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N-[3-NITRO(AMINO)COUMARIN-4-YL]ANTHRANILIC ACID AMIDES. SYNTHESIS OF 6,7,8,13-TETRAHYDRO[1]BENZOPYRANO[4,3-b][1,4] BENZODIAZEPINE-6,8-DIONE*

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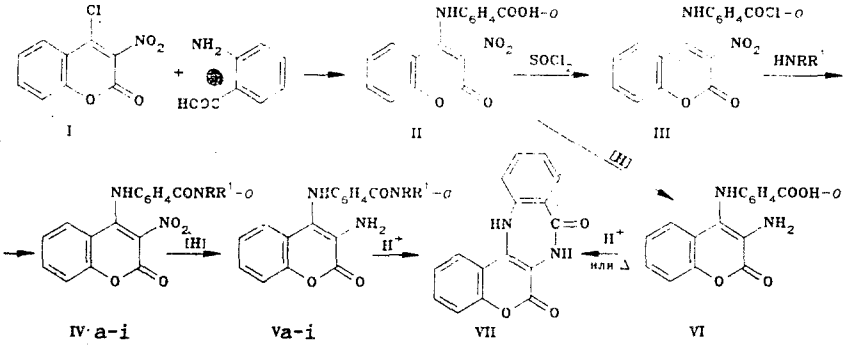
The reaction of 3-nitro-4-chlorocoumarin with anthranilic acid was used to synthesize N-(3-nitro-4-coumarinyl)-anthranilic acid, from which, through the acid chloride, we obtained a number of amides, which were reduced to N-(3-amino-4-coumarinyl)anthranilic acid amides The latter are cyclized under the influence of hydrochloric acid to 6,7,8,13-tetrahydro[1]benzopyrano-[4,3-b][1, 4]benzodiazepine-6,8-dione, which was also obtained from N-(3-amino-4-coumarinyl)anthranilic acid by its thermolysis or treatment with hydrochloric acid.

Substances with different forms of pharmacological activity have been found among derivatives of N-hetaryl-substituted anthranilic acids [2-6]. On the other hand, as we have previously shown [7, 8], 3-substituted 4-aminocoumarins have a depressive or stimulating effect on the central nervous system and also display a pronounced anticonvulsive effect [8].

In this connection by means of the reaction of 3-nitro-4-chlorocoumarin (I) with anthranilic acid we obtained N-(3-nitro-4-coumarinyl)anthranilic acid (II), which served as the starting compound for further syntheses via the following scheme:



IV, V a R=R¹=H; b R=H, R¹=*i*-C_3H_7; c R=H, R¹=*n*-C_4H_9; d R=H, R¹=$CH_2C_6H_5$; e R=H, R¹=C_6H_5; f R+R¹=$(CH_2)_4$; g R+R¹=$(CH_2)_5$; h R+R¹=$O(CH_2CH_2)_2$; i R+R¹=$CH_3N(CH_2CH_2)_2$

Characteristic absorption bands of an NH group are observed in the IR spectra of amides IVa-i at 3200-3300 cm^{-1}; absorption of the carbonyl group of the coumarin ring shows up in the form of intense bands at 1710-1740 cm^{-1}, while the frequency of the vibrations of the amido group ranges from 1610 to 1670 cm^{-1}, which is evidently explained by the possibility of the formation of intramolecular hydrogen bonds of two types (A and B), depending on the substituents in the amido group.

*See [1] for our preliminary communication.

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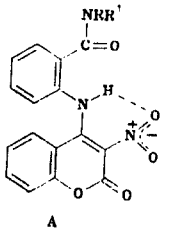
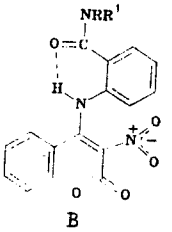


A



B

Replacement of the nitro group in IVa-i by an amino group leads to the development of a number of new bands in the IR spectra of amides Va-i in the region of the ν_{NH} stretching vibrations. The 30-40 cm^{-1} decrease in the $\nu_{C=O}$ frequency of the coumarin ring in Va-g as compared with nitro analogs IVa-g is evidently associated with the existence of an intramolecular hydrogen bond in the amino derivatives. A separate communication will be devoted to the fine structures of these compounds.

Under the influence of dilute hydrochloric acid amides Va-i undergo intramolecular cyclization with the formation of a new heterocyclic system, viz., 6,7,8,13-tetrahydro[1]benzopyrano[4,3-b][1, 4]benzodiazepine-6,8-dione (VII), which was also synthesized by refluxing in dilute hydrochloric acid or simply by heating amino acid VI, which was obtained by hydrogenation of nitro acid II in dimethylformamide over Pd/C.

Dione VII is a high-melting orange substance that is only slightly soluble in ordinary organic solvents. A highly stable molecular ion M^+ (278, 100%), which eliminates successively HNCO and CO (ions with m/z 235 and 207) or two molecules of CO (ions with m/z 250 and 222) with subsequent fragmentation of the heterorings of the resulting fragments, is observed in the mass spectrum of this compound.

A study of the character of the dissociative ionization of Va-i and VI showed that their mass spectra contain highly intense peaks of molecular ions M^+, the primary process of the fragmentation of which is the elimination of a molecule of water (in the case of acid VI) or the corresponding amine (in the case of amides Va-i); an ion with m/z 278, the peak of which is maximal, is formed. In other words, the formation of an energically more favorable and, consequently, more stable heterocyclic form, viz., an ion of dione VII, the subsequent fragmentation of which coincides completely with the fragmentation of molecular ion M^+ in the mass spectrum of VII, occurs.

Pharmacological tests conducted via the screening scheme adopted for the study of neurotropic activity [7] showed that amides IVa-i and some amides V have a depressive effect on the central nervous system; IVf was the most active compound in this respect. Acid II has a stimulating effect, while VII has a depressive effect on the central nervous system. Amides IVb-f and acid II also displayed low analgesic activity.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds (0.5 to 1.0 mg of the substance per 200 mg of KBr) were recorded with a Perkin–Elmer 580B spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Bruker AC-250 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT-112 spectrometer with a system for direct introduction of the samples into the ion source at 100-120°C and an ionizing voltage of 70 eV. The course of the reactions and the purity of the products were monitored by means of TLC on Silufol UV-254 plates in an ethyl acetate–hexane system (2:1) and on Al_2O_3 60F-254 plates in chloroform with development in UV light and with iodine. The results of elementary analysis of the compounds were in agreement with the calculated values.

N-(3-Nitro-4-coumarinyl)anthranilic Acid (II, $C_{16}H_{10}N_2O_6$). A mixture of 22.5 g (0.1 mole) of coumarin I and 27.4 g (0.2 mole) of anthranilic acid in 400 ml of absolute benzene was refluxed for 2 h, after which it was cooled, and the precipitate was removed by filtration, washed with benzene and water, and dried to give 28.5 g (87%) of a product with mp 227-228°C (dec., from n-butanol). IR spectrum: 3320 (NH), 1728 (C=O), 1674 (COOH), 1615, 1560, 1530 cm^{-1}. Mass spectrum: M^+ 326.

N-(3-Nitro-4-coumarinyl)anthranilic Acid Chloride (III, $C_{16}H_9ClN_2O_5$). A suspension of 8.2 g (25 mmole) of acid II and 15 g (125 mmole) of thionyl chloride in 250 ml of absolute benzene was refluxed with stirring for 6 h, after which the mixture was cooled, and the pre-

cipitate was removed by filtration, washed with benzene and water, and dried to give 7.3 g (85%) of a product with mp > 300°C. IR spectrum: 3315 (NH), 1750 (COCl), 1695 (C=O), 1615, 1555 cm^{-1}.

N-(3-Nitro-4-coumarinyl)anthranilic Acid Amides IVa-i. A) A stream of dry ammnoia was passed for several minutes through a suspension of 1.03 g (3 mmole) of acid chloride III in 60 ml of absolute benzene, after which the precipitate was removed by filtration, washed successively with benzene, 10% aqueous HCl solution, and water, and dried to give 0.8 g of amide IVa.

B) A 22-mmole sample of the amine was added dropwise with stirring to a suspension of 3.5 g (10 mmole) of acid chloride III in 100 ml of absolute benzene. Gradual dissolving of the starting compound and the formation of a new precipitate occurred during the addition. The mixture was stirred for 3 h at 20°C (in the reaction with aniline the mixture was additionally refluxed for 1 h) and was then worked up as a function of the amine used. In the case of isopropylamine, butylamine, benzylamine, or morpholine, the precipitate was removed by filtration, washed with water, and dissolved in chloroform. The solution was washed successively with 5% aqueous HCl solution, sodium bicarbonate solution, and water, dried over calcium chloride, and evaporated. In the reaction with pyrrolidine, piperidine, or N-methylpiperazine the mixture was treated with water (in the last two cases small amounts of amides IVg and IVi were removed by filtration), the layers were separated, and the organic layer was then treated as described above. In the case of the reaction with aniline the mixture was filtered, and the precipitate on the filter was washed with 5% HCl solution, sodium bicarbonate solution, and water and air dried. Data on the amides IVa-i obtained are presented in Table 1.

N-(3-Amino-4-coumarinyl)anthranilic Acid Amides Va-i. A suspension of 5 mmole of amide IVa-i in 100 ml of alcohol was hydrogenated over 0.3 g of 10% $Pd/BaSO_4$ until hydrogen absorption ceased. In the hydrogenation of amides IVa,e the reaction mixture was filtered. The residue was refluxed with dioxane, the catalyst was removed by filtration and washed with hot dioxane, and the combined filtrates were evaporated. In the hydrogenation of amides IVb,c,i the catalyst was removed by filtration and washed with alcohol, and the combined filtrates were evaporated. In the hydrogenation of amides IVd,f-h 50 ml of alcohol was added to the reaction mixture, after which the mixture was heated to the boiling point and filtered, the catalyst was washed with hot alcohol, and the combined filtrates were evaporated. The amides Va-i obtained were crystallized from an appropriate solvent (Table 1).

N-(3-Amino-4-coumarinyl)anthranilic Acid (VI, $C_{16}H_{12}N_2O_4$). A solution of 1.63 g (5 mmole) of acid II in 70 ml of purified dimethylformamide was hydrogenated over 0.3 g of 10% Pd/C until hydrogen absorption ceased, after which the catalyst was removed by filtration and washed with dimethylformamide. The filtrate was diluted with water and allowed to stand for 1 h at 20°C. The precipitate was removed by filtration, washed with water, dried, and crystallized from aqueous dimethylformamide to give 1.28 g (86%) of product. Acid VI did not have a distinct melting point: at 250-260°C the white substance was converted, with sublimation, to an orange substance (diazepine VII, see below), which melted with decomposition at 305-310°C. IR spectrum: 3480, 3370, 290 (NH_2, NH). 1717 (C=O), 1675 (COOH), 1640, 1610, 1597, 1580, 1575, 1565, 1515 cm^{-1}. Mass spectrum: M^+ 296.

6,7,8,13-Tetrahydro[1]benzopyrano[4,3-b][1,4]benzodiazepine-6,8-dione (VII, $C_{16}H_{10}N_2O_3$). A) A suspension of 1.48 g (5 mmole) of acid VI in 80 ml of 18% hydrochloric acid was refluxed with stirring for 1 h, after which it was cooled, and the orange precipitate was removed by filtration, washed with 5% aqueous alkali solution and water, and dried to give 1.1 g (79%) of a product with mp 310-313°C (deg. from aqueous DMF). IR spectrum: 3390, 3350, 3380 (NH), 1700 (C=O), 1645, 1625, 1610, 1540 cm^{-1}. PMR spectrum: 7.00-7.80 (7H, m, aromatic). 8.24 (1H, d, 1-H), 8.46 (1H, s, 13-H), 8.70 ppm (1H, s, 7-H). Mass spectrum, m/z (≥6%): 278 (M^+, 100), 250 (8), 235 (10), 222 (25), 207 (6), 194 (8), 180 (7).

B) A 0.15-g (0.5 mmole) sample of acid VI was heated for 1 h at 270-280°C; the substance gradually turned red as it was heated. The reaction product was cooled and triturated in 5% aqueous alkali solution, and the orange precipitate was removed by filtration, washed with water, and dried to give 0.1 g (71%) of diazepine VII.

C) A suspension of 1 mmole of amide Va-c or a solution of 1 mole of amide Vf-i in 20 ml of 18% HCl was maintained for, respectively, 1 or 3 days with periodic stirring, whereas a suspension of amide Vd,e or a solution of amide Vh in 20 ml of 18% HCl was refluxed for 30 min. In the case of amides Va-e dissolving of the initial substance and the simultaneous formation of a new orange precipitate occurred, whereas in the case of amides Vf-i an orange precip-

TABLE 1. Characteristics of Amides IVa-i and Va-i

Compound	Empirical formula	mp.* °C (dec.)	IR spectrum,† cm^{-1}				M^+	Yield, %
			ν_{NH}	coumarin $\nu_{C=O}$	Amide I $\nu_{C=O}$	$\nu_{C=C}$, $\nu^{as}_{NO_2}$ σNH_2, $\nu_{C=C}$ arom, amide II		
IVa	$C_{16}H_{11}N_3O_5$	212	3420, 3340, 3205	1725	1665	1610, 1550, 1522	325	82
IVb	$C_{19}H_{17}N_3O_5$	190...191	3243	1735	1612	1597, 1553, 1520	367	80
IVc	$C_{20}H_{19}N_3O_5$	153...154	3320	1730	1630	1610, 1595, 1526	381	88
IVd	$C_{23}H_{17}N_3O_5$	154...156	3400, 3360	1740, 1700	1650	1615, 1560, 1530	415	80
IVe	$C_{22}H_{15}N_3O_5$	174...175	3325	1712	1670	1610, 1600, 1532	401	87
IVf	$C_{20}H_{17}N_3O_5$	208...210	3260	1740	1615	1600, 1550, 1520	379	86
IVg	$C_{21}H_{19}N_3O_5$	212...214	3200	1734	1623	1609, 1596, 1550, 1520	393	83
IVh	$C_{20}H_{17}N_3O_6$	225...227	3420, 3280	1720	1620	1600, 1565, 1525	395	89
IVi	$C_{21}H_{20}N_4O_5$	205...207	3191	1707	1670	1610, 1599, 1557, 1526	408	86
Va	$C_{16}H_{13}N_3O_3$	263...267	3487, 3425, 3340, 3260	1690	1665	1610, 1600, 1510	295	78
Vb	$C_{19}H_{19}N_3O_3$	127...130	3440, 3350	1700	1633	1595, 1583, 1560, 1510	337	79
Vc	$C_{20}H_{21}N_3O_3$	133...134	3440, 3390, 3320	1695	1640, 1627	1594, 1562, 1540, 1510	351	83
Vd	$C_{23}H_{19}N_3O_3$	157...159	3450, 3380, 3340, 3320	1700	1645	1585, 1535, 1520	385	68
Ve	$C_{22}H_{17}N_3O_3$	220...223	3455, 3425, 3360, 3200	1702	1654	1630, 1602, 1550, 1517, 1506, 1500	371	80
Vf	$C_{20}H_{19}N_3O_3$	152...154	3475, 3445, 3325	1710	1640, 1620	1600, 1515	349	83
Vg	$C_{21}H_{21}N_3O_3$	181...182	3480, 3360	1695	1628	1618, 1590, 1562, 1522	363	84
Vh	$C_{20}H_{19}N_3O_4$	184...185	3460, 3430, 3330	1720	1642	1625, 1595, 1568, 1510	365	78
Vi	$C_{21}H_{22}N_4O_3$	122...125	3429, 3393, 3349, 3250	1708	1620	1600, 1516, 1500	378	66

*Amide IVa was crystallized from glacial acetic acid, amides IVb, c,f,i and Vd,h were crystallized from alcohol, IVd,e,g,h and Va,e were crystallized from n-butanol, Vb,c,f,g were crystallized from 70% alcohol, and Vi was crystallized from benzene–hexane (1:1).
†The spectra were registered in a data bank (from 400 to 4000 cm^{-1}) formed via the method in [9].

itate formed gradually. The precipitate was removed by filtration, washed with water, and dried. Diazepine VII was obtained in 80-97% yields.

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