SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 4-AMINO-3-NITROCOUMARINS

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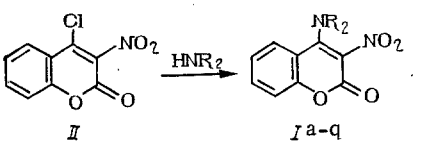
There have recently been a number of reports on the analgesic and antibacterial activity of some 4-aminocoumarins [1-5].

The results of pharmacological tests on 4-amino-3-coumarins (Ia-q) are presented in this paper.



II Ia-q

NR_2=NH_2 (a), CH_3NH (b), n-C_4H_9NH (c), tert-C_4H_9NH (d), $C_6H_{11}NH$ (e), $C_6H_5CH_2NH$ (f), C_6H_5NH (g), pyridyl-2-amino (h), $(C_2H_5)_2N$ (i), $(n\text{-}C_3H_7)_2N$ (j), $(n\text{-}C_4H_9)_2N$ (k), pyrrolidyl (l), piperidyl (m), morpholinyl (n), 4-methylpiperazinyl-1 (o), 4-phenylpiperazinyl-1 (p), 1,4-diazabicyclo[4,3,0]nonyl-1 (q).

The synthesis of compounds Ia-d, f, g, i, j, m, and n has already been described [6]. The remaining compounds Ie, h, k, l, and o-q were prepared according to the method described in [6], by reacting 4-chloro-3-nitrocoumarin (II) with 2 moles of the corresponding amine dissolved in absolute benzene or dimethyl sulfoxide (see Table 1). Reaction takes place very rapidly and the products are formed in high yield; they are all intensely yellow, crystalline substances. Their structures were confirmed by elemental analysis and by spectroscopic means. The infrared spectrum of I in chloroform has absorption bands characteristic of the carbonyl group (1720-1730 cm^{-1}), the nitro group (ν_{as} 1550-1560 and ν_s 1310-1320 cm^{-1}), and the double bond of the coumarin ring (1605-1615 cm^{-1}).

The overall effect, toxicity, and neurotropic activity of the synthesized compounds were studied. Tests were carried out with white mice weighing 20-22 g and with rabbits. Doses of the compounds corresponding to 1/10 LD_{50} for mice were used.

The neurotropic activity was studied using the following tests: attenuation of the narcotic effect of sodium thiopental (30 mg/kg), potentiation of the narcotic effect of a subthreshold dose of sodium thiopental (12.5 mg/kg), spontaneous motor activity (using the actometer described by K. S. Raevskii and V. A. Timofeev in 1965), amphetamine antagonism — to a standard amphetamine (10 mg/kg) hyperactivity of mice, analgesic action — by the "hot plate" method, muscle-relaxing action — by the "rotating rod" method, anesthetizing action — by Renyi's method.

The results of the tests show that the majority of the compounds synthesized possess neurotropic activity, and that this activity is dependent on the structure of the amino group. Thus, Ia with a primary amino group lowers the spontaneous motor ac-

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TABLE 1. 4-Amino-3-nitrocoumarins

Compound	Yield, %	Melting point (in deg)*	Rf	Found, %			Empirical formula	Calculated, %		
				C	H	N		C	H	N
Ie	80	199—201	0,47	62,52	5,62	9,88	$C_{15}H_{16}N_2O_4$	62,49	5,59	- 9,72
Ih	86	183—4(decomp.)	0,29	57,42	3,57	14,36	$C_{14}H_{9}N_3O_4 \cdot {}^1/_2H_2O$	57,55	3,42	14,38
Ik	97	91—2	0,74	64,11	6,88	8,88	$C_{17}H_{22}N_2O_4$	64,12	6,96	8,76
Il	85	188—90	0,26	60,00	4,59	10,72	$C_{13}H_{12}N_2O_4$	60,02	4,60	10,76
Io†	89	195—6	0,32	58,10	5,26	14,45	$C_{14}H_{15}N_3O_4$	58,12	5,22	14,52
Ip	98	183—4	0,81	64,99	4,88	12,00	$C_{19}H_{17}N_3O_4$	64,94	4,87	11,96
Iq	96	145—6,5	0,44	61,02	5,46	13,16	$C_{16}H_{17}N_3O_4$	60,94	5,43	13,32

*Compounds Ie, o, and p crystallized from benzene, Ih and q from alcohol, Ik from hexane, Il from glacial acetic acid.

†Hydrochloride obtained by treating a solution of the base in absolute dioxane with a saturated solution of hydrogen chloride in ether, mp 246.5-247.5° (decomp.). Found, %: C 1.242; H 4.98, Cl 10.95; N 12.58. $C_{14}H_{15}N_3O_4 \cdot HCl$. Calculated, %: C 51.61; H 4.94; Cl 10.88; N 12.90.

tivity considerably (6-10 times), increases the amphetamine hyperactivity slightly, and shortens the sodium thiopental induced sleep of mice by 30%. Compounds with a substituted amino group exert a depressing action on the central nervous system. Those compounds with a secondary amino group (Ib, d-h) decrease spontaneous motor activity by 1.3-1.6 times, decrease amphetamine hyperactivity by 1.5-5 times, and increase the duration of thiopental sleep by 25-40%. Compound Ie was found to be the most active in this group; it decreases amphetamine hyperactivity by 2-5 times, and lengthens sodium thiopental induced sleep by 2 times. Compound Ic is inactive. Compounds Ii-l and o, with a tertiary amino group, decrease spontaneous motor activity by 1.6-3 times, lower amphetamine hyperactivity by 1.5-2 times, and lengthen the duration of thiopental sleep by 1.5-2 times. Compound Ii exerts the most pronounced, unreconciled influence on the central nervous system; compound Im is inactive. Of the compounds Io-q, the most active proved to be Iq; it lengthens sodium thiopental induced sleep of mice by 1.5-1.7 times, depresses motor activity by 3-4 times, and slightly decreases amphetamine hyperactivity. The compounds tested do not exhibit muscle-weakening action. With the exception of Id and Iq, the compounds synthesized have relatively low toxicity (LD_{50}>1000 mg/kg).

EXPERIMENTAL METHOD

The purity of the compounds prepared was checked by thin-layer chromatography on aluminum oxide (activity IV and V) using chloroform and benzene respectively as solvents (R_f values for the first system are given in Table 1).

4-Amino-3-nitrocoumarins (Ie, k, l, and o-q). These are prepared by adding II (6.75 g , 0.03 mole) to the corresponding amine (0.06 mole) in absolute benzene (90 ml) and mixing for 1 hour. In the case of compounds Ie, l, and o-q, the precipitate is filtered off, washed with water, and dried. In some instances concentration of the benzene filtrate yielded additional material. In the case of Ik the reaction mixture is washed with 5% hydrochloric acid and water, dried and concentrated.

4-[N-(Pyridyl-2)-amino]-3-nitrocoumarin (Ih). 2-Aminopyridine (0.95 g) is added to a solution of II (1.12 g) in absolute dimethylsulfoxide (10 ml), the mixture is stirred for 30 min and then poured into water. The precipitated Ih is filtered off, and washed with water and benzene.

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