, undistillable oils (Table 2).

(IV) → (Va) (R = R' = CH_3). A mixture of 2.6 g (0.009 mole) of (IV), 10 ml of 50% sodium hydroxide solution, and a catalytic amount of trimethylbenzylammonium chloride in 100 ml of acetone was warmed slightly on the water bath, then 10.6 g (0.08 mole) of freshly-distilled dimethyl sulfate was added dropwise. The solution was boiled for 5 h, then cooled, filtered from the turbidity which formed, and diluted with 200-250 ml of water. The liquid was decanted from the oily residue, which was dissolved in ether. The ether solution was washed twice with water and dried over sodium sulfate. After concentration to a small volume, the residue was passed through a column of alumina, and the solvent removed to give a bright yellow undistillable oil. Yield 2.3 g (84.2%). Found, %: C 76.40; H 7.50; N 9.72; $C_{18}H_{22}N_2O$. Calculated, %: C 76.59; H 7.80; N 9.92. PMR spectrum ($CDCl_3$), TMS): 3.7 (3H, N–CH_3), 1.7 (3H, –C–CH_3). No absorption at 3400 cm^{-1}, characteristic of the indole imino-group, was present in the IR spectrum. TLC (benzene–alcohol, 5:1); R_f = 0.39 (0.49), 0.90.

N-Methyl(benzyl)-3-alkylindolo[2,3-a]quinolizines (VIa-h). To a solution of 3.7 g (0.1 mole) of lithium aluminohydride in 200 ml of dry ether was added 0.03 mole of the lactam (V) in 60 ml of dry tetrahydrofuran. The mixture was boiled with stirring for 20 h, then decomposed by the addition of a 10% solution of sodium hydroxide. The precipitate was washed with ether, and the combined ether-tetrahydrofuran solutions were dried over potassium hydroxide.

The hydrochloride separated on adding an ethereal solution of hydrogen chloride. The free base was obtained by treating an aqueous solution of the hydrochloride with caustic alkali, and purified by passing its ethereal solution through an alumina column. The base was obtained as an oil (Table 3).

TABLE 2. N-Methyl(benzyl)alkyl-4-oxoindolo[2,3-a]quinolizines (Va-h)

Compound	Yield, %	Molecular formula	Found, %			Calculated, %			R_f
			C	H	N	C	H	N	
Va	93,5	$C_{18}H_{22}N_2O$	76,30	7,90	9,82	76,59	7,80	9,92	0,41 (0,51) 0,92
Vb	81,0	$C_{18}H_{24}N_2O$	76,81	8,00	9,62	77,02	8,10	9,46	0,40 (0,60) 0,70
Vc	95,2	$C_{20}H_{26}N_2O$	77,31	8,26	8,96	77,41	8,38	9,03	0,41 (0,65) 0,75
Vd	71,9	$C_{21}H_{28}N_2O$	77,65	8,85	8,42	77,77	8,64	8,64	0,41 (0,70) 0,78
Ve	92,0	$C_{24}H_{26}N_2O$	80,46	6,90	7,55	80,44	7,26	7,82	0,46 (0,58) 0,64
Vf	94,4	$C_{25}H_{28}N_2O$	80,32	7,22	7,42	80,64	7,52	7,52	0,52 (0,57) 0,65
Vg	90,2	$C_{26}H_{30}N_2O$	80,59	7,48	7,44	80,82	7,77	7,25	0,52 (0,60) 0,66
Vh	84,0	$C_{27}H_{32}N_2O$	81,02	8,40	6,86	81,00	8,00	7,00	0,64 (0,65)

TABLE 3. N-Methyl(benzyl)-3-alkylindolo[2,3-a]quinolizines (VIa-h)

Compound	Yield, %	Molecular formula	Found, %			Calculated, %			mp, °C	Hydrochloride, % Cl		R_f
			C	H	N	C	H	N		found	calculated	
VIa	62,9	$C_{18}H_{24}N_2$	80,40	9,10	10,64	80,59	8,95	10,41	175—177	11,70	11,65	0,41 (0,60) 0,69
VIb	74,5	$C_{19}H_{26}N_2$	80,87	9,46	10,02	80,85	9,21	9,92	184—186	11,00	11,14	0,41 (0 60) 0,69
VIc	65,5	$C_{20}H_{28}N_2$	81,38	9,26	9,30	81,08	9,45	9,42	187—189	10,31	10,67	0,41 (0,61) 0,76
VId	45,5	$C_{21}H_{30}N_2$	81,40	10,00	9,31	81,29	9,67	9,03	210—212	10,11	10,24	0,40 (0,69) 0,78
VIe	71,2	$C_{24}H_{28}N_2$	83,82	8,24	8,47	83,72	8,13	8,13	172—174	9,12	9,32	0,35 (0,46)
VIf	63,4	$C_{25}H_{30}N_2$	82,20	8,72	7,68	82,79	8,37	7,82	150—152	8,63	8,99	0,38 (0,52)
VIg	67,7	$C_{26}H_{32}N_2$	84,14	9,05	7,67	83,87	8,60	7,52	180—182	8,12	8,69	0,33 (0,47)
VIh	62,7	$C_{27}H_{34}N_2$	83,53	8,62	7,22	83,93	8,80	7,25	171—173	8,56	8,90	0,30 (0,41)

EXPERIMENTAL PHARMACOLOGICAL PART

In experiments on mongrel mice weighing 18-22 g and rats weighing 150-180 g, some pharmacological properties of N-methyl(benzyl)-substituted indoloquinolizines (Table 3, Va-h) were studied in comparison with indopan. Using methods described previously [8-10], the effects were examined on behavior, motor activity, the tonus of the skeletal musculature, the central depressant effects of reserpine (ptosis, hypothermia, and catalepsy), the toxicity of phenamine (amphetamine) in grouped mice, the duration of nembutal-induced sleep and hyperkinesis induced by 5-HT, and on the concentrations of serotonin (5-HT) and noradrenalin in rat urine. The LD_{50} values of the active compounds (Va and b) were determined.

The compounds were administered subcutaneously in doses of 10 and 100 μg/kg, and in the determination of the LD_{50}, intraperitoneally.

Reserpine (2 mg/kg), amphetamine (20 mg/kg), and nembutal (20 mg/kg) were administered intraperitoneally one hour after the compounds, and 5-HT (50 mg/kg) 30 min after the compounds. The experimental data were subjected to Student-Fisher, and Litchfield and Wilkinson statistical treatment.

The N-methyl-substituted compounds (Table 3, Va-d) caused a substantial fall in temperature in rats, and especially so in mice. The greatest effects were produced by compounds with methyl and ethyl groups on the tertiary carbon atom (Va, b), reducing the temperature of mice by 8.2-8.4°C. The hypothermic effect was accompanied by the development of catalepsy. The cataleptogenic effect was not dose-dependent, and lasted for more than 5 h. Narrowing of the eyelid slit (blepharoptosis) was also noted.

Replacement of the methyl radical on the nitrogen atom of the indole ring by benzyl resulted in a change in the effects on mice and rats. Thus, (Ve-h) (Table 3) had excitatory effects on rats, increasing tactile sensitivity, causing exophthalmos and increased frequency of defecation, and slightly raising the skin temperature (0.6-0.8°C). However, administration of (Ve, f, and g) to mice in a dose of 100 mg/kg resulted in a reduction in temperature of 6, 4, 3, 1, and 2.5°C respectively.

Unlike indopan, these compounds had no effect on the effects of reserpine in mice or rats, nor did they modify the effects of 5-HT or the toxicity of amphetamine in grouped mice.

N-Methylated indoloquinolizidines shortened nembutal sleep, whereas the N-benzyl compounds had no effect on the soporific effects of nembutal.

The LD_{50}'s of the most active compounds (Va and b, Table 3) in mice were 76 (68.5-86.4) and 92 (88.9-95.1) mg/kg, for indopan 137 (121.2-154.8) mg/kg.

Compounds (Va) reduced the noradrenalin level of rat urine by 27% ($P < 0.02$), and (Vb) increased the urine serotonin content by 25% ($P < 0.02$). Under these conditions, indopan raised the levels of both serotonin and noradrenalin ($P < 0.05$).

Thus, the N-methylated indoloquinolizidines are reminiscent in their ability to inhibit motor activity, and to cause hypothermia, catalepsy, and blepharoptosis of previously described indoloquinolizines with an angular methyl group, unsubstituted on the pyrrole nitrogen atom [8]. Replacement of the methyl radical by benzyl confers on the compounds properties typical of compounds which stimulate the central nervous system.

It is known [11] that a deficiency of serotonin is of pathogenic significance in the development of depression. The ability of (Vb) to selectively accumulate serotonin in the urine indicates that it may have antidepressant properties. Unlike the antidepressant indopan, which is used in medical practise, (Vb) is more toxic.

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SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF N-ORGANOSILYLMETHYLENELACTAMS

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UDC 615.281:547.466.3].012.1

Lactam derivatives, and particularly silylated lactams, have recently attracted the attention of chemists and pharmacologists as valuable physiologically active compounds. They mediate central nervous system inhibition, and they possess anticonvulsive, acaricidal, and psychoactivating properties [1, 2].

The object of this investigation was to synthesize organosilicon lactams with triorganosilylmethylene groups on the nitrogen atom, and to study their physicochemical and bactericidal properties.

The synthesis of triorganosilylmethylenepyrrolidines and triorgansilylmethylenecaprolactams was accomplished by reaction of 2-pyrrolidone or ε-caprolactam with the appropriate chloromethyltriorganosilane at 120-150°C in the presence of anhydrous Na_2CO_3 or K_2CO_3, with a molar ratio of reactants of 1:1, for 4-6 h either in toluene or in the absence of a solvent. The reaction proceeds as follows:

$$\overline{\text{CO}-(\text{CH}_2)_n-\text{NH}}| + \text{ClCH}_2\text{SiR}_2\text{R}' \longrightarrow \overline{\text{CO}-(\text{CH}_2)_n-\text{N}}|\text{CH}_2\text{SiR}_2\text{R}',$$

where $n = 3$; $R = CH_3$; $R' = C_2H_5$ (I), C_4H_9 (II), C_6H_5 (III);

$n = 5$; $R = CH_3$; $R' = C_2H_5$ (IV), C_3H_7 (V), C_4H_9 (VI), C_6H_5 (VII).

We have also carried out the reaction between 2-pyrrolidone or ε-caprolactam and 1,3-bis(chloromethyl)-1,3-tetramethyldisiloxane with a molar ratio of starting materials of 2:1 at 150°C in the presence of K_2CO_3 as follows:

$$\overline{\text{CO}-(\text{CH}_2)_n-\text{NH}}| + \text{ClCH}_2-\text{Si}(\text{CH}_3)_2-\text{O}-\text{Si}(\text{CH}_3)_2-\text{CH}_2\text{Cl} + \text{HN}|\overline{-(\text{CH}_2)_n-\text{CO}} \longrightarrow$$

$$\overline{\text{CO}-(\text{CH}_2)_n-\text{N}}|\text{CH}_2\text{Si}(\text{CH}_3)_2-\text{O}-\text{Si}(\text{CH}_3)_2\text{CH}_2\text{N}|\overline{-(\text{CH}_2)_n-\text{CO}},$$

where n = 3 (VIII) or 5 (IX).

All the compounds prepared were colorless, odorless, viscous liquids. They were readily soluble in benzene, toluene, acetone, alcohols, and other organic solvents.

The compounds were identified by their elemental analyses and determination of their molecular weights, and their structures were confirmed by IR spectroscopy.

The compounds synthesized contained no bands in their IR spectra for stretching vibrations of the C–Cl bond at 774 cm^{-1}. Instead, all the spectra showed bands characteristic of deformational vibrations of the Si–CH_3 groups at 1260-1250 cm^{-1}, and antisymmetrical and symmetrical stretching vibrations of the Si–CH_2 bond at 820-760 and 700-650 cm^{-1} respectively.

Tbilisi University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 5, pp. 560-562, May, 1982. Original article submitted September 9, 1981.

