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HYDROACRIDINES AND RELATED COMPOUNDS.

18.* N-SUBSTITUTED 2,3,5,6-BISTRIMETHYLENEPYRIDINES AND 2,3-TRIMETHYLENEHYDROQUINOLINES

V. A. Kaminskii, I. V. Stepanchenko, and M. N. Tilichenko

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Only a few examples of syntheses of derivatives of 2,3,5,6-bistrimethylenepyridine and 2,3-trimethylenetetrahydroquinoline are known, and no compounds substituted at the nitrogen atom have been obtained [2, 3].

We studied the reaction of 2,2'-methylenebiscyclopentanone (Ia) and 2-(2'-oxocyclopentylmethyl)cyclohexanone (Ib) with primary aromatic amines for the purpose of ascertaining the possibilities of synthesizing N-substituted derivatives of 2,3,5,6-bistrimethylenepyridine and 2,3-trimethylenetetrahydroquinoline, as well as for the purpose of comparing the reactivity of diketones Ia and Ib in the present reaction with the previously studied 2,2'-alkylidenedicyclohexanones (ADCH).

Unlike the ADCH's, diketones Ia and Ib did not react with most of the amines we chose (p-aminophenol, methyl p-aminobenzoate, p-phenylenediamine, and benzidine) with the exception of o-aminophenol and o-phenylenediamine. It was possible to isolate the products of the reaction of IIa and IIb only with o-aminophenol, and in the case of o-phenylenediamine, the reaction was accompanied by intense resinification.

Compounds IIa and IIb, like the products based on the ADCH's [4], are derivatives of oxazolinotetrahydropyridine. In their IR spectra there is no absorption due to OH groups, and their is a single absorption band of a C=C bond at 1670 cm^{-1} instead of the two characteristic of the decahydroacridines [4]. Compounds IIa and IIb, like the well-known compound IIc [4], provide solutions of methylene blue after being preliminarily converted into the dihydropyridine form A. The time for the production of the dye by compounds IIb and IIc is approximately of the same order of magnitude (IIb is somewhat faster), while compound IIa produces the dye two orders of magnitude more rapidly. Since the rate of reduction of the dye is clearly determined mainly by the rate of the opening of the oxazoline ring, it may be postulated that in the nonsymmetric compound IIb the oxazoline ring is in a spiro linkage with the cyclohexane, rather than with the cyclopentane fragment. In the latter case, the opening should be significantly easier owing to the stresses.

The reaction of diketones Ia and Ib with primary amines in the presence of an oxidizing agent, viz., carbon tetrachloride, proceeds fairly readily to form pyridinium chlorides IIIa, IIIb, and IIIe, which were converted into the respective perchlorates IVa, IVb, and IVe. We found that a convenient method for the synthesis of 4-aryl-2,3,5,6-bistrimethylenepyridinium salts (in the example of perchlorates IVc and IVd) is to react cyclopentanone, benzaldehyde, and a primary amine in a 2:1:1 molar ratio in benzene in the presence of carbon tetrachloride and p-toluenesulfonic acid. A similar method has been described for cyclohexanone [5]. The IR spectra of perchlorates IVa-IVe contain an intense absorption band of ClO_4^- at 1100 cm^{-1}, but they do not contain absorption due to C=C bonds between 1600 and 1700 cm^{-1}, and in the spectra of perchlorates IVb and IVe there is also absorption of an esteric carbonyl at 1730 cm^{-1}.

By carrying out the reduction of chlorides IIIb and IIIc (without isolating them from the reaction mixture following their synthesis) with sodium borohydride in an aqueous solution, we obtained the corresponding 1,4-dihydropyridine derivatives Va and Vb, and from chloride IIIf we obtained the known decahydroacridine Vc [6]. Thus, this method opens up possibilities for the transition from diketones Ia and Ib to compounds with a 1,4-dihydropyridine structure.

* For report 17, see [1].

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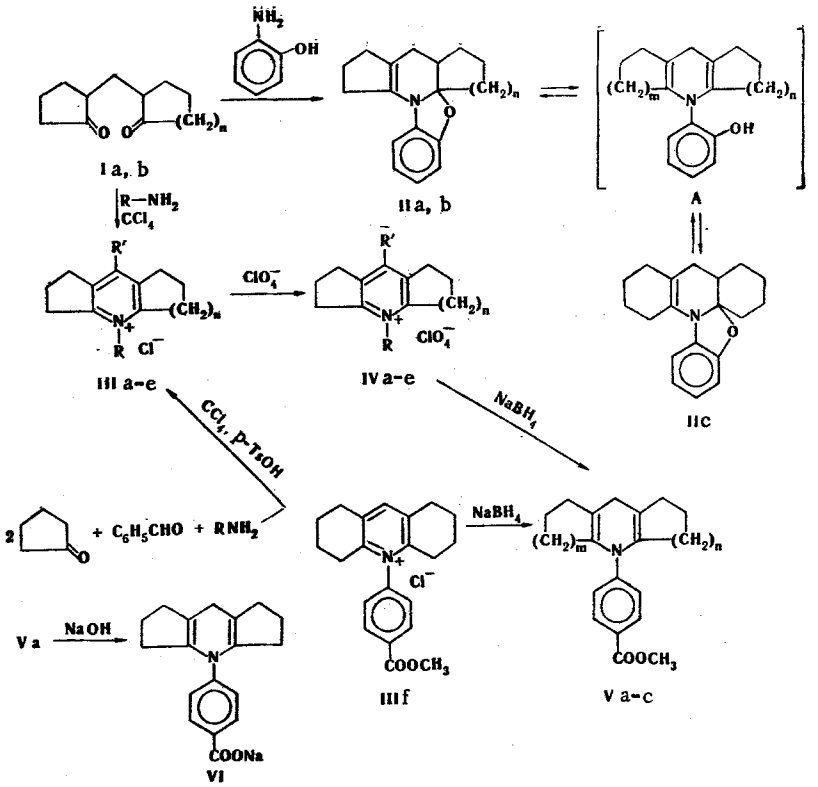

I, II a n=1; b n=2; III, IV a–d n=1; a R=C_6H_5, R′=H; b R=$C_6H_4COOCH_3$-4, R′=H; c R=R′=C_6H_5; d R=$CH_2C_6H_5$, R′=C_6H_5; e n=2, R=$C_6H_4COOCH_3$-4, R′=H; V a m=n=1; b m=1, n=2; c m=n=2

The IR spectra of compounds Va and Vb have absorption bands at 1660 and 1690 cm^{-1}, which are similar to those for decahydroacridines. In the PMR spectra there is no absorption due to vinyl protons, but there is a slightly split signal (2 H) at 2.9 ppm, which is assigned to the protons in position 4 of the dihydropyridine ring. In accordance with its structure compounds Va and Vb readily provide solutions of methylene blue.

Alkaline hydrolysis of Va yielded the water-soluble sodium salt VI. This compound readily reduces acridine to acridane and benzalaniline to benzylaniline under mild conditions and may be considered a water-soluble model of the coenzyme NADH.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in liquid petrolatum and chloroform. The PMR spectra were obtained on a Bruker HE-90X instrument, and the internal reference was TMS. The TLC was carried out on Silufol plates in a petroleum ether–ethyl acetate system (from 3:1 to 15:1). The characteristics of the compounds synthesized are presented in Table 1.

Reaction of 1,5-Diketones Ia and Ib with Primary Amines. A. A solution of 10 g of diketone Ia or Ib, a 10% molar excess of o-aminophenol, and ~50 mg of p-toluenesulfonic acid in 150 ml of benzene was boiled with a Dean–Stark trap for 1 h 30 min, the benzene was distilled off, the residue was treated with 10 ml of ethanol, and compounds IIa and IIb, respectively, were filtered off. They rapidly darken during storage in the air; however, they are fairly stable in sealed ampuls in the dark.

B. A 10-g portion of diketone Ia or Ib and an equimolar amount of the amine were boiled in a solution of 60 ml of benzene and 20 ml of CCl_4 for 10 h. The reaction mixture was extracted with water (three 50-ml portions), the aqueous extract was extracted with ether (five 20-ml portions), a solution of NH_4ClO_4 was added to the transparent aqueous layer, and perchlorates IVa, IVb, and IVe were filtered off.

4-Phenyl-1-R-2,3,5,6-bistrimethylenepyridinium Perchlorates (IVc and IVd). A solution of 20 g of cyclopentanone, 13 g of benzaldehyde, 0.12 mole of the amine, and ~100 mg of p-toluenesulfonic acid in a mixture of 200 ml of benzene, 30 ml of acetic acid, and 20 ml of CCl_4 was boiled with a Dean–Stark trap for 10 h. The mixture was extracted with water (three 50-ml portions), the aqueous layer was neutralized by a solution of

TABLE 1. Derivatives of 2,3,5,6-Bistrimethylenepyridine and 2, 3-Trimethylenehydroquinolines

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IIa	91—92	80,1	7,4	5,6	$C_{17}H_{19}NO$	80,6	7,5	5,5	64
IIb	83—84	80,9	8,3	6,0	$C_{18}H_{21}NO$	80,9	8,3	5,3	61
IVa	220—222*	61,2	5,6	4,3	$C_{17}H_{18}NClO_4$	60,7	5,4	4,2	43
IVb	148—149*	56,9	5,4	3,5	$C_{19}H_{20}NClO_6$	56,9	5,1	3,6	38
IVc	222—223	66,8	6,3	3,6	$C_{23}H_{22}NClO_4$	67,1	5,4	3,4	27
IVd	205—206	67,3	5,9	2,9	$C_{24}H_{24}NClO_4$	67,8	5,6	3,3	44
IVe	163—164*	58,2	5,8	3,0	$C_{20}H_{22}NClO_6$	58,8	5,4	3,4	46
Va	81—82	77,1	7,3	5,2	$C_{19}H_{21}NO_2$	77,3	7,1	4,8	42
Vb	70—71	76,9	7,1	5,0	$C_{20}H_{23}NO_2$	77,5	7,4	4,5	14

*From water. The remaining compounds were recrystallized from ethanol.

Na_2CO_3 and extracted with ether (10 20-ml portions), a solution of NH_4ClO_4 was added to the aqueous layer, and perchlorate IVc or IVd was filtered off.

1-(4'-Carbomethoxyphenyl)-2,3,5,6-bistrimethylene-1,4-dihydropyridine (Va) and 1-(4'-Carbomethoxyphenyl)-2,3-trimethylenehexahydroquinoline (Vb). The reaction of diketones Ia and Ib with methyl p-aminobenzoate was carried out according to variant B up to the moment preceding the addition of NH_4ClO_4. A solution of an equimolar amount of $NaBH_4$ in 20 ml of water was added dropwise with intense stirring to an aqueous solution of pyridinium chloride cooled to 5°C. This resulted in the immediate formation of a yellow precipitate of Va or Vb, which was filtered off and recrystallized from ethanol in an argon atmosphere.

Hydrolysis of Va. A solution of 2 g of dihydropyridine Va in 30 ml of absolute ethanol was hydrolyzed by an equivalent amount of 2 N NaOH in absolute ethanol with boiling for 2 h. The precipitated product VI was filtered off and washed with absolute ethanol. The yield was 90%.

Reduction of Acridine by VI. A mixture of 0.1 g acridine with a two-fold molar excess of VI in 8 ml of a 1:1 ethanol–water mixture was held for 30 min at room temperature and diluted with water. Acridine was filtered off (the yield was quantitative) and identified by the absence of melting-point depression in a mixture with a known specimen.

Reduction of Benzalaniline by VI. A solution of 0.14 g of benzalaniline and a two-fold molar excess of VI in 7 ml of ethanol was acidified by acetic acid to pH 5. After 1 h TLC showed the disappearance of the original compound, and there was only a spot corresponding to benzylaniline.

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