Thus, the replacement of a hydroquinone C ring in the benzo[b]phenanthridines by a quinoid ring resulted in lowered antitumor activity. An analogous phenomenon was observed in the case of mytomycin C where the *in vivo* reduction of the quinone ring was essential to the manifestation of this activity.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 9-[(N,N-DIALKYLAMINOACETYL)AMINO]-1,2,3,4-TETRAHYDROACRIDINES

L. P. Dontsova, V. É. Kolla, S. N. Nikulina, and M. E. Konshin

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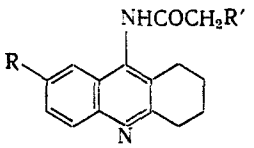
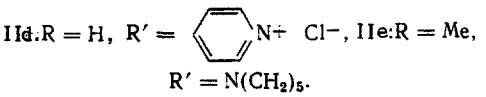
9-Amino-1,2,3,4-tetrahydroacridine (tacrine) is a drug which is effective for the treatment of mental disturbances caused by esters of substituted glycol acids [4]. 9-[(N,N-diethylaminoacetyl)amino]-1,2,3,4-tetrahydroacridine has a strong local anesthetic action at comparatively low toxicity [5]. The present work was under taken as part of a search for new 9-[(N,N-dialkylaminoacetyl)amino]-1,2,3,4-tetrahydroacridines (IIa-e) with antidepressant properties (see Table 1).



Ia-c, IIa-e

Ia: R = H, Ib: R = Me, Ic: R = Br; Ia-c: R^1 = Cl;
IIa: R = H, R′ = $N(CH_2CH_2)_2O$, IIb: R = Br,
R′ = $N(CH_2)_5$, IIc: R = Me, R′ = NEt_2,



IId: R = H, R′ = N+ Cl−, IIe: R = Me,
R′ = $N(CH_2)_5$.

9-Chloroacetylamino-1,2,3,4-tetrahydroacridines (Ia-c) were obtained by heating a mixture of the corresponding 9-amino-1,2,3,4-tetrahydroacridine with chloracetyl chloride.

Experiments showed that compounds Ia-c reacted with dialkylamines when a mixture of the starting compounds in alcohol was heated under reflux. The desired products IIa-e were obtained in yields of 52-71%, as colorless crystalline substances which absorbed in the IR at 3246-60 cm^{-1} (NH) and at 1660-1680 cm^{-1} (CO). The compounds were basic and formed hydrochlorides with HCl. Refluxing a mixture of the amide Ia and pyridine in ethanol gave the chloride of 9-(pyridinoacetyl)amino-1,2,3,4-tetrahydroacridine (IId).

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

Compound	Yield, %	mp., °C	Empirical formula
Ib	68,4	221—222	$C_{16}H_{16}ClN_2O$
Ic	71,5	229—230	$C_{15}H_{14}BrClN_2O$
IIa	59	101—103	$C_{19}H_{23}N_3O_2$
IIb	70,5	121—123	$C_{20}H_{24}BrN_3O$
IIc	52,3	78—80	$C_{20}H_{27}N_3O$
IId	63	251 (decom)	$C_{20}H_{21}ClN_2O$
IIe	62,5	112—114	$C_{21}H_{27}N_3O$

Note. Elemental analysis was in good agreement with calculated values.

TABLE 2. Toxicity and Antidepressant Activity of Compounds IIa-e

Compound	Acute toxicity	Time of immobilization in 6 minute swimming test	Change in reserpine hypothermia
IIa	230 (207,2—255,3)	206,3±10,7	—
IIb	340 (306,3—377,4)	201,8±17,3	—
IIc	220 (205,6—235,4)	186,3±33,0	—
IId	35,5 (27,3—46,1)	138,1±33,5	—2,6
IIe	290 (247,8—339,3)	157,0±33,6	—2,8
Amitriptyiine	76,0	46,2±20,8	—2,01
Control (2% starch suspension)	—	203,4±17,6	—3,5

EXPERIMENTAL (CHEMICAL)

7-Substituted 9-chloracetylamino-1,2,3,4-tetrahydroacridine (Ib and c).* Chloroacetyl chloride (2.2 g; 0.02 mole) was added with cooling to 9-amino-1,2,3,4-tetrahydroacridine (0.01 mole) and the mixture heated at 130-135°C for 1 h. When cool, the reaction mixture was diluted with water, and the resulting solution filtered from mechanical impurities. The filtrate was made alkaline with 10% Na_2CO_3 solution, the precipitated material filtered off, dried, and recrystallized from ethanol.

7-Substituted 9-[N,N-dialkylaminoacetyl)amino]-1,2,3,4-tetrahydroacridine (IIa-e). A mixture of 9-chloracetylamino-1,2,3,4-tetrahydroacridine Ia-c (0.01 mole) and the corresponding amine (0.01 mole) in ethanol (50 ml) was refluxed for 6 h. The reaction mixture was then refluxed for a further 10 min with activated charcoal (1 g), the solution filtered, and the ethanol and excess amine evaporated off. The residue was treated with water and recrystallized from aqueous ethanol.

Chloride of 9-(pyridinoacetyl)amino-1,2,3,4-tetrahydroacridine (IId). A mixture of 9-chloroacetylamino-1,2,3,4-tetrahydroacridine (2.8 g; 0.01 mole) and pyridine (0.8 g; 0.01 mole) in ethanol (50 ml) was refluxed for 5 h. The reaction mixture was diluted with acetone and the precipitated material filtered off and purified by repeated recrystallization from a mixture of ethanol and acetone.

*Compound Ia is reported in [5].

EXPERIMENTAL (PHARMACOLOGICAL)

The acute toxicity of the compound was obtained by the method of G. N. Pershin using a single intraperitoneal injection of a 2% starch suspension into white mice weighing 16-20 g; the animals were observed over a period of 10 days [2].

Antidepressant activity was evaluated by the "swimming" test proposed by Rusanov and Yal'dman [3] and by the test described in "the effect of antidepressants on reserpine hypothermia" [1]. the presence of antidepressant action in the compounds is indicated by a decrease in the time of "immobilization" of the swimming mice during the first 6 min. The antidepressant amitriptyline was used as a standard; both the standard and the test compounds were injected intraperitoneally in doses of 10 mg/kg as 2% starch suspensions 30 min before testing. Active compounds were tested for their effect on hypothermia in white mice; hypothermia was induced by the intraperitoneal administration of 2.5 mg/kg of reserpine 4 h before testing. The test compounds and amitriptyline were administered 30 min before the test.

The results of the tests are presented in Table 2. Compared with the control, compounds IId and e decreased the immobilization time for the animals during the first 6 min of swimming, and also decreased reserpine-induced hypothermia. At equal dosages, (10 mg/kg), the amitriptyline was 3 times more effective in the "immobilization" test and 1.3 times more effective in the reserpine hypothermia test compared with compounds IId and 3. However, compound IIe was 3.8 times less toxic than amitriptyline. Compound IId was 2.1 times more toxic than amitriptyline.

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