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SYNTHESIS OF NAPHTHYRIDINES

I. NEW METHOD FOR THE PREPARATION OF 2,3-DIHYDROBENZO[h][1,6]NAPHTHYRIDIN-4-(1H)-ONES

F. S. Mikhailitsyn, E. M. Braude, and A. F. Bekhli

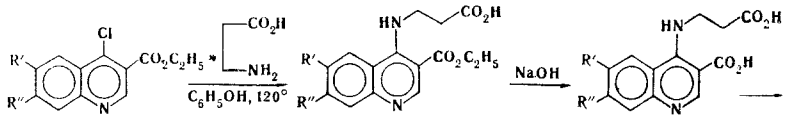
UDC 547.831.3'834.2.07

A new method for the synthesis of 2,3-dihydrobenzo[h][1,6]naphthyridin-4-(1H)-ones, which consists in cyclization of 4-(β-carboxyethylamino)quinoline-3-carboxylic acids by heating them in acetic anhydride in the presence of potassium acetate, is proposed.

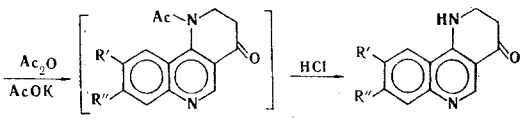
In the development of our research on the synthesis of heterocyclic ketones by cyclization of the corresponding dicarboxylic acids by heating them with acetic anhydride in the presence of potassium acetate [1-3] we accomplished the synthesis of 2,3-dihydrobenzo[h][1,6]naphthyridin-4-(1H)-ones (Va-c).

The only described representatives of the benzo[h][1,6]naphthyridin-4-ones – 2,3-dihydro-8,9-dimethoxybenzo[h][1,6]naphthyridin-4(1H)-one – was obtained in 41% yield by cyclization of 4-(β-carboxyethylamino)-6,7-dimethoxyquinoline [4] – the product of multistep synthesis by the method in [4, 5] – in polyphosphoric acid (PPA).

We synthesized the same compound on the basis of the reaction of the more accessible ethyl 4-chloroquinoline-3-carboxylates (Ia, b) [6-8] with β-alanine via the scheme



I a-c II a-c III a-c



IV a-c V a-c

I-V a R′=R″=H; b R′=H, R″=Cl; c R′=R″=OCH_3

The 4-(β-carboxyethylamino)quinoline-3-carboxylates (IIa-c) formed in the reaction of Ia-c with β-alanine were hydrolyzed and converted to dicarboxylic acids IIIa-c, which were then subjected to cyclization to N-acetyl derivatives IVa-c, which in turn were hydrolyzed, without isolation, to Va-c. We were able to purify Vc only in the form of its hydrochloride, inasmuch as base Vc is a highly insoluble compound.

The presence of an oxo group in Va-c is confirmed by the IR spectra ($\nu_{C=O}$ 1663-1676 cm^{-1}) and also by the formation of hydrazones (in the case of Va).

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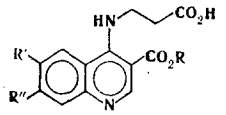
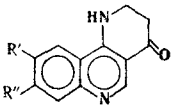
TABLE 1



Compound	R	R′	R″	mp, °C (dec.)	Empirical formula	N, % found	N, % calc.,	Yield, %
IIa	C_2H_5	H	H	219—221	$C_{15}H_{16}N_2O_4$	9,4	9,7	79
IIb	C_2H_5	H	Cl	243—245	$C_{15}H_{15}ClN_2O_4$*	8,5	8,7	81
IIc	C_2H_5	CH_3O	CH_3O	259—262	$C_{17}H_{20}N_2O_6$	7,9	8,0	92
IIIa	H	H	H	252—256	$C_{13}H_{12}N_2O_4$	10,6	10,8	80
IIIb	H	H	Cl	249—251	$C_{13}H_{11}ClN_2O_4$ †	9,3	9,5	91
IIIc	H	CH_3O	CH_3O	238—241	$C_{15}H_{16}N_2O_6$	8,8	8,8	90

*Found %: Cl 11.1. Calculated %: Cl 11.0.
†Found %: Cl 11.9. Calculated %: Cl 12.0.

TABLE 2



Compound	R′	R″	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %
Va	H	H	279—280[a]	$C_{12}H_{10}N_2O$	72,3	5,0	14,6	72,7	5,1	14,2	47
Vb	H	Cl	~305[b]	$C_{12}H_9ClN_2O$ [d]	61,9	3,7	12,3	61,9	3,9	12,0	58
Vc	CH_3O	CH_3O	272—275[c]	$C_{14}H_{14}N_2O_3 \cdot HCl$ [e]	—	—	9,6	—	—	9,5	52

[a]After recrystallization from pyridine (pale-yellow crystals). UV spectrum, λ_{max}, nm (log ε): 220 (4.25), 235 (4.28), 258 (4.34), 276 (3.21), 304 (3.83), 315 (3.92), and 357 (3.74). [b]After recrystallization from methyl cellosolve (pale-yellow crystals). UV spectrum, λ_{max}, nm (log ε): 220 (4.25), 235 (4.24), 266 (4.40), 280-282 (shoulder) (4.13), 310 (3.78), 322 (3.89), and 357 (3.72). [c]Found %: Cl 15.5. Calculated %: Cl 15.2. [d]According to [4], this compound has mp 266-270° (after recrystallization from 10% HCl). [e]After recrystallization from 10% HCl. Found %: Cl 11.8. Calculated %: Cl 12.0.

EXPERIMENTAL

The melting points of the compounds were determined with a Mel-Temp apparatus [9] and were not corrected. The UV spectra of alcohol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

Ethyl 4-(β-Carboxyethylamino)quinoline-3-carboxylates (IIa-c). A mixture of 0.05 mole of the corresponding ethyl 4-chloroquinoline-3-carboxylate (I), 8.9 g (0.1 mole) of β-alanine, and 50 g of phenol was stirred at 120-125° for 4 h, after which the phenol was removed by distillation, and the residue was separated by steam distillation, washed with water and alcohol, and dissolved by boiling in 15% Na_2CO_3. The solution was filtered, and the reaction product was isolated by acidification with acetic acid. Compounds IIa-c were obtained as colorless substances that melted with decomposition (Table 1).

4-(β-Carboxyethylamino)quinoline-3-carboxylic Acids (IIIa-c). A mixture of 0.04 mole of the corresponding ester IIa-c, 0.12 mole of KOH, 200 ml of methanol, and 90 ml of water was refluxed for 1 h, after which the resulting solution was filtered, and the filtrate was acidified with acetic acid. The precipitate was removed by filtration, washed with water and alcohol, and crystallized from water or aqueous dimethylformamide (DMF) (Table 1).

2,3-Dihydrobenzo[h][1,6]naphthyridin-4(1H)-ones (Va-c). A mixture of 0.025 mole of the corresponding IIIa-c, 6.9 g (0.05 mole) of freshly fused potassium acetate, and 100 ml of acetic anhydride was heated at 115°

for 2 h and at 125° for ~15 min (until CO_2 evolution ceased). The volatile products were removed by vacuum distillation, and 100 ml of water was added to the residue. The resulting oily product began to solidify on standing. The solid was removed by filtration, washed with water, refluxed with 20 ml of concentrated HCl for 30 min, and evaporated to dryness. The residue was treated with 10% NaOH, and the insoluble reaction product was removed by filtration, washed with water, and crystallized (Table 2).

Hydrazone of Va. A mixture of 0.2 g (1 mmole) of Va, 2 ml of hydrazine hydrate, and 5 ml of DMF was refluxed for 30 min, after which it was cooled, and the liberated crystals were separated and washed with water to give a light-yellow product that did not melt on heating up to 350°. Found %: N 26.1. $C_{12}H_{12}N_4$. Calculated %: N 26.4.

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SYNTHESIS OF NAPHTHYRIDINES

II.* 2,3,9,10-TETRAHYDRO[1,4]BENZODIOXINO[6,7-h][1,6]NAPHTHYRIDIN-4(1H)-ONE

F. S. Mikhailitsyn and A. F. Bekhli

UDC 547.834.2'841.07

A method for the preparation of 2,3,9,10-tetrahydro[1,4]benzodioxino[6,7-h][1,6]naphthyridin-4(1H)-one by cyclization of 2,3-dihydro-9-[(2-carboxyethyl)amino][1,4]dioxino[2,3-g]quinoline-8-carboxylic acid in acetic anhydride in the presence of potassium acetate is described.

In the present research we used a new method for the construction of the naphthyridine structure [1] in order to obtain 2,3,9,10-tetrahydro[1,4]benzodioxino[6,7-h][1,6]naphthyridin-4(1H)-ones – the first representative of the benzodioxino[6,7-h][1,6]naphthyridine heterocyclic system.

For this we obtained starting VI from 2,3-dihydro[1,4]benzodioxine (I) via a known scheme [2], which includes nitration of I, reduction of 6-nitro derivative II to corresponding amine III, condensation of the latter with ethoxymethylenemalonic ester to give substituted diethyl malonate IV, thermal cyclization of IV to [1,4]-dioxano[2,3-g]quinoline derivative V, and treatment of V with phosphorus oxychloride.

*See [1] for communication I.

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