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CONDENSED PYRIDINE BASES. REACTIONS OF 1-OXO-3,3,6-TRIMETHYL-1,2,3,4-TETRAHYDROBENZO[b]FURO-, BENZO[b]THIENO-, AND INDOLO[2,3-c]QUINOLINES WITH ELECTROPHILIC REAGENTS

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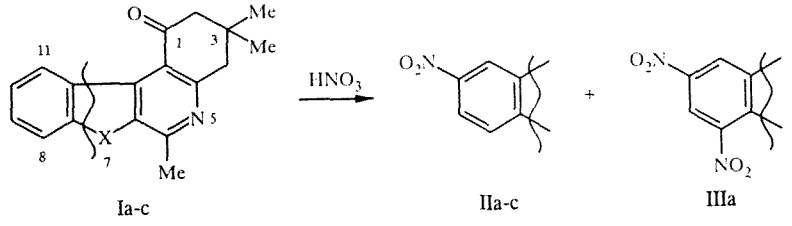
A study has been made of the nitration and bromination of 1-oxo-3,3,6-trimethyl-1,2,3,4-tetrahydrobenzo[b]furo-, benzo[b]thieno-, and indolo[2,3-c]quinolines. It has been shown that the nitration is directed to the benzene ring (position 10). Bromination by molecular bromine takes place at the 6-CH_3 group of the pyridine fragment and yields a mixture of the corresponding monobromomethyl and dibromomethyl derivatives, whereas a dimethylacetamide–bromine complex brominates the methylene group in position 2, forming the α-bromoketone. The Schmidt reaction of 1-oxo-3,3,6-trimethyl-1,2,3,4-tetrahydrobenzo[b]furo-, benzo[b]thieno-, and indolo[2,3-c]quinolines have been investigated, as well as conversions of their oximes under conditions of the Beckmann rearrangement.

Continuing our work on the synthesis and study of the properties of condensed pyridine bases, with the further aim of elucidating the structure–activity relationship, we investigated the reactions of previously synthesized 1-oxo-3,3,6-trimethyl-1,2,3,4-tetrahydrobenzo[b]furo-, benzo[b]thieno-, and indolo[2,3-c]quinolines (Ia-c) with nitric acid, bromine, and HN_3 [1-3].

The course of the nitration of systems Ia-c is similar to that of their tricyclic analogs [2]. Under the selected conditions (85% HNO_3), we recovered products of monosubstitution at the $C_{(10)}$ atom of compounds Ib,c (IIb,c), and a mixture of products of mono- and disubstitution of compound Ia (IIa and IIIa, respectively).



Ia-c IIa-c IIIa

I–III: a) X = NH, b) X = O, c) X = S

The positions of the substituents were determined on the basis of PMR spectra (Table 2). We also performed a counter-synthesis of the product IIa by acylation of (5-nitro-3-indolyl)dimedone (IV) and subsequent conversion of the pyrylium salt (V) to compound IIa by the action of alcoholic ammonia.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	R_f	Eluent for chromatography	Yield, %
		C	H	N	Cl or Br (S)				
IIa	$C_{18}H_{17}N_3O_3$	66.8 66,7	5.3 5,3	13.0 13,1	–	283	0,02	Ethanol	52
IIb	$C_{18}H_{16}N_2O_4$	66.7 66,6	4.9 5,0	8.6 8,7	–	188...189	0,93	Methylene chloride	80
IIc	$C_{18}H_{16}N_2O_3S$	63.5 63,3	4.7 4,8	8.2 8,3	(9.4) (9,4)	250...251	0,90	Methylene chloride	85
IIIa	$C_{18}H_{16}N_4O_5$	58.7 58,6	4.3 4,5	15.2 15,2	–	334	0,44	Methylene chloride	17
IV	$C_{16}H_{16}N_2O_4$	64.2 64,0	5.0 5,1	9.4 9,6	–	256	–	–	41
V	$C_{18}H_{17}N_2ClO_8$	50.9 51,1	4.0 4,2	6.6 6,4	8.4 8,6	180 (decomp.)	–	–	26
VII	$C_{18}H_{16}NBrO_2$	60.3 60,0	4.5 4,3	3.9 4,0	22.3 22,5	145	0,39	Benzene–chloroform, 20:3	18
VIII	$C_{18}H_{15}NBr_2O_2$	49.4 49,6	3.4 3,5	3.3 3,0	39.6 36,8	166...167	0,82	Benzene–chloroform, 20:3	22
IX	$C_{18}H_{16}NBrO_2$	60.3 60,4	4.5 4,4	3.9 3,7	22.3 22,5	138	0,74	Benzene–ethyl acetate, 5:1	89
XIa	$C_{18}H_{19}N_3O$	73.7 73,6	6.5 6,4	14.3 14,4	–	324...325	–	–	82
XIb	$C_{18}H_{18}N_2O$	73.5 73,7	6.1 6,0	9.5 9,3	–	291...292	0,71	Chloroform–ethyl acetate–isopropyl alcohol, 10:3:1	87
XIc	$C_{18}H_{18}N_2OS$	69.7 69,6	5.8 5,9	9.0 9,1	(10.3) (10,1)	292...293	0,67	Same	80
XIIIa	$C_{18}H_{17}N_3$	78.6 78,4	6.2 6,2	15.3 15,1	–	233...234	–	–	50
XIIIb	$C_{18}H_{16}N_2O$	78.3 78,4	5.8 5,7	10.2 10,2	–	171	0,61	Benzene–chloroform, 2:1	70
XV	$C_{20}H_{18}N_2O_2$	75.5 75,6	5.7 5,7	8.8 8,8	–	315...320	–	–	95

*Compounds IIa-c and IIIa were recrystallized from an alcohol–DMF mixture, VII-IX from acetone, and XIa-c and XV from DMF.

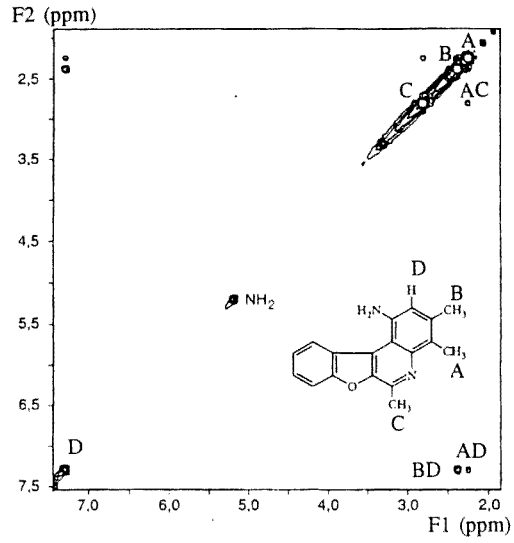
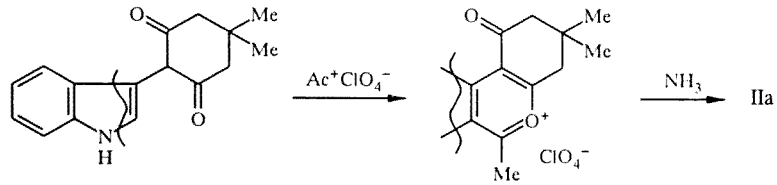


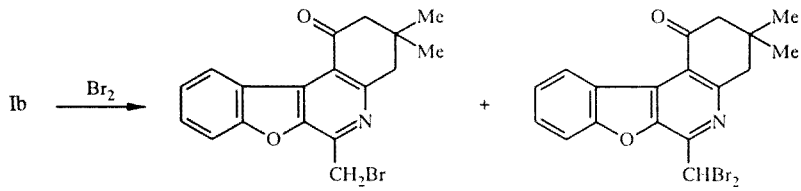
Fig. 1. 2M COSY spectrum of compound XIIIb (DMSO-d_6, TMS).

We did not perform the analogous counter-synthesis of the product IIc, since we were unable to accomplish the acylation of 2-(5-nitrobenzo[b]-3-thienyl)dimedone (VI). (Compounds IV and VI were obtained for the first time by us, on the basis of known procedures; see Experimental section.)



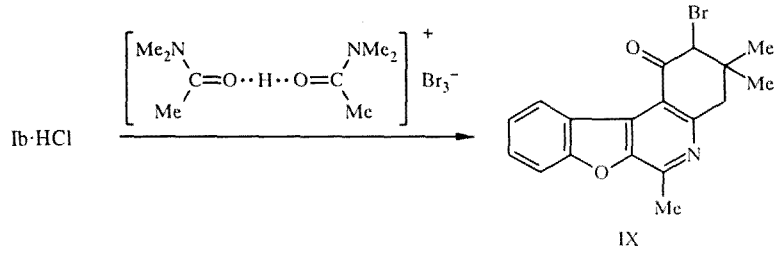
IV V

Bromination of these tetracyclic systems was studied in the example of compound Ib. Reaction of this compound with one equivalent of bromine in acetic acid affords a mixture of products of bromination on the methyl group in position 6, namely, the monobromomethyl derivative (VII) and the dibromomethyl derivative (VIII).



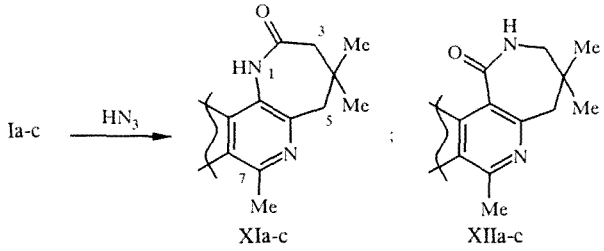
VII VIII

In the PMR spectra of products VII and VIII, singlet signals of protons of the CH_2Br group are observed at 5.03 ppm, and of the $CHBr_2$ group at 7.72 ppm, respectively. It is interesting to note that under the conditions indicated above, bromination does not affect the CH_2CO group. It was shown recently [4, 5] that the complex of dimethylacetamide with bromine is a mild brominating agent for ketones and certain aromatic compounds, an agent that does not act on the methyl groups of a pyridine ring. And indeed, we found that the action of this complex in acetic acid on the hydrochloride of the ketone Ib gave the α-bromoketone IX.

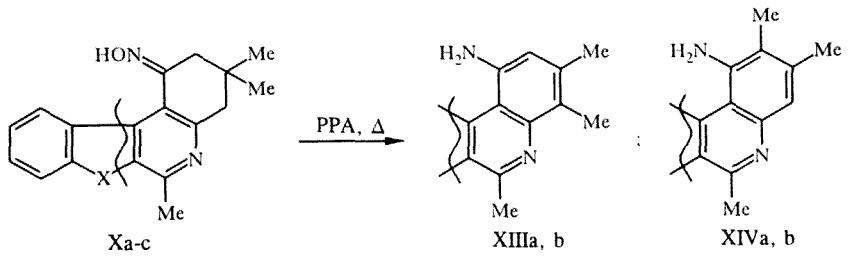


(The base Ib is not brominated by the dimethylacetamide–bromine complex, owing to the formation of the poorly soluble perbromate of Ib). In the PMR spectrum of compound IX, a singlet signal of the proton of the COCHBr group is observed in the 4.26 ppm region.

When the Schmidt reaction is performed with the annelated tetrahydroquinolones Ia-c, followed by a Beckmann rearrangement of the oxime products Xa-c, two isomeric pyridoazepinones XI and XII may be formed, as described in the literature for compounds containing a dimedone fragment in the base structure [6, 7]. We have shown that the Schmidt reaction of the ketones Ia-c affords the corresponding 5H-4,4,7-trimethyl-1,2,3,4-tetrahydrobenzo[b]furo-, benzo[b]thieno-, and indolo[2,3-c]pyrido[2,3-e]azepin-2-ones (XIa-c). In the spectra of these products, we observe singlet signals of protons of the 3-CH_2 and 5-CH_2 groups in the regions 2.05-2.39 and 2.85-3.15 ppm, respectively. In the case of formation of the isomeric pyridoazepinones XIIIa-c, the protons of the 3-CH_2 group would have given a doublet [6].



Under conditions of the Beckmann rearrangement (holding in polyphosphoric acid at 120°C), the oximes Xa,b undergo an entirely different conversion. Only in the case of compound Xb were we able to detect (by TLC) traces of the benzofuropyridoazepinone XIb; for both compounds, the main products were found to be the quinoline derivatives XIIIa,b or XIVa,b, as evidenced by elemental analyses and PMR spectra. The PMR spectra differ significantly from those of the above-described compounds IIa-c, IIIa, VII, VIII, and XIa,b in that they do not include any of the signals that are characteristic for fragments of a gem-dimethyl-substituted tetrahydroquinolone or azepinone–singlets of two CH_2 groups and a singlet of the gem-dimethyl grouping. For the XIIIa,b and XIVa,b, in contrast, we find in the weak field region a set of one-proton, two-proton, and two three-proton singlets, which can be assigned on the basis of their chemical shifts to aromatic ring-bonded protons, the NH_2 group, and the two methyl substituents, respectively. In order to determine the position of the latter, we used the 2M COSY spectrum of compound XIIIb. A fragment of this spectrum is shown in Fig. 1. From the signal at 2.85 ppm, which we assigned to the 6-CH_3 group, a C-A-B chain of methyl groups is built up, with no cross-peak observed for the C and B signals. The most interesting are the cross-peaks of signals A and B with a one-proton singlet at 7.33 ppm. Let us note that the intensity of interaction of signal B with the latter is substantially greater than that of signal A. For the existing carbon skeleton, this scheme of interactions is realized only with the positioning of the substituents that is indicated for the structure XIIIa,b. Our conclusion is further supported by a comparison of the PMR spectra of compound XIIIb and the product of its acylation (XV): In the latter, the signal of the proton in position 2 of the aromatic ring is shifted 0.6 ppm downfield (from 7.33 to 7.93 ppm), while the positions of the other signals remain practically unchanged. Thus, the principal products formed when the oximes Xa,b are held in PPA (polyphosphoric acid) at 120°C have the structure of the quinoline derivatives XIII.



Xa-c XIIIa, b XIVa, b

EXPERIMENTAL

The PMR spectra were taken in a Gemini-200 instrument (200 MHz), internal standard TMS. The characteristics of the synthesized compounds are listed in Table 1, and PMR spectral data in Table 2. The purities of the products and the isomers contained in the products were monitored by means of TLC on Alufol plates for compounds IIa-c and IIIa, and on Silufol UV-254 plates for the other compounds.

Elemental analyses of the synthesized compounds for C, H, N, S, Cl, and Br matched the calculated values (see Table 1).

3,3,6-Trimethyl-10-nitro-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]quinoline (IIa) and 3,3,6-Trimethyl-8-10-dinitro-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]quinoline (IIIa). A 1-g quantity (3.6 mmoles) of compound Ia was added in small portions, with mixing, to 6 ml of 85% HNO_3 at a temperature no higher than 4°C, over the course of 1 h. The reaction mixture, which had a red color, was held for 3 h at 2°C and then poured onto a mixture of 30 g of ice and 15 ml of ammonia. The precipitated products were filtered off, washed with water, and dried, obtaining 1 g of a mixture of IIa and IIIa, which was separated in a column with Al_2O_3, eluting IIIa with methylene chloride and IIa with ethanol (weight ratio IIa:IIIa = 73:27).

3,3,6-Trimethyl-10-nitro-1-oxo-1,2,3,4-tetrahydrobenzo[b]furo[2,3-c]quinoline(IIb)and3,3,6-Trimethyl-10-nitro-1-oxo-1,2,3,4-tetrahydrobenzo[b]thieno[2,3-c]quinoline (IIc). A 5-mmole quantity of compound Ib or Ic was added over the course of 5 min to 13 ml of 85% HNO_3 while mixing and holding at 15-20°C. The reaction mixture was held at this same temperature for 2 h, after which it was poured onto ice with 20 ml of ammonia. The precipitated product, IIb or IIc, was filtered off, washed with water, dried, and purified by column chromatography on Al_2O_3.

Counter-synthesis of Compound IIa: 2-(5-Nitroindolyl-3)dimedone (IV). Compound IV was obtained by a method described in [8], from N-acetyl-3-acetoxy-5-nitroindole.

3,3,6-Trimethyl-10-nitro-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]pyrylium Perchlorate (V). To a mixture of 5 ml of acetic anhydride and 0.3 ml of 70% $HClO_4$, cooled to 0°C, 0.8 g (2.68 mmoles) of the dimedone IV was added while stirring. The precipitate of product V that was formed after 45 min was filtered off and washed with dry ether.

3,3,6-Trimethyl-10-nitro-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]quinoline (IIa). A 0.3-g quantity (0.71 mmole) of the perchlorate V in 10 ml of an alcoholic ammonia solution was refluxed for 15 min. After cooling the reaction mixture, 10 ml of water was added, and the precipitate was filtered off. Obtained 0.2 g (87.7%) of compound IIa, identical to the sample obtained by nitration of the quinoline Ia; a mixed sample of the products obtained by the two different methods did not show any melting point depression.

2-(5-Nitrobenzo[b]thienyl-3)dimedone (VI, $C_{16}H_{15}NO_4S$). Compound VI was obtained by a procedure given in [1], from 5-nitrobenzo[b]thieno(2H)-3-one. Yield 40%, mp 287°C.

The synthesized dimedone VI (0.6 g, 2 mmoles) was not acylated over the course of 5 h at 35°C by a mixture of 5 ml of acetic anhydride and 0.3 ml of $HClO_4$; 0.5 g of the original compound was recovered from the reaction mixture.

6-Bromomethyl-3,3-6-trimethyl-1-oxo-1,2,3,4-tetrahydrobenzo[b]furo[2,3-c]quinoline (VII) and 6-Dibromomethyl-3,3,6-trimethyl-1-oxo-1,2,3,4-tetrahydrobenzo[b]furo[2,3-c]quinoline (VIII). To a solution of 1.4 g (5 mmoles) of compound Ib in 12 ml of glacial acetic acid, at room temperature with stirring, a solution of 0.8 g (5 mmoles) of bromine in 4 ml of acetic acid was added. The reaction mass was stirred for 4 h and then filtered, obtaining 1.5 g of a mixture of hydrobromides of the annelated tetrahydroquinolones VII and VIII. This mixture was suspended in 30 ml of a 5% $NaHCO_3$ solution, after which the bases VII and VIII were extracted by chloroform. The extract was washed with water and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was chromatographed in a column with silica gel.

TABLE 2. PMR Spectra of Synthesized Compounds*

Compound	Chemical shifts δ, ppm, and SSCC (J, Hz)
IIa*[2]	1,21 (6H, s, 3-$(CH_3)_2$), 2,85 (2H, s, 2-CH_2), 3,05 (3H, s, 6-CH_3), 3,21 (2H, s, 4-CH_2), 7,20 (1H, d, J = 10,8, 8-H), 7,95 (1H, d J = 10,8, 9-H), 9,50 (1H, s, 11-H)
IIb	1,19 (6H, s, 3-$(CH_3)_2$), 2,76 (2H, s, 2-CH_2), 2,96 (3H, s, 6-CH_3), 3,20 (2H, s, 4-CH_2), 7,33 (1H, d, J = 9,0, 8-H), 8,03 (1H, d, J = 9,0, 9-H), 9,33 (1H, s, 11-H)
IIc	1,14 (6H, s, 3-$(CH_3)_2$), 2,75 (2H, s, 2-CH_2), 2,90 (3H, s, 6-CH_3), 3,14 (2H, s, 4-CH_2), 7,46 (1H, d, J =9,0, 8-H), 7,85 (1H, d, J = 9,0, 9-H), 9,32 (1H, s, 11-H)
IIIa*[2]	1,17 (6H, s, 3-$(CH_3)_2$), 2,73 (2H, s, 2-CH_2), 3,08 (3H, s, 6-CH_3), 3,15 (2H, s, 4-CH_2), 8,70 (1H, s, 9-H), 8,73 (1H, s, 11-H)
VII	1,11 (6H, s, 3-$(CH_3)_2$), 2,73 (2H, s, 2-CH_2), 3,16 (2H, s, 4-CH_2), 5,03 (2H, s, 6-CH_2Br), 7,50 (1H, t, 10-H), 7,75 (1H, t, 9-H), 7,82 (1H, d, J =8,0, 8-H), 9,10 (1H, d, J = 8,0, 11-H)
VIII	1,12 (6H, s, 3-$(CH_3)_2$), 2,77 (2H, s, 2-CH_2), 3,21 (2H, s, 4-CH_2), 7,57 (1H, t, 10-H), 7,72 (1H, s, 6-$CHBr_2$), 7,84 (1H, t, 9-H), 7,93 (1H, d, J = 8,0, 8-H), 9,13 (1H, d, J = 8,0, 11-H)
IX	0,87 (3H, s, 3-CH_3), 0,96 (3H, s, 3-CH_3), 2,63 (3H, s, 6-CH_3), 2,94 (1H, d, J = 16,0, 4-CH), 3,43 (1H, d, J = 16,0, 4-CH), 4,26 (1H, s, 2-CHBr), 7,52 (1H, t, 10-H), 7,64 (1H, t, 9-H), 7,86 (1H, d, J = 8,0, 8-H), 9,02 (1H, d, J = 8,0, 11-H)
XIa	1,26 (6H, s, 4-$(CH_3)_2$), 2,39 (2H, s, 3-CH_2), 2,79 (3H, s, 7-CH_3), 3,15 (2H, s, 5-CH_2), 7,49 (1H, t, 11-H), 7,60 (1H, t, 10-H), 8,36 (1H, d, J = 8,0, 9-H), 9,00 (1H, d, J = 8,0, 12-H), 11,60 (1H, s, 1-NH), 13,00 (1H, s, 8-H)
XIb	1,15 (6H, s, 4-$(CH_3)_2$), 2,05 (2H, s, 3-CH_2), 2,73 (3H, s, 7-CH_3), 2,85 (2H, s, 5-CH_2), 7,60 (1H, t, 11-H), 7,60 (1H, t, 10-H), 8,18 (1H, d, J = 8,0, 9-H), 8,50 (1H, d, J = 8,0, 12-H), 10,00 (1H, s, 1-NH)
XIc	1,20 (6-H, s, 4-$(CH_3)_2$), 2,05 (2H, s, 3-CH_2), 2,70 (3H, s, 3-CH_3), 2,80 (2H, s, 5-CH_2), 7,58...7,70 (2H, m, 10-H, 11-H), 8,18 (1H, d, J = 8,0, 9-H), 8,50 (1H, d, J = 8,0, 12-H)
XIIIa	2,43 (3H, s, 4-CH_3), 2,50 (3H, s, 3-CH_3), 3,10 (3H, s, 6-CH_3), 5,50 (1H, s, 1-NH_2), 7,44 (1H, t, 10-H), 7,59 (1H, t, 9-H), 7,79 (1H, d, J = 8,0, 8-H), 8,00 (1H, s, 2-H), 9,53 (1H, d, J = 8,0, 11-H), 13,00 (1H, s, 7-NH)
XIIIb	2,28 (3H, s, 4-CH_3), 2,42 (3H, s, 3-CH_3), 2,84 (3H, s, 6-CH_3), 5,35 (2H, s, 1-NH_2), 7,31 (1H, s, 2-H), 7,52 (1H, t, 10-H), 7,61 (1H, t, 9-H), 7,86 (1H, d, J = 8,0, 8-H), 9,02 (1H, d, J = 8,0, 11-H)
XV	2,22 (3H, s, 4-CH_3), 2,34 (3H, s, 3-CH_3), 2,48 (3H, s, 1-NH-$COCH_3$), 2,90 (3H, s, 6-CH_3), 7,55 (1H, t, 10-H), 7,69 (1H, t, 9-H), 7,91 (1H, d, J = 8,0, 8-H), 7,93 (1H, s, 2-H), 8,62 (1H, d, J = 8,0, 11-H), 10,34 (1H, s, 1-NH)

*Spectra of compounds IIa-c and IIIa were taken in CF_3COOH; spectra of compounds VII–IX, XIb,c, XIIIb, and XV were taken in $(CD_3)_2SO$; spectra of compounds XIa and XIIIa were taken in C_5D_5N.

**Signal of proton of NH group in pyrrole fragment is not manifested in CF_3COOH.

2-Bromo-3,3,6-trimethyl-1-oxo-1,2,3,4-tetrahydrobenzo[b]furo[2,3-c]quinoline (IX). To a solution of 1.58 g (5 mmoles) of the hydrochloride of Ib in 25 ml of glacial acetic acid, at room temperature, 2.28 g (5.5 mmoles) of a complex of dimethylacetamide with bromine was added in small portions. The reaction mixture was stirred for 3 h at 30°C, after which it was cooled, neutralized with an aqueous sodium acetate solution, and poured into water. The product IX was extracted with chloroform and dried over $MgSO_4$; the solvent was taken off, and the residue was chromatographed in a column with silica gel.

4,4,7-Trimethyl-1,2,3,4-tetrahydrobenzo[b]furo[2,3-c]-, Benzo[b]thieno[2,3-c]-, and Indolo[2,3-c]pyrylo[2,3-e]azepin-2-ones (XIa-c). To a mixture of 5 mmoles of compound I1-c, 6 ml of concentrated H_2SO_4 and 50 ml of chloroform, at 10°C, 5.5 mmoles of NaN_3 was added in portions over the course of 1 h while stirring. The mixture was stirred for 24 h, the chloroform was decanted off, and the residue was poured into 20 ml of water and neutralized with $NaHCO_3$. The resulting precipitate of the product XIa-c was filtered off and dried.

1-Amino-3,4,6-trimethylindolo[2,3-c]- and Benzo[b]furo[2,3-c]quinolines (XIIIa,b). The oximes Xa,b were held for 1 h at 120°C with a tenfold quantity of polyphosphoric acid. The mixture was cooled, poured into water, and neutralized with $NaHCO_3$ to pH 9; the product XIIIa,b was extracted with chloroform.

1-Acetylamino-3,4,6-trimethylbenzo[b]furo[2,3-c]quinoline (XV). To a solution of 0.1 g (0.3 mole) of compound XIIIb in glacial acetic acid, 1 ml of acetic anhydride was added. The reaction mixture was held on a water bath at 80-90°C for 0.5 h. After cooling, the precipitated product XV was filtered off.

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