RESEARCH ON NAPHTHYRIDINES

II.* SYNTHESIS OF 4-ARYLAMINO-6-METHYL-5,6,7,8-TETRAHYDRO-2,3-BENZO-1,6-NAPHTHYRIDINES

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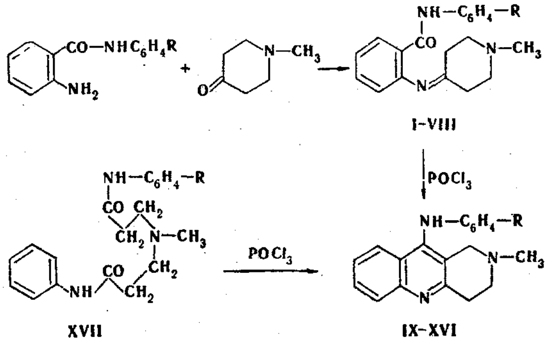
4-Arylamino-6-methyl-5,6,7,8-tetrahydro-2,3-benzo-1,6-naphthyridines are obtained from N-(1-methyl-4-piperidylidene)anthranilic acid arylamides.

A recent paper described some compounds of the 4-amino-5,6,7,8-tetrahydro-2,3-benzo-1,6-naphthyridine series and demonstrated that they have an effect on the central nervous system [2]. In this connection, the present investigation was undertaken to develop a method for the synthesis of models of this sort. We decided upon N-(1-methyl-4-piperidylidene)anthranilic acid arylamides, in which there are structural prerequisites for closing of the naphthyridine ring.



N-(1-Methyl-4-piperidylidene)anthranilic acid arylamides (I-VIII, Table 1) are obtained in good yields by heating anthranilic acid arylamides with 1-methyl-4-piperidone in benzene solution in the presence of one drop of alcoholic hydrogen chloride solution.

When I-VIII are heated in phosphorus oxychloride they undergo intramolecular cyclization to 4-arylamino-6-methyl-5,6,7,8-tetrahydro-2,3-benzo-1,6-naphthyridines (IX-XVI, Table 2) in satisfactory yields.

An attempt was made to cyclize bis(β-phenylcarbamoylethyl)methylamine (XVII) to naphthyridine IX as in the case of the previously described cyclization of pimelic acid dianilide [3]. In fact, heating XVII with phosphorus oxychloride in toluene gave IX in 17% yield.

In both cases, the reaction apparently proceeds through a step involving the formation of the corresponding chloroimides.

EXPERIMENTAL

The IR spectra of 0.01 M solutions in CCl_4 were recorded with an IKS-14 spectrometer. The UV spectra of ethanol solutions were recorded with an SF-4 spectrophotometer.

N-(1-Methyl-4-piperidylidene)anthranilic Acid Arylamides (I-VIII). A solution of 0.01 mole of anthranilic acid arylamide and 0.013 mole of 1-methyl-4-piperidone in 5 ml of dry benzene containing one

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*See [1] for communication I.

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TABLE 1. N-(1-Methyl-4-piperidylidene)anthranilic Acid Arylamides (I-VIII)

Comp.	R	mp, °C*	Empirical formula	N, %		Yield, %
				found	calc.	
I	H	213—214	$C_{19}H_{21}N_3O$	13,6	13,7	52
II	*p*-CH_3	236—238	$C_{20}H_{23}N_3O$	13,0	13,1	53
III	*m*-CH_3	210—211	$C_{20}H_{23}N_3O$	13,3	13,1	70
IV	*o*-CH_3	205—208	$C_{20}H_{23}N_3O$	13,1	13,1	60
V	*p*-Br	237—238	$C_{19}H_{20}BrN_3O$	11,2	10,9	60
VI	*m*-Br	225—227	$C_{19}H_{20}BrN_3O$	10,7	10,9	60
VII	*p*-Cl	228—230	$C_{19}H_{20}ClN_3O$	12,5	12,3	46
VIII	*p*-CH_3O	233—235	$C_{20}H_{23}N_3O_2$	12,5	12,5	60

*Compounds I, III, IV, VI, and VII were recrystallized from benzene, II and V were recrystallized from ethanol, and VIII was recrystallized from dimethylformamide.

TABLE 2. 4-Arylamino-6-methyl-5,6,7,8-tetrahydro-2,3-benzo-1,6-naphthyridines (IX-XVI)

Comp.	R	mp, °C	Empirical formula	N, %		Yield, %
				found	calc.	
IX	H	201—202	$C_{19}H_{19}N_3$	14,2	14,6	37
X	*p*-CH_3	163—163,5	$C_{20}H_{21}N_3$	13,9	13,9	35
XI	*m*-CH_3	145—146,5	$C_{20}H_{21}N_3$	13,7	13,9	34
XII	*o*-CH_3	145,5—147,5	$C_{20}H_{21}N_3$	13,8	13,9	43
XIII	*p*-Br	187—188	$C_{19}H_{18}BrN_3$	11,6	11,9	36
XIV	*m*-Br	196.5—197	$C_{19}H_{18}BrN_3$	11,6	11,9	43
XV	*p*-Cl	179—180	$C_{19}H_{18}ClN_3$	13,1	13,0	42
XVI	*p*-CH_3O	94— 96	$C_{20}H_{21}N_3O$	12,8	13,2	22

drop of alcoholic hydrogen chloride solution was heated for 12 h. It was then cooled, and the precipitate was removed by filtration, washed on the filter with sodium bicarbonate solution, and crystallized.

The products were obtained as colorless crystalline substances that were only slightly soluble in organic solvents. The IR spectra of I-VIII contained ν_{NH} bands at 3418-3426 cm^{-1}, $\nu_{=CH}$ bands at 3026-3045 cm^{-1}, $\nu_{as\,CH_2}$ bands at 2916-2934 cm^{-1}, $\nu_{s\,CH_2}$ bands at 2840-2858 cm^{-1}, $\nu_{s\,CH_3}$ bonds from N$-$CH$_3$ groups at 2780-2796 cm^{-1}, and ν_{CO} bands at 1636-1656 cm^{-1}.

4-Arylamino-6-methyl-5,6,7,8-tetrahydro-2,3-benzo-1,6-naphthyridines (IX-XVI). A mixture of 0.003 mole of arylamide I-VIII and 2 ml of phosphorus oxychloride was heated at 100° for 2 h, after which it was poured into water. The aqueous mixture was filtered, and the filtrate was neutralized with dilute sodium hydroxide solution. The precipitate was removed by filtration and dried, and a benzene solution of it was chromatographed on Al_2O_3. The product was crystallized from benzene–petroleum ether.

Naphthyridines IX-XVI were obtained as yellowish crystalline substances of basic character that form hydrochlorides; the hydrochlorides could not be isolated because of their hygroscopicity.

Four absorption bands at 231-232, 247-252, 322-324, and 340-352 nm are observed in the UV spectra of IX-XVI. The IR spectra of these compounds contain the following bands: ν_{NH} 3400-3440, $\nu_{=CH}$ 3077-3082, $\nu_{as\,CH_2}$ 2933-2957, $\nu_{s\,CH_2}$ 2840-2857, $\nu_{s\,CH_3}$ from N$-$CH$_3$ 2780-2797 cm^{-1}. In contrast to the spectra of I-VIII, the spectra of naphthyridines IX-XVI do not contain the band of a carbonyl group.

Bis(β-phenylcarbamoylethyl)methylamine (XVII). A solution of 0.05 mole of bis(β-carbethoxyethyl)methylamine in dry ether was added to dimagnesylamine, obtained from 0.1 mole of aniline, 0.2 mole of ethyl bromide, and 0.2 g-atom of magnesium. The mixture was heated for 30 min and then decomposed with ammonium chloride solution. The ether layer was worked up in the usual manner to give an oily product, a benzene solution of which was chromatographed on silica gel and crystallized from benzene–petroleum ether to give 4 g (25%) of a product with mp 105-106°. Found,%: N 13.2. $C_{19}H_{23}N_3O_2$. Calculated,%: N 12.9.

Cyclization of Bis(β-phenylcarbamoylethyl)methylamine. A 2.5-ml sample of phosphorus oxychloride was added to a solution of 1 g of XVII in 10 ml of toluene, and the mixture was refluxed for 2 h. It was then poured into water, and the aqueous mixture was neutralized. The resulting precipitate of base

IX was chromatographed on Al_2O_3 and crystallized from benzene–petroleum ether to give 0.15 g (17%) of a product with mp 200-201°. No melting-point depression was observed for a mixture of this product with the substance obtained by cyclization of I.

LITERATURE CITED

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3. I. Brauni, A. Heymons, and G. Mans, Ber., 64, 227 (1931).