NAPHTHYRIDINES.

14*. 2-METHYLQUINOLINE-3-CARBOXANILIDES AND THE SYNTHESIS THEREFROM OF 2-SUBSTITUTED 1-OXO-3-PHENYL-1,2,3,4-TETRAHYDROBENZO[b]-1,6-NAPHTHYRIDINES

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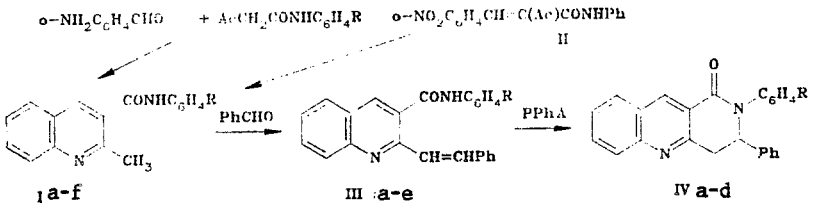
The reaction of 2-aminobenzaldehyde with acetoacetanilides has given 2-methylquinoline-3-carboxanilides. Condensation of these with benzaldehydes gives 2-styrylquinoline-3-carboxanilides, which on heating in polyphosphoric acid cyclize to 2-substituted 1-oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines.

1,2,3,4-Tetrahydrobenzo[b]-1,6-naphthyridines merit attention as biologically active compounds [2]. We have previously described a method for the synthesis of 10-arylamino-derivatives of this heterocycle [3]. 1-Oxo-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines have not hitherto been examined.

It has been shown [1] that 5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridines may be obtained by cyclization of 2-styrylnicotinamides. In developing these studies, it was of interest to examine the possible synthesis of benzo[b]-1,6-naphthyridines in a similar manner form substituted 2-methylquinoline-3-carboxamides, which are also of interest as potential biologically active compounds [4].

The 2-methylquinoline-3-carboxanilides (Ia-f) required for this investigation were obtained in high yields by reacting 2-aminobenzaldehyde with acetoacetanilides in ethanol in the presence of catalytic amounts of 10% potassium hydroxide solution. The anilide (Ia) was also obtained in 41% yield by reducing 2-acetyl-3-(2-nitrophenyl)acrylanide (II) with iron in acetic acid. The latter compound was obtained from acetoacetanilide and 2-nitrobenzaldhyde by the Knoevenagel reaction.



I, III a R=H, b R=*p*-CH_3, c R=*o*-CH_3, d R=*p*-CH_3O, e R=*o*-Cl, f R=*o*-CH_3O; IV a R=H, b R=*p*-CH_3, c R=*o*-CH_3, d R=*o*-Cl

The IR spectra of the amides (Ia-f), obtained in Nujol mull, showed absorption at 1640-1650 (CO), 3230-3280 (associated NH), and 3430-3470 cm^{-1} (free NH); however, in CCl_4 solution the NH group gave only absorption at 3440-3450 cm^{-1}.

The PMR spectra of the amides (I) contained a singlet at 2.16-2.66 (CH_3), a multiplet at 7.26-7.40 (5-...8-H_4 and benzene ring protons), a singlet at 8.0-8.3 (4-H), and a singlet at 9.83-10.40 ppm (NH).

Condensation of the anilides (Ia-e) with benzaldehyde in xylene in the presence of piperidine at 170-175°C gave the 2-styrylquinoline-3-carboxanilides (IIIa-e), the IR spectra of which showed absorption at 1645-1650 (CO) and 3270-3320 cm^{-1} (NH). The signals for the

*For Part 13, see [1].

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TABLE 1. Properties of Compounds Obtained

Compound	Empirical formula	mp, °C	Yield %	Compound	Empirical formula	Tmp, °C	Yield, %
Ia	$C_{17}H_{14}N_2O$	185...187	92	IIIc	$C_{25}H_{20}N_2O$	220...222	70
Ib	$C_{18}H_{16}N_2O$	174...175	94	IIId	$C_{25}H_{20}N_2O_2$	218...220	40
Ic	$C_{18}H_{16}N_2O$	195...196	91	IIIe	$C_{24}H_{17}ClN_2O$	214...215	55
Id	$C_{18}H_{16}N_2O_2$	175...176	87	IVa	$C_{24}H_{18}N_2O$	228...230	94
Ie	$C_{17}H_{13}ClN_2O$	165...166	94	IVb	$C_{25}H_{20}N_2O$	203...205	70
If	$C_{18}H_{16}N_2O_2$	122...124	94	IVc	$C_{25}H_{20}N_2O$	168...170	70
IIIa	$C_{24}H_{18}N_2O$	227...228	61	IVd	$C_{24}H_{17}ClN_2O$	197...198	89
IIIb	$C_{25}H_{20}N_2O$	238...239	80				

protons in the PMR spectra of the amides (III) are seen as a multiplet at 7.5-7.6 (5-...8-H_4, benzene ring and CH=CH protons), and singlets at 8.16-8.43 (4-H) and 10.5 ppm (NH).

Compounds (IIIa-c, e) on heating in polyphosphoric acid undergo intramolecular cyclization to give high yields of the 2-substituted 1-oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines (IVa-d), the IR spectra of which show absorption at 1650-1660 (CO) but, unlike the starting amides (III), no absorption for stretching vibrations of the NH group. The PMR spectra of (IVa-d) contain signals for the protons at 3.66-3.76 (4-H_2), 5.13-5.5 (3-H), 8.83-8.96 (10-H), and 7.46-7.60 ppm (protons of the condensed benzene ring and the phenyl radicals).

EXPERIMENTAL

IR spectra were obtained on a UR-20 in Nujol mull, and in the case of (Ia-f), in CCl_4 also. PMR spectra were recorded on an RYa-2310 instrument (60 MHz) for 5% solutions of the compounds in DMSO-D_6, internal standard HMDS. The properties of the products are shown in Table 1.

The elemental analyses for C, H, N, and Cl were in agreement with the calculated values.

2-Methylquinoline-3-carboxanilides (Ia-f). A solution of 4 mmole of the substituted acetoacetamide, 0.5 g (4 mmole) of 2-aminobenzaldehyde, and five drops of a 10% solution of KOH in 5 ml of ethanol was kept for 12 h at 20°C. The solid which separated was filtered off, and recrystallized from ethanol to give colorless crystals of the anilides (I).

2-Acetyl-3-(2-nitrophenyl)acrylanide (II, $C_{17}H_{14}N_2O_4$). A solution of 3 g (0.02 mole) of 2-nitrobenzaldehyde, 3.5 g (0.02 mole) of acetoacetanilide, and five drops of piperidine in 20 ml of ethanol was boiled for one hour, cooled, and the solid which separated filtered off, and crystallized from ethanol to give 2.48 g (40%) of product, mp 161-162°C.

2-Methylquinoline-3-carboxanilide (Ia, $C_{17}H_{14}N_2O$). To a solution of 2 g (6 mmole) of the anilide (II) in 25 ml of glacial acetic acid was added 2.5 g of iron filings, and the mixture heated on the water bath for 6 h, filtered, and the filtrate diluted with water and basified with sodium bicarbonate solution. The solid which separated was filtered off, and crystallized from ethanol to give 0.7 g (41%) of product, mp 185-187°C. A mixed melting point with a sample obtained from 2-aminobenzaldehyde and acetoacetanilide gave no depression.

2-Styrylquinoline-3-carboxanilides (IIIa-e). A mixture of 3 mmoles of the amide (Ia-e), 0.55 g (5 mmole) of benxaldehyde, 3-4 drops of piperidine, and 2 ml of p-xylene was heated for 5 h at 170-175°C. The resulting anilides (III) were crystallized from a mixture of ethanol and dioxane (1:1).

2-Substituted 1-Oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines (IVa-d). A mixture of 3 mmole of the amide (IIIa-c, e) and 40 g of polyphosphoric acid was kept for 4 h at 135°C, then diluted with water and neutralized with sodium carbonate solution. The solid which separated was filtered off and crystallized from ethanol.

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