2-Dimethylamino-4-(β-N,N-dimethylaminoethoxy)quinoline (Vb). Sodium hydride (0.92 g) was added in portions to a suspension of I (3.76 g) in anhydrous dimethylformamide (DMF; 40 ml) at 40° and the mixture was maintained at 90° for 2 h. A solution of β-(N,N-dimethylamino)ethyl chloride in anhydrous DMF (10 ml) was added dropwise to the mixture which was then heated at 100° for 3 h, and the DMF distilled off in vacuum. The residue was dissolved in water, the solution extracted with chloroform, the extract dried with anhydrous sodium sulfate, and the chloroform distilled off. The residue was dissolved in acetone, the solution was acidified with an alcoholic solution of hydrogen chloride, and Vb hydrochloride was obtained. Compounds Va, VIa, and VIb were obtained similarly (see Table 2).

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N-DERIVATIVES OF ANABASINE.

PREPARATION OF N-DERIVATIVES OF ANABASINE HAVING NICOTINOLYTIC PROPERTIES

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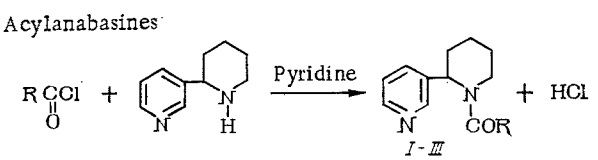
The alkaloid anabasine, which comprises 69.0-79.8% of the total alkaloid content of the plant *Anabasis aphylla* (central Asia) [1], has a whole series of nicotine-like biological properties. We have found [2] that certain N-aryl and N-alkyl derivatives of anabasine, containing bulky acyl or alkyl radicals on the nitrogen of the piperidine ring, display antinicotinic activity. Such substances can be of interest for conducting pharmacological investigations on experimental animals.

Our search for compounds which block nicotinic choline receptors in the substituted anabasine series was based, first of all, on the structural similarity between anabasine and nicotine; secondly, on the availability of a hydrogen atom on the nitrogen of the piperidine ring, which facilitates the synthesis of N derivatives; and, finally, on the fact that raw materials are readily available for native production of anabasine itself.

The synthesis of anabasine derivatives was carried out according to the following scheme:



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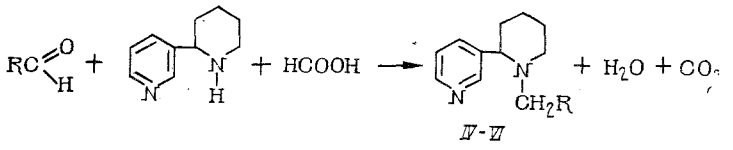
Alkylanabasines



IV-VI

I, IV: R=$CH_3(CH_2)_3$; II, V: R=$(CH_3)_2CHCH_2$; III, VI: R=$CH_3(CH_2)_4$

For the synthesis of I-VI we used anabasine which had been isolated from technical anabasine sulfate by nitrosation of a mixture of alkaloids followed by decomposition of the nitrosoanabasine [3]. For the synthesis of acyl derivatives I-III, anabasine in dry pyridine was treated with valeric, isovaleric, and caproic acid chlorides at a temperature of 125-130°. The bases valeryl- (I), isovaleryl- (II), and hexanoylanabasine (III) are viscous oils, light yellow in color. They crystallize as well as the picrates and picrolonates, whereas the hydrochlorides form as noncrystalline oils. For pharmacological investigation we prepared 0.5 M acylanabasine hydrochloride as a solution of the base in the calculated quantity of aqueous hydrochloric acid. Compounds I-III have not been described in the literature. We obtained the acid chlorides of valeric, isovaleric, and caproic acids by the usual method — the reaction of phosphoryl chloride with the appropriate acid.

Amyl- (IV), isoamyl- (V), and hexylanabasine (VI) were obtained by prolonged heating of anabasine with the corresponding aldehyde and formic acid. The alkylanabasine bases are colorless or yellowish oils, which can be distilled readily under vacuum. In contrast to the corresponding acylanabasines, the alkylanabasines give crystalline hydrochlorides which, although hygroscopic, can be obtained in pure form. With picric and picrolonic acids they give diacid salts which crystallize readily. We did not manage to obtain the picrolonate of IV as a solid. For pharmacological testing we prepared 0.5 M solutions of the hydrochloride salts. Compounds IV and VI were first synthesized in our laboratory; compound V was described in the literature [4], along with a picrate with a melting point of 187.5-188.5°; apparently this was the monopicrate, as the dipicrate we obtained has a melting point of 157.5-158°.

EXPERIMENTAL

Pharmacology

We conducted pharmacological investigations on white mice and atropine-treated cats. We determined toxicity (LD_{50}), hypotensive activity, and anticonvulsive antinicotinic activity. We found that the acylanabasines are less toxic (LD_{50} 600-1000 mg/kg) than the corresponding alkylanabasines (LD_{50} 470-35.5 mg/kg); of the latter, V (LD_{50} 35.5 mg/kg) is particularly toxic, with a value equal to that of anabasine itself (LD_{50} 39.0 mg/kg). Acyl- and alkylanabasines show hypotensive activity,which is especially pronounced in III and IV. These preparations as the 0.5 M solutions, even at doses of 0.1 mg/kg (III) and 0.05 mg/kg (IV), reduce by 54% and 60-70%, respectively, the maximum elevation of arterial pressure produced by subsequent administration of an additional dose of anabasine. (Anabasine is analogous in its peripheral activity to nicotine, with two to three times its activity [5-7].) Only I and III show weak anticonvulsive activity, and they partially relieve nicotine hyperkinesis.

EXPERIMENTAL

Chemistry

Acylanabasines I-III. These are obtained by stirring equimolar quantities of the acid chloride and freshly distilled anabasine (n_D^{20} 1.5440) with a twofold molar excess of dry pyridine. The mixture is heated at 125-130° for 5 hours. On cooling, the dark mass is dissolved in water, benzene is added, the aqueous layer is separated, and the benzene layer is washed three times with small quantities of water. The combined aqueous extracts are washed with 50 ml benzene. The benzene layer is added to the original benzene extract and dried over potassium hydroxide; the benzene is distilled off, and the dark, viscous oil is distilled under vacuum. The yields and properties are given in Table 1.

Alkylanabasines IV-VI. To 7.7 ml (8.1 g, 0.05 mole) anabasine (n_D^{20} 1.5440) under cooling is added a 10-ml quantity of 95% formic acid. As the mixture is slowly warmed, it turns pink. Subsequently, the appropriate aldehyde (0.0625 mole) is added, and the mixture is heated on a water bath for 15-18 hours. When the reaction is complete, the mixture is acid-

TABLE 1. N-Acyl- and N-Alkylanabasines

Compound	Yield, %	Melting point or boiling point, deg	Found, %			Empirical formula	Calculated, %			LD_{50}	Hypotensive activity‡
			C	H	N		C	H	N		
I:											
base*	61,8	170 (2—3 mm)	72,84	9,59	11,66	$C_{15}H_{22}N_2O$	73,13	9,00	11,38	981,9	58
picrate	79,8	139—42	—	—	14,66	$C_{15}H_{22}N_2O \cdot C_6H_3N_3O_7$	—	—	14,73	—	—
picrolonate	65,0	100—7	—	—	16,41	$C_{15}H_{22}N_2O \cdot C_{10}H_8N_4O_5$	—	—	16,46	—	—
II:											
base*	76,9	168 (2—3 mm)	73,21	9,13	11,43	$C_{15}H_{22}N_2O$	73,13	9,00	11,38	684,37	63
picrate	53,0	147—7	—	—	15,37	$C_{15}H_{22}N_2O \cdot C_6H_3N_3O_7$	—	—	14,73	—	—
dipicrolonate	56,8	113—5	—	—	18,95	$C_{15}H_{22}N_2O \cdot 2C_{10}H_8N_4O_5$	—	—	18,08	—	—
III:											
base*	55,9	174—7 (2—3 mm)	73,80	9,08	10,95	$C_{16}H_{24}N_2O$	73,80	9,29	10,76	857,1	46
dipicrolonate	92,0	99—105	—	—	14,18	$C_{16}H_{24}N_2O \cdot C_6H_3N_3O_7$	—	—	14,31	—	—
picrolonate	63,5	108—10	—	—	15,67	$C_{16}H_{24}N_2O \cdot C_{10}H_8N_4O_5$	—	—	16,02	—	—
IV:											
base*	67,0	126—8 (2—3 mm)	77,40	10,47	12,66	$C_{15}H_{24}N_2$	77,53	10,41	12,06	—	—
dihydrochloride	50,4	135—41	—	—	9,45	$C_{15}H_{24}N_2 \cdot 2HCl$	—	—	9,18	—	40—30
dipicrate	63,0	179—80	46,95	4,35	16,29	$C_{15}H_{24}N_2 \cdot 2C_6H_3N_3O_7$	46,96	4,38	16,23	—	—
V:											
base*	65,5	135—6** (2—3 mm)	—	—	—	$C_{15}H_{24}N_2$	—	—	—	—	—
hydrochloride†	95,5	195—8 (hygroscopic)	—	—	10,38	$C_{15}H_{24}N_2 \cdot HCl$	—	—	10,42	35,53	50
dipicrate	70,4	157,5—8	46,88	4,31	15,90	$C_{15}H_{24}N_2 \cdot 2C_6H_3N_3O_7$	46,96	4,38	16,23	—	—
dipicrolonate	60,6	222—4	54,98	5,49	18,35	$C_{15}H_{24}N_2 \cdot 2C_{10}H_8N_4O_5$	55,26	5,30	18,41	—	—
VI:											
base*	46,8	135—6 (2—3 mm)	77,41	10,46	12,00	$C_{16}H_{26}N_2$	77,99	10,64	11,37	—	—
hydrochloride†	90,2	163—4	—	—	10,20	$C_{16}H_{26}N_2 \cdot HCl$	—	—	10,64	471—69	57
dipicrate	31,7	169—70	—	—	16,48	$C_{16}H_{26}N_2 \cdot 2C_6H_3N_3O_7$	—	—	15,97	—	—
dipicrolonate	54,4	165—6	—	—	17,91	$C_{16}H_{26}N_2 \cdot 2C_{10}H_8N_4O_5$	—	—	18,08	—	—

*n_D^{20} of the base: I) 1.5350; II) 1.5341; III) 1.5311; IV) 1.5112; V) 1.5115; VI) 1.5120.
†Chlorine analyses for the hydrochlorides. Found % Cl: IV, 22.83; V, 12.99; VI, 12.34. Calculated, % Cl: IV, 23.23; V, 13.19; VI, 12.54.
‡Reduction of arterial pressure in percent (in relation to the hypotensive activity produced by 0.3 mg/kg anabasine).
**Given in the literature [5]: bp 149-151° (8 mm); picrate, mp 187.5-188.5°.

ified with 4 N hydrochloric acid and extracted with three 40-ml portions of ether. To the aqueous layer, after cooling with ice water, is added a substantial excess of 30% sodium hydroxide. The yellow or brown oily layer which separates is extracted three times with ether or chloroform, the extract is dried over potassium hydroxide, the solvent is removed by distillation, and the residual viscous oil is distilled under vacuum. Yields and properties are given in Table 1.

Picrates of I-VI. These are obtained by mixing a solution of 0.001 mole of the base in 2-3 ml alcohol with a solution of 0.001-0.002 mole of picric acid in 3-6 ml alcohol, boiling for 2-3 minutes, and then cooling. The precipitate is filtered off and recrystallized from a minimal quantity of alcohol.

Picrolonates of I-VI. These are obtained by a method analogous to that used for the picrates, using 50% alcohol. The salts sometimes separate in the form of an oil which solidifies slowly.

Hydrochlorides of Alkylanabasines IV-VI. A 0.003-mole quantity of the freshly distilled base is dissolved in 25 ml absolute ether; to this mixture, cooled with ice, is added dropwise a solution of hydrogen chloride in absolute alcohol, until the mixture tests neutral or weakly acidic. The salts separate as oils which solidify slowly when scratched. After 1.5 hours, the precipitated salt is filtered quickly, washed a few times with absolute ether, and dried under vacuum over calcium chloride. Hydrochlorides of IV and V are hygroscopic; they melt indistinctly and give low results on analysis. The salt of VI, which is more stable, can be recrystallized from dry acetone.

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