SYNTHESIS AND PROPERTIES OF ARYLAMIDES OF N-ANISOYLANTHRANILIC ACID

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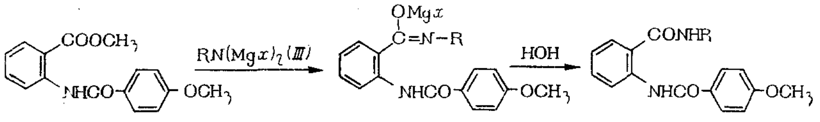
The arylamides of N-acylanthranilic acids are known to cyclize to 2,3-disubstituted 3,4-dihydroquinazolin-4-ones, and compounds of this type are of interest as some of them have proved to be biologically active [1, 2].

The present investigation is concerned with the synthesis of arylamides (I) of N-anisoylanthranilic acid and with a study of the intramolecular cyclization of such arylamides to 3-aryl-2-p-methoxy-phenyl-3,4-dihydroquinazolin-4-ones. The desired arylamides were obtained by the interaction of methyl N-anisoylanthranilate (II) with the di-magnesyl derivatives (III) of aryl- (as well as of two alkyl-) -amines in accordance with the following scheme:



II I

The structure of the resulting products was confirmed by reversing the sequence of operations, that is to say by acylating the arylamides of unsubstituted anthranilic acid [3] with anisoyl chloride.

The arylamides (I), (see Table 1), are colorless, crystalline solids, neutral in reaction, and moderately soluble in organic solvents.

The UV and IR spectra were determined in certain cases. The arylamides (I) furnish UV diagrams showing two absorption maxima, one in the 230-234, and the other in the 268-273 nm range (see Fig. 1); this is in conformity with the results previously obtained [4]. The IR spectra show acid amide bands at 1640 and 1525 cm^{-1} [5].

TABLE 1. Aryl- (and Alkyl-) -Amides of N-Anisoylanthranilic Acid

Compound*	R	Yield, %	Mp (°C)	Found, N, %	Empirical formula	Calc., N, %
Ia	$CH(CH_3)_2$	80	192—3	8,79; 8,83	$C_{18}H_{20}N_2O_3$	8,98
Ib	$CH_2CH(CH_3)_2$	48	222—3	8,30; 8,44	$C_{19}H_{22}N_2O_3$	8,58
Ic	C_6H_5	72	223—5	8,31; 8,25	$C_{21}H_{18}N_2O_3$	8,08
Id	$2\text{-}CH_3C_6H_4$	63	193—4	7,80; 7,88	$C_{22}H_{20}N_2O_3$	7,77
Ie	$3\text{-}CH_3C_6H_4$	70	185—6	7,46; 7,58	$C_{22}H_{20}N_2O_3$	7,77
If	$4\text{-}CH_3C_6H_4$	83	189—90	7,51; 7,80	$C_{22}H_{20}N_2O_3$	7,77
Ig	$2\text{-}ClC_6H_4$	88	183—4	7,13; 7,41	$C_{21}H_{17}ClN_2O_3$	7,36
Ih	$3\text{-}ClC_6H_4$	70	222—4	7,21; 7,48	$C_{21}H_{17}ClN_2O_3$	7,36
Ij	$4\text{-}ClC_6H_4$	92	211—2	7,19; 7,25	$C_{21}H_{17}ClN_2O_3$	7,36
Ik	$2\text{-}BrC_6H_4$	86	191—2	6,73; 6,81	$C_{21}H_{17}BrN_2O_3$	6,58
Il	$4\text{-}BrC_6H_4$	74	208—9	6,45; 6,76	$C_{21}H_{17}BrN_2O_3$	6,58
Im	$2,4\text{-}(CH_3)_2C_6H_3$	55	168—9	7,54; 7,57	$C_{23}H_{22}N_2O_3$	7,48

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*The compounds [I(a–d)] were crystallized from ethanol; the others from toluene: [I(b)], 1640, 1538, 1308, 1267. [I(c)], 1642, 1525, 1322, 1264. [I(g)], 1642, 1527, 1322, 1260.

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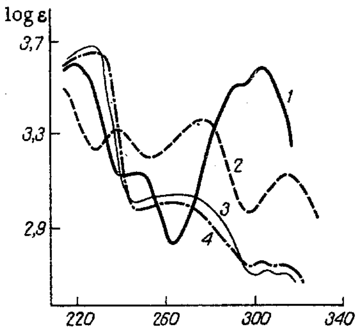

Fig. 1. UV Spectra. 1) 2-p-Methoxyphenyl-4H-3,1-benzoxazin-4-one (IV); 2) methyl N-anisoylanthranilate (II); 3) p-toluidide of N-anisoylanthranilic acid [I(f)]; 4) anilide of N-anisoyl-acid [I(c)].

Cyclization of the arylamides (I) to dihydroquinazolinones was attempted by methods previously described [6], but it was now found that phosphorus trichloride in toluene was incapable of producing the desired effect, and that boiling the said compounds in acetic anhydride solution in the presence of anhydrous sodium acetate gave rise instead to 2-p-methoxyphenyl-4H-3,1-benzoxazin-4-one (IV). The structure of (IV) was deduced by spectroscopic means as well as from the products of its hydrolysis. Such a de-amination of the arylamides is, evidently, to be seen as a 1,6-involvement between reacting groups. These results are in harmony with literature data [7].

The compounds described in this paper were tested in white mice as hypnotics and as anticonvulsants.* The materials were introduced in the form of suspensions in a 2% starch paste. The hypnotic effect was determined by means of the "lying-on-one-side posture" test, and the anticonvulsant activity was measured by the "maximal elecro-shock seizure" test of Toman et al. [8]. N-anisoylanthranilic acid (V) proved to have hypnotic power at a dose level of 200 mg/kg, but the other compounds were inactive.

EXPERIMENTAL

IR spectra were obtained by means of an IR spectrophotometer S-14, and a specimen of the compound to be measured was set up in the form of a paste in petroleum jelly. UV spectra were obtained by means of an SF-4 instrument, the solvent being 96% ethanol and the concentration 1×10^{-5} mole/liter.

N-Anisoylanthranilic Acid (V). Anisoyl chloride (9.4 g) was gradually added to a solution of anthranilic acid (6.8 g) in 20 ml of DMF. The mixture was warmed for 1 h at 60°C and then poured into 300 ml of cold water. The resulting precipitate was washed with water, dried, and recrystallized from a mixture of toluene and dioxan (1 : 1). Yield, 6.5 g; prisms, mp 226-227°C in agreement with that given in [9].

Methyl N-Anisoylanthranilate (II). A solution of a mixture of methyl anthranilate (15.1 g) and anisoyl chloride (17 g) in benzene (50 ml) was boiled for 2 h. The benzene was then driven off in a vacuum, and the residue crystallized from methanol. Yield, 18.6 g (65%); prisms, mp 110-111°C. UV spectrum in ethanol: $\lambda_{max} = 242$ nm ($\log \varepsilon = 3.309$), 278 ($\log\varepsilon = 3.34$), and 316 ($\log\varepsilon = 3.1$). Found % N 5.10, 5.17. $C_6H_{15}NO_4$. Calculated, %: N 4.90.

N-Anisoylanthranilic Acid Anilide [I(c)]. (A) Aniline (3.7 g) was added to an ethereal solution of ethyl magnesium bromide (prepared from 8.7 g of ethyl bromide, 1.9 g of metallic magnesium, and 30 ml of ether); the mixture was warmed on a water bath for 20 min, and then treated with a solution of (II) (5.6 g) in ether (30 ml). This final mixture was heated afresh, this time for 30 min, and then decomposed by adding a 10% solution of acetic acid. The ethereal layer was separated, the solvent driven off, and the residue crystallized. Yield, 4 g.

(B) Anisoyl chloride (1.9 g) was added to a solution of anthranilic acid anilide (2.1 g) in pyridine (3 ml). The mixture was allowed to stand for 30 min and then treated with 200 ml of water. The resulting precipitate was washed with water, dried, and crystallized. Yield, 2.4 g.

The identity of the two products, A and B, was established by mixed mp. UV spectrum in ethanol: $\lambda_{max} = 234$ nm ($\log\varepsilon = 3.65$), 268 ($\log\varepsilon = 2.99$), 304 ($\log\varepsilon = 2.76$), and 312 ($\log\varepsilon = 2.76$).

2-p-Methoxyphenyl-4H-3,1-Benzoxazin-4-one (IV). (A) The material (8.1 g) was boiled with 15 ml of acetic anhydride for 2 h. The sediment formed on cooling was filtered off, dried, and crystallized from ethanol. Yield, 6.5 g (85.5%); needles, mp 150°C; ([7] gives mp 152°C). UV spectrum in ethanol: $\lambda_{max} = 220$ nm ($\log\varepsilon = 3.6$), 252 ($\log\varepsilon = 3.16$), 288 ($\log\varepsilon = 3.51$), and 306 ($\log\varepsilon = 3.56$). IR spectrum: 1766 cm^{-1} $(-\underset{\overset{\|}{O}}{C}-O-)$, 1267 (as = C−O−C), and 1022 (s = C−O−C).

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[*] This work was carried out in N. E. Kharchenko's Pharmacology Department of the Perm Pharmaceutical Institute under the general direction of Professor V. M. Grishina.

[†] A mixture of [I(b)] (1.7 g), acetic anhydride (15 ml), and anhydrous sodium acetate (1.5 g) was boiled for

(B) A mixture of [I(b)] (1.7 g), acetic anhydride (15 ml), and anhydrous sodium acetate (1.5 g) was boiled for 3 h, and then poured out into 100 ml of water. The precipitate which remained after the acetic anhydride had been destroyed by hydrolysis was filtered off and crystallized from ethanol. The resulting product gave no depression of mp when admixed with a specimen of the product obtained by method (A).

Hydrolysis of 2-p-Methoxyphenyl-4H-3,1-Benzoxazin-4-one (IV). A mixture of (IV), obtained by method (B), (1.2 g) and 10 ml of a 10% solution of sodium hydroxide was boiled for 1h. The filtrate was acidified with diluted hydrochloric acid and the resulting precipitate crystallized from a mixture of toluene and dioxan (1 : 1). The product gave no depression of mp when admixed with a specimen of the acid (V).

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