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2-ARYLAMINO-3-CYANO-5,6,7,8-TETRAHYDROQUINOLINES AND 2-SUBSTITUTED 1-ARYL-6,7,8,9-TETRAHYDROPYRIMIDO[4,5-b]-QUINOLIN-4-ONES DERIVED THEREFROM

M. Yu. Gavrilov and M. E. Konshin

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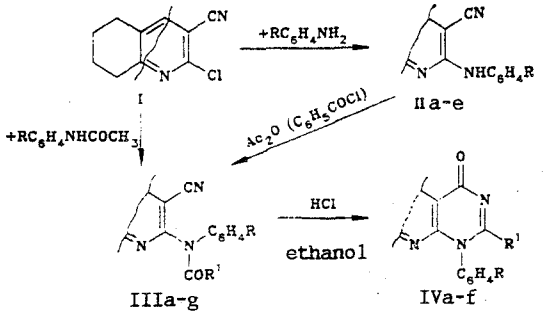
Reaction of 2-chloro-3-cyano-5,6,7,8-tetrahydroquinoline with arylamines gives 2-arylamino-3-cyano-5,6,7,8-tetrahydroquinolines, which on reaction with acetic anhydride or benzoyl chloride are converted into the N-acyl derivatives, and on further treatment with hydrogen chloride in anhydrous ethanol, into 2-substituted 1-aryl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones.

6,7,8,9-Tetrahydropyrimido[4,5-b]quinolines are not known. We have shown that the related 1-aryl-7-methyl-4-oxopyrido[2,3-d]pyrimidines are obtained in high yields on cyclizing N-acyl-2-arylamino-6-methylnicotinonitriles [1]. In order to examine the possibility of synthesizing 6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones in a similar way, the 2-arylamino-3-cyano-5,6,7,8-tetrahydroquinolines (IIa-e) (Table 1) were obtained. The latter compounds are of interest as starting materials for the synthesis of naphthyridines [2], and as synthons in the preparation of potentially biologically active quinolines [3].

The nitriles (IIa-e) were obtained in 60-95% yields by heating (180°C) a mixture of equimolar amounts of 2-chloro-3-cyano-5,6,7,8-tetrahydroquinoline and the arylamine for 4 h. Attempts to carry out the reaction in boiling butanol for 6 h were unsuccessful. When the reaction was carried out in butanol with the arylamine hydrochloride rather than the aryl-



II—IVa R=H, b R=*p*-CH_3, c R=*o*-CH_3, d R=*m*-CH_3, e R=*p*-CH_3O, IIIf, IVf R=H, IIIg R=*p*-C_2H_5O; III, IV a-e R^1=CH_3; f R^1=C_6H_5; IIIg R^1=CH_3

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TABLE 1. Properties of Compounds Obtained

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIa	116—118	77,0	5,8	17,1	$C_{16}H_{15}N_3$	77,1	6,0	17,0	69
IIb	145—146	77,0	6,4	16,1	$C_{17}H_{17}N_3$	77,5	6,5	16,0	60
IIc	136—138	77,9	6,5	15,6	$C_{17}H_{17}N_3$	77,5	6,5	16,0	94
IId	83—84	77,2	6,6	16,2	$C_{17}H_{17}N_3$	77,5	6,5	16,0	95
IIe	110—112	73,0	6,0	15,0	$C_{17}H_{17}N_3O$	73,1	6,1	15,1	68
IIIa	85—87	74,2	5,7	14,5	$C_{18}H_{17}N_3O$	74,2	5,9	14,4	78
IIIb	116—118	74,7	6,0	13,9	$C_{19}H_{19}N_3O$	74,7	6,3	13,8	67
IIIc	109—111	75,0	6,2	14,0	$C_{19}H_{19}N_3O$	74,7	6,3	13,8	56
IIId	120—122	74,4	6,0	13,9	$C_{19}H_{19}N_3O$	74,7	6,3	13,8	71
IIIe	53—55	71,4	5,8	13,1	$C_{19}H_{19}N_3O_2$	71,0	6,0	13,1	73
IIIf	113—115	77,9	5,0	11,7	$C_{23}H_{19}N_3O$	78,2	5,4	11,9	61
IVa	207—209	74,6	5,6	14,7	$C_{18}H_{17}N_3O$	74,2	5,9	14,4	41
IVb	223—225	74,4	6,3	13,7	$C_{19}H_{19}N_3O$	74,7	6,3	13,8	64
IVc	189—191	75,0	6,4	13,7	$C_{19}H_{19}N_3O$	74,7	6,3	13,8	24
IVd	224—226	74,5	6,0	13,5	$C_{19}H_{19}N_3O$	74,7	6,3	13,8	63
IVe	217—219	70,8	6,1	13,0	$C_{19}H_{19}N_3O_2$	71,0	6,0	13,1	50
IVf	214—216	77,8	5,6	11,7	$C_{23}H_{19}N_3O$	78,2	5,4	11,9	33

amine itself, the nitriles (II) were obtained, but longer reaction times were required, and the yields of product were lower.

The IR spectra of (IIa-e) show absorption at 2230 (CN) and 3350 cm^{-1} (NH).

Acylation of the nitriles (IIa-e) with acetic anhydride or benzoyl chloride gave the N-acyl-2-arylamino-3-cyano-5,6,7,8-tetrahydroquinolines (IIIa-f). In the case of (IIIa) and (IIIg), it was shown that such compounds can be obtained by heating the nitrile (I) with an excess of the N-acetylarylamine at 190°C for 6 h. The IR spectra of (IIIa-f) contain absorption at 1700 (CO) and 2240 cm^{-1} (CN). When dry hydrogen chloride is passed into solutions of (IIIa-f) in anhydrous ethanol, they undergo smooth cyclization to the 2-substituted 1-aryl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones (IVa-f). These are colorless, crystalline solids, absorbing in the IR at 1650-1660 (CO), 2860-2870 and 2940-2950 (CH_2 and CH_3), and 3050 cm^{-1} (CH). The PMR spectrum of (IVa) contains (δ, ppm): singlet (3H, methyl) (2.2), a triplet and broadened signal for the 8H of the methylene groups (1.76 and 2.73), a multiplet (5H, benzene ring) centered at 7.3 ppm, and a singlet (1H, pyridine ring) (8.17). The PMR spectra of (IVb-f) were also in agreement with their structures.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in Vaseline oil (II, III) or in solution in CCl_4 (IV). PMR spectra were recorded on a PC-60 spectrometer for 5% solutions in $CDCl_3$, internal standard HMDS.

The properties of the compounds obtained are given in Table 1.

2-Arylamino-3-cyano-5,6,7,8-tetrahydroquinolines (IIa-e). A mixture of 1.92 g (0.01 mole) of 2-chloro-3-cyano-5,6,7,8-tetrahydroquinoline and 0.01 mole of the arylamine was heated at 180°C for 4 h. The mixture was cooled, and treated three times with 50 ml of hot water. The residue was crystallized from ethanol.

Reaction of 2-Chloro-3-cyano-5,6,7,8-tetrahydroquinoline with Aniline Hydrochloride. A solution of 1.92 g (0.01 mole) of (I) and 2.08 g (0.01 mole) of aniline hydrochloride in 30 ml of butanol was boiled for 7 h. Sodium carbonate (0.84 g, 0.01 mole) was added, and the solvent and volatile impurities distilled in steam. The residue was crystallized from ethanol to give the nitrile (IIa), yield 0.86 g (45%). A mixed melting point with a sample of (IIa) obtained in the previous preparation gave no depression.

N-Acetyl-2-arylamino-3-cyano-5,6,7,8-tetrahydroquinolines (IIIa-e). A mixture of 0.01 mole of the nitrile (IIa-e) in 15 ml of acetic anhydride and 15 ml of dry pyridine was boiled for 5 h, then poured into water, and the solid filtered off and crystallized from methanol.

N-Benzoyl-2-anilino-3-cyano-5,6,7,8-tetrahydroquinoline (IIIf) was obtained similarly, from 0.01 mole of the nitrile (IIa) and 4 ml of benzoyl chloride in 10 ml of dry pyridine.

N-Acetyl-2-(p-phenetidino)-3-cyano-5,6,7,8-tetrahydroquinoline (IIIg). A mixture of 1.92 g (0.01 mole) of (I) and 0.01 mole of N-acetyl-p-phenetidine was heated for 6 h at 190°C, treated with hot water, and the solid filtered off and crystallized from ethanol to give 1.21 g (63%) of product, mp 115-117°C. Found: C 71.7; H 6.2; N 12.4%. $C_{20}H_{21}N_3O_2$. Calculated: C 71.6; H 6.3; N 12.5%.

Similarly, the nitrile (I) and acetanilide gave 76% of (IIIa). A mixed melting point with (IIIa) obtained from (IIa) and acetic anhydride gave no depression.

2-Substituted 1-Aryl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones (IVa-f). Dry hydrogen chloride was passed for 3 h into a solution of 0.01 mole of (IIIa-f) in 40 ml of anhydrous ethanol, and the solid which separated was filtered off, treated with aqueous sodium acetate, and crystallized from ethanol to give (IVa-f).

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ACETALS OF LACTAMS AND ACID AMIDES.

51.* CYCLIZATION OF α-CYANO-β-PHENYLAMINO-N-DIMETHYLAMINOMETHYLENEACRYLAMIDE TO PYRIMIDO[5,4-c]QUINOL-4-ONE

L. V. Ershov, N. Z. Tugusheva, and V. G. Granik

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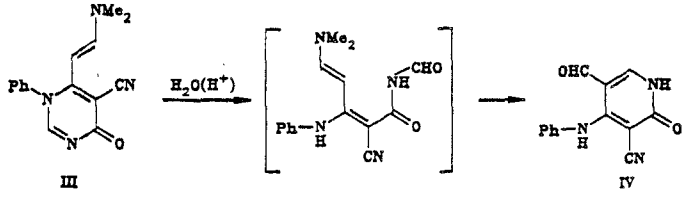
Cyclization of α-cyano-β-phenylamino-N-dimethylaminomethyleneacrylamide to pyrimido[5,4-c]quinol-4-one proceeds via the intermediate formation of 1-phenyl-5-cyano-1,4-dihydropyrimidin-4-one and α-cyano-β-phenyl-amino-N-formylacrylamide.

We have recently found that α-cyano-β-phenylamino-N-dimethylaminomethyleneacrylamide (I) cyclizes on boiling in acetic acid to give high yields of pyrimido[5,4-c]quinol-4-one [2]. Bearing in mind that enamidoacylamidines such as (I) are readily convertible into pyrimidin-4-ones [2], it would be expected that this stage would mediate in the conversion of (I) into (II). It is also known that acid hydrolysis of 1-phenyl-5-cyano-6-β-dimethylaminovinyl-1,4-dihydropyrimidin-4-one (III) gives 3-cyano-4-phenylamino-5-formylpyrid-2-one (IV), which clearly calls for the intermediate formation of the N-formyl derivative [3]:



III IV

In 1-phenyl-5-cyano-1,4-dihydropyrimidin-4-one (V) [2], the complicating factor present in the pyrimidinone (III), namely the presence of the dimethylaminomethylene group, is absent. Consequently, it was possible to attempt to isolate the intermediate α-cyano-β-phenylamino-N-formylacrylamide (VI), which is the second likely stage in the formation of the tricycle (II) from the acylamidine (I).

*For Communication 50, see [1].

S. Ordzhonikidze Research Institute for Pharmaceutical Chemistry, Moscow 119021.

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