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AMINOMETHYLATION OF PEMOLINE

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Aminomethylation of pemoline with primary amines has given the corresponding oxazolo[3,2-a]-1,3,5-triazines or oxazolo[3,2-a]-1,3,5,7-tetrazocines. When secondary amines were used, the 5-amino- or 3,5-bis(aminomethyl) derivatives were obtained.

2-Amino-5-phenyl-4-oxazolinone (pemoline, I) is an efficient psychic stimulant [1]. Its aminomethyl derivatives, which may be regard as prodrug forms of the compound [2], have not been examined. We here report the Mannich reaction of (I) with primary amines.

The structures of the Mannich bases obtained depend in the first instance on the amine used. When butylamine, tert-butylamine, N,N-dimethylpropane-1,3-diamine, or aniline is used as the amino-component, the oxazolo[3,2-*a*]-1,3,5-triazines (IIa-d) are obtained, while methylamine and cyclohexylamine give the oxazolo[3,2-*a*]-1,3,5,7-tetrazocines (IIIa-c) (Table 1).

The structures of compounds (IIa-d) were confirmed by the presence in their PMR spectra of signals for the protons of the two methylene groups of the annelated tetrahydrotriazine ring [3, 4] (Table 1), and for the protons of one R radical.

The PMR spectra of (IIa, b, d) also show pairs of doublets for the prochiral methylene protons of the $C_{(7)}$–CH_2OH methylene group, while that of (IIc) shows two doublets for the analogous protons of the $C_{(7)}$–$CH_2NHC_4H_9$-t aminomethyl group. In the IR spectra of this compound, the absorption for the nonassociated NH group at 3300 cm^{-1} is unusual in appearance, being narrow and intense.

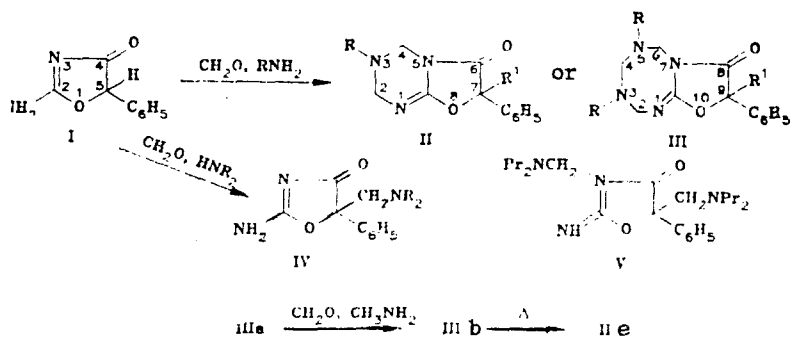

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TABLE 1. Conditions for and Products of Aminomethylation of Pemoline (I).

Compound	Empirical formula[*1]	R (R_2)	R' h	Reaction conditions		mp, °C[*2]	UV spectrum, λ_{max}, nm (log ε)[*3]	IR spectrum, cm^{-1}		PMR spectrum, ppm[*4]						Yield, %
										2-CH_2			4-CH_2			
				t,	T, °C			C=O	C=N	H_A	H_B	J_{AB}, Hz	H_A	H_B	J_{AB}, Hz	
IIa	$C_{16}H_{21}N_3O_3$	C_4H_9	CH_2OH	6,5	0...5	141	215 (4,33)	1770	1700	4,38		—	4,58	4,82	12,0	5
IIb	$C_{17}H_{24}N_4O_3$	$(CH_3)_2N\times$ $\times(CH_2)_3$	CH_2OH	0,5	60	125	220 (4,35)	1765	1690	4,34		—	4,47	4,77	12,0	3
IIc	$C_{20}H_{30}N_4O_2$	t-C_4H_9	$CH_2NH\times$ $\times C_4H_9$-t	6,0	20	146	—	1755	1690	4,33	4,51	13,5	4,49	4,85	13,5[*5]	12
IId	$C_{18}H_{17}N_3O_3$		CH_2OH	1,5	64	88	—	1760	1680	4,71		—	5,10		—	16
IIe	$C_{13}H_{15}N_3O_3$	C_6H_5	CH_2OH	4,0	100	153	218 (4,31)	1740	1695	4,17		—	4,51		—	100
IIIa	$C_{14}H_{18}N_4O_2$	CH_3	H	6,5	0...5	125	225 (4,40)	1730	1610	4,28		—	3,44		—	4
IIIb	$C_{15}H_{20}N_4O_3$	CH_3	CH_2OH	4,0	25...30	114	—	1750	1600	4,38	4,64	12,0	3,45	3,51	11,5	9
IIIc	$C_{25}H_{36}N_4O_3$	C_6H_{11}	CH_2OH	4,0	80	153	215 (4,18)	1690	1600	4,43	4,71	12,5	3,71	3,82	12,5[*5]	6
IVa	$C_{14}H_{19}N_3O_2$	$(C_2H_5)_2$		1,0	78	209	—	1740	1670	—	—	—	—	—	—	30
IVb	$C_{15}H_{19}N_3O_2$	$(CH_2)_5$		1,0	64	220	—	1750	1680	—	—	—	—	—	—	11
V	$C_{23}H_{38}N_4O_2$			1,0	40	60	—	1755	1710	—	—	—	4,54	4,82	13,0[*6]	14

[*1](IIa). Calculated, M 303.36. Found (mass spectrum) 303. (IVa). Calculated, M 261.17. Found (mass spectrum) 261.

[*2]Compounds (IIa, b, d, e) were crystallized from carbon tetrachloride, (IIc) from benzene–hexane (1:4), (IIIc) from acetone–hexane (1:1), (IVa) from ethanol, and (IVb) from dioxane.

[*3]No maxima seen with (IIc, d), (IIIb), (IVa, b), or (V).

[*4]Obtained in $CDCl_3$ (IIa-c, IIIa-c), DMSO-D_6 (IId, e, IVa, b), or CCl_4 (V).

[*5]270 MHz.

[*6]$N_{(3)}CH_2$.

When pemoline (I) was aminomethylated with methylamine and aqueous formaldehyde at 5°C, the main reaction product was (IIIa). The formation of the hexahydrotetrazocine moiety was clearly shown by the spectral data for (IIIa): the IR spectrum showed no NH or OH absorption, while in the PMR spectrum two signals for methyl protons appeared on the three resonance signals for the methylene protons. The mass spectrum showed no molecular ion peak, but strong peaks for the ions $[CH_3NCH_2]^+$ (m/z 43) and $[M - CH_3NCH_2]^+$ (m/z 231) were present.

When the reaction was carried out at 30°C, the reaction mixture was found to contain two products, the oxazolotetrazocine (IIIa) mentioned above, and its 9-hydroxymethyl derivative (IIIb), the spot for (IIIa) appearing first on the chromatogram, then a second spot for (IIIb). The final ratio of yields of (IIIa) and (IIIb) was ~1:6. The IR spectrum of (IIIb) differed from that of (IIIa) in the presence of strong absorption above 3000 cm^{-1}, in the form of two intense bands at 3450 and 3240 cm^{-1}. The PMR spectrum in $CDCl_3$ was complicated in comparison with that of (IIIa) by the geminal splitting of the signals for the 2-CH_2 and 4-CH_2 protons, and in the presence of a geminal AB quadruplet for the methylene protons of the $C_{(9)}CH_2OH$ group. No signal for the hydroxyl proton was seen in $CDCl_3$, but this signal was present in solutions of (IIIb) in DMSO-D_6 (5.44 ppm, t, J_{CH_2OH} = 6 Hz), each peak in the AB quadruplet for the prochiral methylene protons of the hydroxymethyl group $C_{(9)}CH_2OH$ being split with a J_{CH_2OH} constant at the hydroxyl proton.

The oxazolotetrazocine (IIIa) was completely converted into the hydroxymethyl compound (IIIb) when the reaction mixture was placed in an open vessel and the solvent allowed to evaporate completely. This reaction also occurred when (IIIa) was treated with methylamine and formaldehyde under the conditions used to obtain (IIIb) directly from pemoline (I).

No molecular ion peak was seen in the mass spectrum of (IIIb), but strong peaks were present for the ions $[CH_3NCH_2]^+$ (m/z 43) and $[M - CH_3NCH_2]^+$ (m/z 261). In accordance with this mode of fragmentation, (IIIb) was converted preparatively into the oxazolotriazine (IIe) on heating in vacuo. The spectral properties of (IIe) were similar to those of the other oxazolotriazines (Table 1). As is the case with (IIIb), the PMR spectrum of a solution of (IIe) in DMSO-D_6 showed vicinal coupling of the $C_{(7)}CH_2OH$ hydroxymethyl group. It was not possible to obtain in this way an oxazolotriazine from (IIIa).

Using cyclohexylamine, aminomethylation of pemoline (I) afforded the oxazolotetrazocine (IIIa). The PMR spectrum of this compound in $CDCl_3$ differed from that of its methyl analog (IIIb) only in that the 6-CH_2 protons gave rise to a geminal AB quadruplet rather than a singlet.

Aminomethylation of pemoline (I) with secondary amines could only be effected in acid solution. Diethylamine and piperidine gave the 5-aminomethyl derivatives (IVa, b), the structures of which followed from their PMR spectra: no signal for the $C_{(5)}H$ proton was seen, but signals were present for the protons of a single aminomethyl group, and a doublet for the protons of the $C_{(1)}$–NH_2 group, characteristic of pemoline itself [5, 6].

It is likely that in the formation of (IVa, b) the $N_{(3)}$-aminomethyl compounds are first formed as intermediates, and after aminomethylation at $C_{(5)}$ the $N_{(3)}$-aminomethyl group is removed by solvolysis. When dipropylamine was used, it was in fact possible to isolate the 3,5-bisaminomethyl compound (V), in the IR spectrum of which the $\nu_{C=O}$ and $\nu_{C=N}$ values (Table 1) were as high as in the 3-methyl derivative of pemoline [7]. Apart from a quadruplet for the diastereotopic protons of the prochiral methylene group $C_{(5)}CH_AH_BN$ in the PMR spectrum of (V), a geminal AB quadruplet for the $N_{(3)}CH_AH_BN$ methylene protons was present in the same field positions as the signals for the analogous 4-CH_2 protons in (IIa-c) (Table 1), which is also reliable evidence for $N_{(3)}$-substitution. No signal for the NH proton was seen, probably as a result of broadening of the peak in consequence of rapid base-catalyzed exchange.

Compound (V) is soluble in all the usual organic solvents, but it is so labile that it was not possible to find a suitable solvent for its recrystallization. Its solutions in benzene and hexane began to become turbid a few hours after preparation as a result of separation of pemoline (I). Attempts to convert (V) into the 5-dipropylaminomethyl derivative of pemoline [i.e., the analog of (IVa, b)] by dissolving it in a hydroxylic solvent did not meet with success, only the starting pemoline (I) being isolated from the solution.

EXPERIMENTAL

PMR spectra were obtained on Tesla BS-497C (100 MHz) and Bruker HX-270 (270 MHz) instruments, internal standard HMDS, IR spectra on an IKS-29 spectrophotometer in KBr disks, and UV spectra on an SF-16 spectrophotometer (in ethanol). The mass spectra of (IIa), (IIIa), (IIIb), and (IVa) were obtained on an MX-1303 with a direct sample introduction system, ionizing voltage 70 eV, admission system temperatures 90, 65, 180, and 160°C, respectively. TLC was carried out on Silufol UV-254 plates, eluent ethanol–chloroform (1:10).

3-Butyl-6-oxo-7-phenyl-7-hydroxymethyl-2,3,4,5,6,7-hexahydrooxazolo-[3,2-*a*]-1,3,5-triazine (IIa). To a suspension of 3.5 g (20 mmoles) of pemoline (I) in 300 ml of methanol was added dropwise with stirring a mix-

ture of 1.5 g (20 mmoles) of butylamine and 6.5 ml (80 mmoles) of formalin, maintaining the temperature of the mixture at 5°C. The mixture was stirred at this temperature for 6.5 h, unreacted starting material (I) filtered off (1.9 g), and the filtrate extracted with benzene (3 × 35 ml). The extract was dried overnight over sodium sulfate, the solvent removed under reduced pressure, and the residue poured into hexane and the solid which separated filtered off. PMR spectrum (in DMSO-D_6, 100 MHz); 7.25-7.50 (5H, m, C_6H_5); 5.76 (1H, t, $J_{CH_2OH}^{vic}$ = 6 Hz, OH); 4.54 (2H, s, 4-CH_2); 4.20 (2H, s, 2-CH_2); 3.92 (1H, d.d, J_{AB}^{gem} = 12, $J_{CH_2OH}^{vic}$ =6 Hz, $C_{(7)}H_A$); 3.63 (1H, d.d, J_{AB}^{gem} = 12, $J_{CH_2OH}^{vic}$ =6 Hz, $C_{(7)}CH_B$); 2.38 (2H, m, $C\underline{H}_2(CH_2)_2CH_3$); 1.26 (4H, m, $CH_2(C\underline{H}_2)_2CH_3$); 0.76 ppm (3H, t, CH_3).

Compounds (IIIb-d) were obtained similarly.

3,5-Dimethyl-8-oxo-9-phenyl-2,3,4,5,6,7-hexanhydrooxazolo[3,2-*a*]-tetrazocine (IIIa). To a suspension of 5.3 g (30 mmoles) of pemoline (I) in 60 ml of methanol was added dropwise with stirring a mixture of 7.4 ml (60 mmoles) of 25% aqueous methylamine and 9.6 ml (120 mmoles) of formalin, maintaining the temperature of the reaction mixture at 5°C. The mixture was stirred at this temperature for 6.5 h, then unreacted pemoline (I) was filtered off (2.4 g), and extracted with benzene (3 × 60 ml). The extract was dried over sodium sulfate overnight, the benzene removed under reduced pressure to dryness, the residue treated with hexane, and the resulting solid filtered off. PMR spectrum (in $CDCl_3$, 100 MHz): 7.06-7.20 (5H, m, C_6H_5); 5.50 (1H, s, 9-CH); 4.44 (2H, s, 6-CH_2); 4.28 (2H, s, 2-CH_2); 3.44 (2H, s, 4-CH_2); 2.32 (3H, s, CH_3); 2.28 ppm (3H, s, CH_3).

Compound (IIIc) was obtained similarly.

3,5-Dimethyl-8-oxo-9-phenyl-9-hydroxymethyl-2,3,4,5,6,7-hexahydrooxazolo-[3,2-*a*]-1,3,5,7-tetrazocine (IIIb). A. To a suspension of 5.3 g (30 mmoles) of pemoline (I) in 60 ml of methanol was added dropwise with stirring a mixture of 7.4 ml (60 mmoles) of 25% aqueous methylamine and 9.6 ml (120 mmoles) of formalin, maintaining the temperature at 5°C. The mixture was then stirred for 4 h at 30°C, filtered from unreacted pemoline (I) (1.5 g), and extracted with benzene (3 × 50 ml). The extract was dried overnight over sodium sulfate, the benzene removed under reduced pressure, and the solid residue recrystallized. PMR spectrum (in DMSO-D_6, 100 MHz); 7.26-7.50 (5H, m, C_6H_5); 5.44 (1H, t, $J_{CH_2OH}^{vic}$ = 6 Hz, OH); 4.51* (1H, d, J_{AB}^{gem} = 11 Hz, 6-CH_A); 4.37* 1H, d, J_{AB}^{gem} = 11 Hz, 6-CH_B); 4.42 (1H, d, J_{AB}^{gem} = 10 Hz, 2-CH_A); 4.28 (1H, d, J_{AB}^{gem} = 10 Hz, 2-CH_B); 3.92 (1H, d.d, J_{AB}^{gem} = 14, $J_{CH_2OH}^{vic}$ = 6 Hz, $C_{(9)}CH_A$); 3.68 (1H, d.d., J_{AB}^{gem} = 14, $J_{CH_2OH}^{vic}$ = 6 Hz, $C_{(9)}CH_B$); 3.42 (2H, s, 4-CH_2); 2.26 (3H, s, CH_3); 2.18 ppm (3H, s, CH_3).

B. To a solution of 0.55 g (2 mmoles) of (IIIa) in 30 ml of methanol was added 9.6 ml (120 mmoles) of formalin and 6.7 ml (54 mmoles) of 25% aqueous methylamine, and the mixture stirred for 10 h at 20-25°C. It was then poured into a crystallizing dish, and the solvent allowed to evaporated completely. The solid which formed on the following day was recrystallized from methanol, mp 113°C, yield 0.38 g (62%). The results of elemental analysis were in agreement with the calculated values. The spectral characteristics were as given in Table 1.

Compounds (IIIa) and (IIIb). To a suspension of 5.3 g (30 mmoles) of pemoline (I) in 60 ml of methanol was added dropwise with stirring a mixture of 6.7 ml (54 mmoles) of 25% aqueous methylamine and 9.6 ml (120 mmoles) of formalin, maintaining the temperature at 5°C, following which the mixture was stirred for 10 h at 30°C, filtered from unreacted pemoline (3.1 g), and extracted with benzene (3 × 50 ml). The extract was dried over sodium sulfate overnight, evaporated to 1/3 of its initial volume, and hexane added to the residue to precipitate (IIIa), which was crystallized from carbon tetrachloride, mp 126°C, yield 0.60 g (7%).

The mixture remaining after extraction was evaporated under reduced pressure, and the resulting solid crystallized from benzene to give 0.11 g (1%) of (IIIb), mp 114°C. The elemental analyses for (IIIa) and (IIIb) were in agreement with the calculated values, and their spectral characteristics were as given in Table 1.

3-Methyl-6-oxo-7-phenyl-7-hydroxymethyl-2,3,4,5,6,7-hexahydrooxazolo-[3,2-*a*]-1,3,5-triazine (IIe). Compound (IIIb) (0.0892, $29 \cdot 10^{-2}$ mmole) was held at 100°C under a residual pressure of 10 mm for 4 h to give 0.0767 g (101%†) of nearly pure (IIe). PMR spectrum (in DMSO-D_6, 100 MHz): 7.30-7.48 (5H, m, C_6H_5); 5.79 (1H, t, $J_{CH_2OH}^{vic}$ = 6 Hz, OH); 4.51 (2H, s, 4-CH_2); 4.17 (2H, s, 2-CH_2); 3.95 [1H, d.d, J_{AB}^{gem} = 13, $J_{CH_2OH}^{vic}$ = 6 Hz, $C_{(7)}CH_A$]; 3.65 (1H, d.d, J_{AB}^{gem} = 13, $J_{CH_2OH}^{vic}$ = 6 Hz, $C_{(7)}CH_B$); 2.30 ppm (3H, s, CH_3).

*Merged into a single signal at 4.44 ppm (2H) on adding D_2O.

†The yield was greater than 100% as a result of the presence of small amounts of (IIIb). The weight loss was 14%, corresponding to a decrease in molecular mass by 42.6 units as compared with the calculated value of 43.1 units.

5-Phenyl-5-diethylaminomethyl-2-amino-4-oxazolinone (IVa). A mixture of 3.6 g (50 mmoles) of diethylamine, 4.0 ml (50 mmoles) of formalin, and 6.7 ml (120 mmoles) of acetic acid was added to a suspension of 2.1 g (12 mmoles) of pemoline (I) in 30 ml of ethanol, and the mixture stirred for 0.5 h at 25°C, then boiled for 0.5 h, until a clear solution was obtained. The solution was cooled to 20°C, 10% aqueous sodium hydroxide added, and the solid which separated was filtered off. PMR spectrum (in DMSO-D_6, 100 MHz)*: 8.60 (1H, s, NH_A); 8.50 (1H, s, NH_B); 7.32-7.43 (5H, M, $C_{\wedge H\%}$); 3.11 (1H, d, J_{AB} = 14 Hz, $C_{(5)}CH_A$); 2.81 (1H, d, J_{AB} = 14 Hz, $C_{(5)}CH_B$); 0.74-0.90 ppm (6H, m, CH_3).

Compound (IVb) was obtained similarly (Table 1).

5-Phenyl-3,5-bis(dipropylaminomethyl)-2-imino-4-oxazolidinone (V). To a suspension of 4.4 g (25 mmoles) of pemoline (I) in 60 ml of methanol was added a mixture of 10.1 g (100 mmoles) of dipropylamine, 8.0 ml (100 mmoles) of formalin, and 13.4 ml (240 mmoles) of acetic acid. The mixture was stirred at 40°C until a clear solution was obtained (1 h), then cooled to 20°C and neutralized with 20% aqueous sodium hydroxide. The oily material which separated was extracted with pentane, the pentane removed under reduced pressure, and the residue washed with pentane cooled to 0°C. PMR spectrum (in CCl_4, 100 MHz): 7.46-7.86 (5H, m, C_6H_5); 4.82 (1H, d, J_{AB} = 13 Hz, $N_{(3)}CH_A$); 4.54 (1H, d, J_{AB} = 13 Hz, $N_{(3)}CH_B$); 3.39 (1H, d, J_{AB} = 15 Hz, $C_{(5)}CH_A$); 3.19 (1H, d, J_{AB} = 15 Hz, $C_{(5)}CH_B$); 2.64-2.290 (8H, m, $CH_2CH_2CH_3$); 1.54-1.88 (8H, m, $CH_2CH_2CH_3$); 0.98-1.22 ppm [12H, m, $(CH_2)_2CH_3$].

Compounds (IIb) and (IIIc) were obtained in benzene, (IIc, d) and (IVb) in methanol. In the preparation of (IIb) and (IIc) the formaldehyde was added to the reaction mixture as formalin, and in the preparation of (IId), (IIc), and (IVb), as paraformaldehyde.

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*The signals for the methylene protons of the ethyl groups were "screened" by the signals of residual protons of the solvent.