VII. SYNTHESIS AND BIOLOGICAL ACTION OF 9-ALKYLAMINO-1,2,3,4-TETRAHYDROACRIDINES

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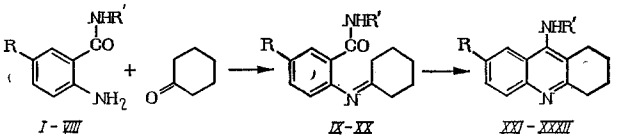
9-Amino-1,2,3,4-tetrahydroacridine ("tacrine") has a number of valuable pharmacological properties [1, 2, 3]. In this paper we describe the synthesis of several N-alkyl derivatives of this compound by a method previously used by us for the preparation of a series of 9-arylamino-1,2,3,4-tetrahydroacridines [4].

The alkylamides [(I)-(VIII), Table 1] of 5-substituted anthranilic acids served as starting materials for most of these preparations. The compounds (I) and (II) were obtained from 5-methylisatoic anhydride



I-VIII IX-XX XXI-XXXII

and the requisite amine by a method described in [5], but for the preparation of (III)-(VIII) the method we used in [6] was adopted, whereby methyl esters of 5-substituted anthranilic acids were treated with the magnesium derivatives of the appropriate amines.

The eight anthranilic acid alkylamides (I)-(VIII), on warming with cyclohexanone in benzene solution, gave in good yield the corresponding cyclohexylidene derivatives [(XIII)-(XX), see Table 2]. The four compounds [(IX)-(XII), Table 2] which carry no substituent in the 5-position were obtained in a similar manner from the appropriate alkylamides of unsubstituted anthranilic acid.*

The twelve cyclohexylideneanthranilic acid alkylamides [(IX)-(XX), Table 2] were cyclized by warming with an excess of phosphorus oxychloride. The reaction proceeded smoothly and gave rise, in yields up to 97%, to the 9-alkylamino-1,2,3,4-tetrahydroacridines (XXI)-(XXXII) listed in Table 3. The compounds (XXX) and (XXXII) were obtained only as hydrochlorides, but in the other cases the free bases were also prepared.

The twelve acridine derivatives (Table 3) are white or slightly yellowish crystalline substances having basic properties and forming with mineral acids salts which are readily soluble in water. The UV spectra† are cognate with those of 4-aminoquinoline [7] and are characterized (bases in ethanol) by three absorption bands at λ_{max} 222-224, 244-252, and 336-344 nm; the spectra of the hydrochlorides show a bathochromic shift in the long-wave band.

These compounds (XXI)-(XXXII) show on biological examination‡ a capacity to lower the excitability threshold of the CNS and to induce convulsions. The LD_{50} (ip) ranges over 20-35 mg/kg. The compounds (XXI), (XXIII), and (XXVII)-(XXX) show analgesic properties in the following order of magnitude: (XXI) > (XXVIII) > (XXX) > (XXIII) > (XXIX) > (XXVII), but the doses needed to produce this effect are rather close to the respective toxic levels. The only compounds to show anti-curare activity were (XXI) and (XXIV).

*Sentence introduced by translator.

†A spectrophotometer SF-4 was used.

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TABLE 1. Alkylamides of 5-Substituted Anthranilic Acids

Compound	R	R¹	Yield, %	Mp (°C)	Found N, %	Empirical formula	Calc. N, %
I	CH_3	CH_3	52	120	17,26	$C_9H_{12}N_2O$	17,09
II	CH_3	C_2H_5	61	121	15,45	$C_{10}H_{14}N_2O$	15,71
III	CH_3	n-C_4H_9	86,5	127	13,29	$C_{12}H_{18}N_2O$	13,47
IV	CH_3	iso-C_4H_9	48,1	157	13,23	$C_{12}H_{18}N_2O$	13,47
V	Cl	n-C_4H_9	79	127—130	12,17	$C_{11}H_{15}ClN_2O$	12,35
VI	Cl	iso-C_4H_9	48,3	138—140	12,03	$C_{11}H_{15}ClN_2O$	12,35
VII	Br	n-C_4H_9	73,5	112	10,10	$C_{11}H_{15}BrN_2O$	10,32
VIII	Br	iso-C_4H_9	56,5	128—130	9,97	$C_{11}H_{15}BrN_2O$	10,32

TABLE 2. Alkylamides of Cyclohexylideneanthranilic Acids

Compound	R	R¹	Yield, %	Mp (°C)	Found N, %	Empirical formula	Calc. N, %
IX	H	CH_3	65,6	212—215	12,50	$C_{14}H_{18}N_2O$	12,22
X	H	C_2H_5	62	210—212	11,30	$C_{15}H_{20}N_2O$	11,50
XI	H	n-C_4H_9	79,8	175—176	10,02	$C_{17}H_{24}N_2O$	10,31
XII	H	iso-C_4H_9	76	170	10,14	$C_{17}H_{24}N_2O$	10,31
XIII	CH_3	CH_3	65	211—214	11,45	$C_{15}H_{20}N_2O$	11,50
XIV	CH_3	C_2H_5	73	183—184	10,52	$C_{16}H_{22}N_2O$	10,8
XV	CH_3	n-C_4H_9	46,5	147	9,62	$C_{18}H_{26}N_2O$	9,80
XVI	CH_3	iso-C_4H_9	46,8	159—160	9,69	$C_{18}H_{26}N_2O$	9,80
XVII	Cl	n-C_4H_9	74	173—175	8,90	$C_{17}H_{23}ClN_2O$	9,12
XVIII	Cl	iso-C_4H_9	60,5	190—191	8,95	$C_{17}H_{23}ClN_2O$	9,12
XIX	Br	n-C_4H_9	51,5	163—167	7,95	$C_{17}H_{23}BrN_2O$	7,98
XX	Br	iso-C_4H_9	64,5	197	7,82	$C_{17}H_{23}BrN_2O$	7,98

TABLE 3. 9-Alkylamino-1,2,3,4- tetrahydroacridines

Compound	R	R¹	Yield %	Mp (°C)	Found N, %	Empirical formula	Calc. N, %	Hydrochloride, mp (°C)
XXI	H	CH_3	97	112 [7]	13,10	$C_{14}H_{16}N_2$	13,20	292
XXII	H	C_2H_5	62	118	12,32	$C_{15}H_{18}N_2$	12,40	—
XXIII	H	n-C_4H_9	77,6	65—66 [7]	10,95	$C_{17}H_{22}N_2$	11,00	203
XXIV	H	iso-C_4H_9	70,6	95—96	10,83	$C_{17}H_{22}N_2$	11,00	207
XXV	CH_3	CH_3	60,5	134	12,14	$C_{15}H_{18}N_2$	12,40	298—302
XXVI	CH_3	C_2H_5	56,4	110—112	11,42	$C_{16}H_{20}N_2$	11,68	238—242
XXVII	CH_3	n-C_4H_9	75,5	69—70	10,27	$C_{18}H_{24}N_2$	10,45	—
XXVIII	CH_3	iso-C_4H_9	56,5	68—69	10,16	$C_{18}H_{24}N_2$	10,45	237—240
XXIX	Cl	n-C_4H_9	71,5	62—64	9,38	$C_{17}H_{21}ClN_2$	9,72	195 (decomp.)
XXX·HCl	Cl	iso-C_4H_9	79,5	—	8,30	$C_{17}H_{21}ClN_2 \cdot HCl$	8,64	265
XXI	Br	n-C_4H_9	54	75	8,20	$C_{17}H_{21}BrN_2$	8,41	—
XXXII·HCl	Br	iso-C_4H_9	76	—	7,25	$C_{17}H_{21}BrN_2 \cdot HCl$	7,56	250

Note. Compounds (XXI), (XXII), (XXV), and (XXVI) were crystallized from a mixture of benzene and petroleum ether; the other compounds from petroleum ether alone.

EXPERIMENTAL

Alkylamides of 5-Substituted Anthranilic Acids (I)-(VIII). Magnesium (0.4 gram atom), ethyl bromide (0.4 mole), and the alkylamine (0.2 mole) gave in the customary manner the dimagnesium derivative of the amine. The reagent so prepared was treated with a solution of the methyl ester of the 5-substituted anthranilic acid (0.1 mole) in 30 ml of ether. The mixture was warmed on a water bath for 0.5 h and then decomposed by means of a 10% solution of acetic acid. The ethereal layer was separated, treated with steam and the residue crystallized from alcohol.

Alkylamides of 5-Substituted Cyclohexylideneanthranilic Acids (XIII)-(XX). Solutions of each of the compounds (I)-(VIII) (0.02 mole) in 5-7 ml of benzene were treated with cyclohexanone (0.02 mole) and heated on a sand bath for 4-6 h. On cooling the reaction mixture, a sediment was obtained; this was filtered off

and crystallized. The compounds (IX)-(XII), carrying no substituent in the 5-position, were obtained in a similar manner from the appropriate alkylamides of unsubstituted anthranilic acid.*

9-Alkylamino-1,2,3,4-Tetrahydroacridines (XXI)-(XXXII). Each of the compounds (IX)-(XX) (0.01 mole) was gradually added to phosphorus oxychloride (5 ml) and the mixture warmed on a water bath for 1 h. After driving off the excess of the $POCl_3$ in vacuo, the residue was dissolved in water and neutralized with a 10% solution of caustic alkali. The base so precipitated was extracted with ether, the extracts dried over potassium hydroxide, and the solvent evaporated. The residue was crystallized.

Hydrochlorides of 9-Alkylamino-1,2,3,4-Tetrahydroacridines. Dry hydrogen chloride gas was passed into ethereal solutions of the bases (XXI)-(XXXII). The resulting precipitates were filtered off and crystallized.

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