N-β-CHLORO- AND DIALKYLAMINOPROPIONYL DERIVATIVES OF SUBSTITUTED 4-AMINOCHROMANE AND 2, 3, 4, 5-TETRAHYDRO-1, 5-BENZOXAZEPINE AND RELATED COMPOUNDS

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With a view to testing their pharmacological properties, syntheses have been effected of N-β-chloro- and dialkylaminopropionyl derivatives of 3-methyl-4-aminochromane, 4-aminoflavan, 4-aminothiochromane, 2, 3, 4, 5-tetrahydro-1, 5-benzox-(and thia)-azepine, and some related compounds.

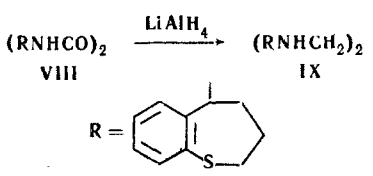
When investigating lithium aluminum hydride reduction of oximes of chroman-4-one and related ketones, we established formation of two series of reaction products: of the corresponding 4-amino derivatives and products of reductive ring opening, of the type 2, 3, 4, 5-tetrahydro-1, 5-benzoxazepine [1–3]. Frequently this method of obtaining the compounds mentioned is of preparative interest. To synthesize 4-amino derivatives, it is sometimes better to resort to catalytic hydrogenation of the corresponding oximes [4, 5].

The class of substituted 4-aminochromanes was found to include vasodilators and local anesthetics [6]. Continuing the search for pharmacologically active compounds among 4-aminochromanes [4], we synthesized N-β-chloro- and dialkylaminopropionyl derivatives of 3-methyl-4-aminochromane, 4-aminoflavan, and 4-aminothiochromane.

By reacting the nitrogen analog of 4-aminochromane, 1-phenyl-4-amino-1, 2, 3, 4-tetrahydroquinoline with chloropropionyl chloride, 1-phenyl-4-β-chloropropionylamino-1, 2, 3, 4-tetrahydroquinoline was also obtained. Table 1 gives data for the compounds (I–VII) prepared.

β-Chloropropionyl derivatives are also obtained by reacting the appropriate amines [1–5] with β-chloropropionyl chloride. β-Dialkylaminopropionyl derivatives are synthesized by exchanging a chlorine atom for an amino group.

Apart from compounds I–VII, 5-aminohomothiochromane and diethyl oxalate gave N, N'-bis(homothiochromanyl-5)oxamide (VIII), reduced by lithium aluminum hydride to N, N'-bis(homothiochromanyl-5)-ethylenediamine (IX).



If the structure and properties of 4-aminochromane closely resemble those of 2-alkoxybenzylamines, the isomeric compound 2, 3, 4, 5-tetrahydro-1, 5-benzoxazepine is a derivative of 2-alkoxyaniline. It is important to note that these two classes of compounds differ sharply chemically, which must also show up in the nature of the pharmacological action. We synthesized, also by the usual route, N-β-chloro- and dialkylaminopropionyl derivatives of 2, 3, 4, 5-tetrahydro-1, 5-benzoxazepine and 2, 3, 4, 5-tetrahydro-1, 5-benzthiazepine (X–XIX, Table 2) from tetrahydrobenzox(and thia)azepines [1–5].

Compound XIV gives slight conduction anesthesia and has a slight curare-like and ganglion blocking activity. Compounds XVII and XVIII cause some motor excitation and have slight cholinolytic activity. Compound XIX is without a curare-like action, at first it causes motor excitation, then braking of motor activity, and to some extent it reduces blood pressure. Compound VIII is a feeble spasmolytic. The diamine IX slightly reduces blood pressure, causes transient excitation of breathing, and exhibits slight antihistamine and cholinolytic actions. None of the compounds mentioned are of potential practical utility.*

EXPERIMENTAL**

3-Methyl-4-(β-chloropropionylamino)chromane (I). A mixture of 0.99 g 3-methyl-4-aminochromane hydrochloride, 0.2 g NaOH, 5 ml water, and 60 ml benzene was stirred, and at 5° 0.63 g β-chloropropionyl chloride and 0.2 g NaOH in 5 ml water added dropwise simultaneously. Stirring was continued for a further 1 hr without cooling, the benzene solution separated off, washed with dilute alkali and water, and then evaporated to dryness, to give I. The chlorides II–IV and X–XIII (Tables 1 and 2) were prepared similarly.

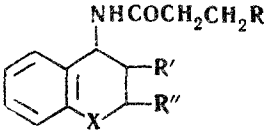
3-Methyl-4-(β-morpholypropionylamino)chromane (V). A mixture of 0.5 g chloride I and 0.34 morpholine in 5 ml toluene was refluxed for 1 hr 30 min, the filtrate evaporated, the oily residue dissolved in ether or benzene, washed with water, the solvent distilled off, dry benzene added and distilled off, the residue dissolved in dry ether, and an ether solution of HCl gas added. Yield of amine hydrochloride V, mp 197–198°, 0.6 g (89%). Amines VI, VII, XIV–XIX (Tables 1 and 2) were prepared similarly.

*The pharmacological tests were carried out by N. B. Vysotska on white mice.

**With the assistance of L. M. Meshcheryakova.

Table 1

N-β-Chloro- and Dialkylaminopropionyl Derivatives of 4-Aminochromanes and Related Compounds

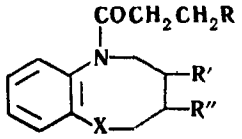


Compound number	X	R	R′	R″	Mp, °C	Formula	Found, %		Calculated, %		Yield, %
							Cl	N	Cl	N	
I	O	Cl	CH_3	H	126—127.5 (ex 50% MeOH)	$C_{13}H_{16}ClNO_2$	13.78 14.09	5.34 5.29	13.97	5.51	81
II	O	Cl	H	C_6H_5	161.5—162 (ex EtOH)	$C_{18}H_{18}ClNO_2$	11.11 11.05	4.28 4.02	11.22	4.43	77
III	S	Cl	H	H	133—135 (ex 75% EtOH)	$C_{12}H_{14}ClNOS$*	13.92 13.95		13.87		86
IV	NC_6H_5	Cl	H	H	142—143 (ex EtOH)	$C_{18}H_{19}ClN_2O$	11.43 11.15	—	11.26	—	60
V	O	Morpholyl-1	CH_3	H	(ex MeOH)	$C_{17}H_{24}N_2O_2 \cdot HCl$	10.35 10.32	—	10.42	—	60
VI	O	Morpholyl-1	H	C_6H_5	235—236 (ex MeOH)	$C_{22}H_{28}N_2O_3 \cdot HCl$	8.65 8.66	6.96 6.96	8.79	6.95	22
VII	S	Pipideryl-1	H	H	123—125	$C_{17}H_{24}N_2OS \cdot HCl$	10.00 9.94	9.12 9.05	10.40	9.40	33

*Found: S 12.13; 12.17%. Calculated S 12.52%.

Table 2

N-β-Chloro- and Dialkylaminopropionyl Derivatives of 2, 3, 4, 5-Tetrahydro-1, 5-benzox (and thia)azepines



Compound number	X	R	R′	R″	Mp, °C	Formula	Found, %		Calculated, %		Yield, %
							Cl	N	Cl	N	
X	O	Cl	H	H	92—93 (ex EtOH)	$C_{12}H_{14}ClNO_2$	14.78 14.81	5.83 5.84	14.79	5.84	94
XI	O	Cl	CH_3	H	90—90.5 (ex 50% MeOH)	$C_{13}H_{16}ClNO_2$	13.93 14.11	—	13.97	—	95
XII	O	Cl	H	C_6H_5	88—89 (ex MeOH)	$C_{18}H_{18}ClNO_2$	10.92 10.87	4.48 4.49	11.23	4.43	Not calculated
XIII	S	Cl	H	H	99.5—101 (ex 75% EtOH)	$C_{12}H_{14}ClNO_3S$*	13.87 14.00	—	13.87	—	95
XIV	O	Piperidyl-1	H	H	117—118 (ex acetone-ether)	$C_{17}H_{24}N_2O_2 \cdot HCl$	10.37 10.38	8.26 8.23	10.91	8.62	47
XV	O	Morpholyl-1	H	H	159—160 (ex acetone-ether)	$C_{16}H_{22}N_2O_3 \cdot HCl$	10.85 10.69	8.24 8.27	10.85	8.57	31
XVI	O	Morpholyl-1	CH_3	H	159—160 (ex EtOH)	$C_{17}H_{24}N_2O_3 \cdot HCl$	10.40 10.39	8.05 8.11	10.42	8.21	67
XVII	S	Morpholyl-1	H	H	191—192 (ex EtOH)	$C_{17}H_{24}N_2OS$** $\cdot HCl$	10.36 10.35	—	10.40	—	73
XVIII	S	Morpholyl-1	H	H	185—186 (ex MeOH-ether)	$C_{16}H_{22}N_2O_2S$*** $\cdot HCl$	10.44 10.25	—	10.35	—	60
XIX	S	4-β-Hydroxyethyl-piperazinyl-1	H	H	239.5—241 (ex MeOH)	$C_{18}H_{27}NOS \cdot 2HCl$	16.77 16.63	9.81 9.78	16.78	9.94	52

*Found S 12.64; 12.75%. Calculated S 12.52%.

**Found S 9.62; 9.65%. Calculated S 9.40%.

***Found S 9.52; 9.49%. Calculated S 9.33%.

N, N'-Bis(homothiochromanyl-5)ethylenediamine (IX). A mixture of 2.35 g 5-aminohomothiochromane, 0.86 g diethyl oxalate, and 5 ml toluene was refluxed for 3 hr, filtered, 2.11 g (80%), N, N'-bis(homothiochromanyl-5)-oxamide VIII, mp > 320°. A suspension of 1.73 g of the latter compound in 20 ml ether was added to 0.52 g $LiAlH_4$ in 15 ml ether, the whole refluxed for 7 hr, diluted with moist ether and 10% NaOH, then extracted with ether. The ether solution was shaken with 10% HCl (30 ml × 2), the acid solution made alkaline, and extracted with ether. The ether solution was dried, and from it the base IX dihydrochloride precipitated, yield 1.35 g (70%), mp 232–233° (ex MeOH + ether). Found: Cl 15.22; 15.17; S 13.93; 13.91%. Calculated for $C_{22}H_{28}N_2S_2 \cdot 2HCl$: Cl 15.49; 14.01%.

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