N-ACYL AND N-ALKYL DERIVATIVES OF 1,10-TRIMETHYLENEPIPERAZINO[1,2-a] INDOLE

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In connection with the interest in piperazino[1,2-a] indole derivatives, which display antihistamine and hypotensive action [1], we have conducted studies with the object of developing a method of synthesizing their N-acyl and N-alkyl derivatives. We succeeded in preparing the N-acyl derivatives (I-IV) by acylating 8-methyl-1,10-trimethylenepiperazino [1,2-a] indole with acetic anhydride or acid chlorides. The alkylation of piperazino[1,2-a] indole derivatives with the usual alkylating agents takes place with complications and leads to the formation of resinous products. The N-alkyl derivatives could be obtained by indirect methods. Hydrogenation of the methiodides (VII, VIII) over Raney nickel leads to the corresponding N-methyl derivatives (IX, X), and the N-ethyl derivative (XI) was obtained by reduction of N-acetyl-8-methyl-1,10-trimethylenepiperazino[1,2-a] indole [1] with lithium aluminum hydride. In an attempt to reduce (I) with sodium in alcohol, deacylation was observed, with formation of a piperazino[1,2-a]indole derivative having a free NH group.

We were successful in carying out direct alkylation of 8- methyl-1,10-trimethylene-piperazino [1, 2-a]indole via the action of alcohols on it in the presence of Raney nickel catalyst. In this case the N-alkyl derivatives X-XI were obtained in nearly quantitative yield.



Structures of the acyl and alkyl piperazino [1,2-a]indole derivatives we prepared were confirmed by IR and UV spectral data. In the IR spectra of the acyl (I-VI) and alkyl (IX-XI) derivatives, the band for NH group stretching vibrations in the 3260-3300 cm⁻¹ region, which is observable in the spectra of piperazino-[1,2-a] indole derivatives not substituted on nitrogen, is absent. Moreover, intense carbonyl group stretching bands appear in the 1650-1700 cm⁻¹ region.

Two peaks characteristic of indole derivatives [2], at $\lambda = 235$ nm (log $\varepsilon = 4.55$) and $\lambda = 285$ nm (log $\varepsilon = 3.88$) are observed in the UV spectra.

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TAB	LE 1. N-Acyl Der	ivativ	es of 8-M	ethyl-1,	10-trim	ethylen	spiperaz	zino [1,2-a]indole				
- mo		Vield	Mp, °C;		Found, 6	10				Calculated	1, %	
punod	κ,	до 1	recrystal- lization solvent, methanol	U	H	z	Ū	Empirical formula	υ	Н	z	ū
11	CH ₂ CI	77,5	1534	67,46	6,60	9,37	11,96	C ₁ ,H ₁ ,CIN ₂ O	67,43	6,32	9,25	11,79
				67,55	6,30	9,38	11,98					
III	CHCl ₂	96	1478	60,50	5, 29	8,42	21,10	C ₁₇ H ₁₈ Cl ₃ N ₂ O	60, 54	5, 37	8,30	21,02
				60,32	5,32	8,16	21,30					
١٧	C ₆ H ₅	70	1378	80,28	6,78	8,47	1	$C_{22}H_{22}N_{2}O$	79,96	6,71	8,47	l
				79,90	6,72	8,39						
>	p=ClC ₆ H ₄	80,8	1757	72,72	5,85	7,35	06'6	C ₂₂ H ₂₁ CIN ₂ O	72,42	5,81	7,67	9,71
				72,30	5,72	7,44	10,07					
ΝI	31, 41, 51 (CH ₃ O) ₃	8	171-2	71,43	6,64	6,70	I	C ₃₅ H ₂₈ N ₂ O ₄	71,40	6,71	6,66	ł
	C ₆ H ₂			71,41	6,55	6,68						

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrophotometer in vaseline oil and the UV spectra on an EPS-3 spectrophotometer in alcoholic solution.

 $\frac{2-\text{Acetyl-8-methyl-1,10-trimethylenepiperazino}}{[1,2-a]\text{indole (I).}} A solution of 3.4 g of 8-methyl-1,10-trimethylenepiperazino [1,2-a]\text{indole in 20 ml of acetic} anhydride was boiled for 2 h; the excess acetic anhydride was stripped off under vacuum, and to the remaining oily product was added 10 ml of ether; the crystals which separated were filtered off. The yield of I was 2.6 g (65%); mp 165-166° (from methanol). Found, %: C 75.92, 76.03; H 7.71, 7.66: N 10.08, 10.20. C₁₇H₂₀N₂O. Calculated %: C 76.09; H 7.51; N 10.44.$

<u>N-Acyl Derivatives of 8-Methyl-1,10-trimethyl-</u> <u>enepiperazino [1,2-a]indole (II-VI).</u> To a solution of 0.05 mole of 8-methyl-1,10-trimethylenepiperazino-[1,2-a]indole base and 0.06 mole of triethylamine in 20 ml of absolute ether was added 0.05 mole of the appropriate acid chloride, dropwise with good stirring. The reaction mixture was heated for 2 h on a water bath, and the precipitate which separated was filtered off, washed with water, and dried. Data on the N-acyl derivatives of 8-methyl-1,10-trimethylenepiperazino-[1,2-a]indole are given in Table 1.

<u>1,10-Trimethylenepiperazino[1,2-a]indole</u> <u>Methiodide (VII).</u> To an ether solution of 10.4 g of 1,10-trimethylenepiperazino[1,2-a]indole was added 28.4 g of methyl iodide. The mixture was allowed to stand for 24 h, and the precipitate which had fallen was filtered off and washed repeatedly with ether. The yield of VII was 14.8 g (85%), mp > 320° (dec., from methanol). Found, %: N 8, 11, 8.27; I 36, 71, 36.30. $C_{15}H_{15}N_{2}I$. Calculated, %: N 7.99; I 36.23.

<u>8-Methyl-1,10-trimethylenepiperazino[1,2-a]in-</u> dole Methiodide (VIII). Under the conditions of the preceding experiment, 15 g (82%) of VIII was obtained from 12.9 g of 8-methyl-1,10-trimethylenepiperazino-[1,2-a]indole, mp > 300° (dec., from methanol). Found, %: N 8.06, 7.73; I 34.83, 35.07. $C_{16}H_{17}N_2I$. Calculated, %: N 7.96, I 34.84.

<u>2-Methyl-1,10-trimethylenepiperazino[1,2-a]</u> indole (IX). Into an autoclaye were placed 6 g of

methiodide VII, 150 ml of ethanol, 1.5 g of diethylamine, and 10 g of a Raney nickel catalyst paste. Hydrogenation was carried out at 60 atm and 160° until absorption of hydrogen ceased. The catalyst was removed, the alcohol was evaporated to a low volume, and the crystals which separated were filtered off. Yield of IX, 3 g (80%); mp 94-95° (from methanol). Found, %: C 79.90, 80.03. H 7.85, 8.10; N 12.76, 12.43. $C_{15}H_{18}N_2$. Calculated, %; C 79.60; H 8.01; N 12.38.

B. The reaction mixture from 2.2 g of 8-methyl-1,10-trimethylenepiperazino[1,2-a]indole, 60 ml of methanol, and 4 ml of a suspension of Raney nickel in methanol was boiled for 4 h. The hot solution was filtered, the catalyst was washed repeatedly with methanol, and the filtrate was evaporated under vacuum. The yield of X was 2.1 g (92%), mp 135-136° (from methanol); it gave no mp depression with the material made by method A.

2-Ethyl-8-methyl-1,10-trimethylenepiperazino [1,2-a] indole (XI). A. To 260 ml of well-cooled absolute ether was added 0.7 g of lithium aluminum hydride in small portions. To the suspension obtained was added, dropwise, a solution of 1.6 g of I in 260 ml of absolute ether, at such a rate that the ether boiled smoothly. The reaction mixture was boiled for 3 h; then the excess LiAlH₄ was decomposed by gradually adding 40 ml of water to the reaction mixture. The ether layer was separated from the aluminum hydroxide, dried over magnesium sulfate, and evaporated to a low volume; to the residue was added an ethereal hydrogen chloride solution, and the precipitate which separated was filtered off. Yield of XI hydrochloride, 1.2 g (70%), mp 235-236° (from methanol). Found, %: C 70.00, 70.01; H 7.95, 7.73; N 9.39, 9.40. $C_{17}H_{22}N_2HC1$. Calculated, %: C 70.25; H 7.97; N 9.63.

B. 8-Methyl-1,10-trimethylenepiperazino[1,2-a]indole (2.2 g), 60 ml of ethanol, and 4 ml of a Raney nickel suspension in ethanol were mixed together. The mixture was heated at 55-60°, with stirring, for 6 h. The catalyst was filtered off and washed repeatedly with alcohol, and the filtrate was evaporated under vacuum. Yield of XI, 2.3 g (92%), mp 105-106° (from methanol). Found, %: C 80.50, 80.10; H 8.75, 8.48; N 11.20, 11.32. $C_{17}H_{22}N_2$. Calculated, %: C 80.27; H 8.71; N 11.01.

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