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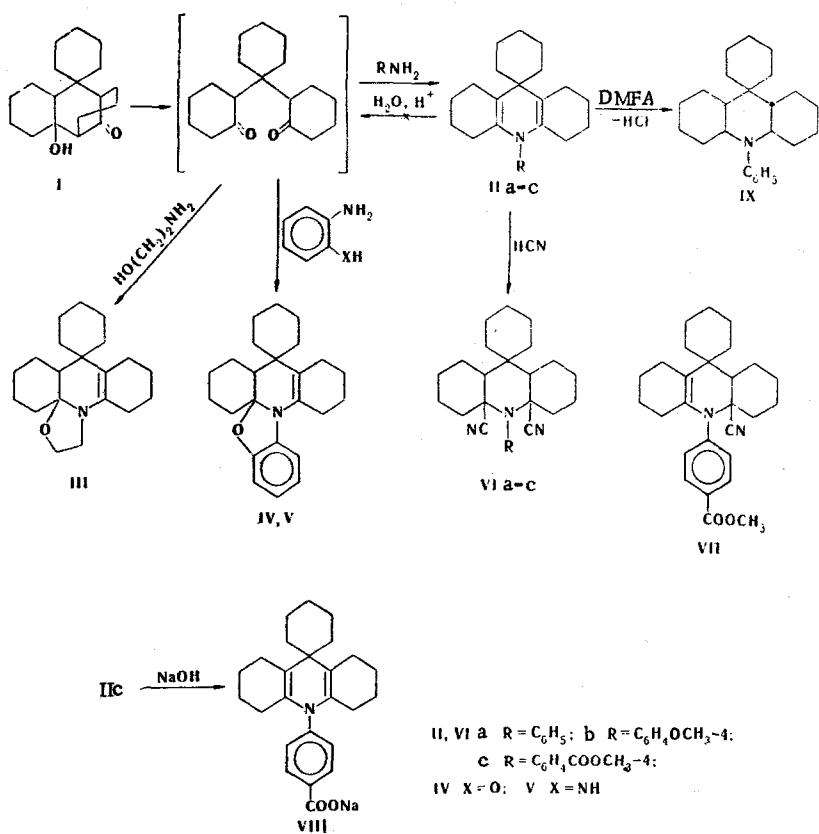
## HYDROACRIDINES AND RELATED COMPOUNDS.

### 17.\* 10-SUBSTITUTED 9,9-PENTAMETHYLENEHYDROACRIDINES

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Rather few examples of the synthesis of 4,4-disubstituted 1,4-dihydropyridines [2, 3] and only a few cases of the synthesis of such derivatives which do not contain electron-acceptor groups [4] are known.



For the purpose of obtaining and studying the properties of compounds of the latter type, we reacted the product of the trimolecular self-condensation of cyclohexanone, i.e., 8,8-pentamethylenetricyclo-[7.3.1,0<sup>2,7</sup>]-tridecan-2-ol-13-one (I) [5, 6], with primary amines. In the present reaction, ketol I behaved similarly to the previously studied self-condensation products of 1,5-diketones [7]. With aniline and its para-substituted derivatives we obtained the corresponding 10-substituted 9,9-pentamethylenedecahydroacridines (IIa-IIc), and with ethanolamine, o-aminophenol, and o-phenylenediamine we obtained products of double cyclization [8] (III-V).

\*For report 16, see [1].

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In the IR spectra of compounds IIa-IIc there are two absorption bands of the C=C bonds at 1630 and 1660  $\text{cm}^{-1}$ . The positions of the bands are shifted by 30  $\text{cm}^{-1}$  toward lower frequencies relative to the bands of the previously studied decahydroacridines [7]. This suggests that there is an increase in the extent of conjugation in the dehydropyridine ring of the compounds of type II due to the additional compression of the ring. This is supported by the fact that unlike the other decahydroacridines, the compounds of type II are resistant to acid hydrolysis. For example, compound IIa remains unchanged even during boiling with 60% sulfuric acid.

In the spectra of compounds III-V there is a single absorption band at 1650  $\text{cm}^{-1}$ . In the spectra of compounds III and IV there is no absorption of an OH group, but in the spectrum of compound V there is a single absorption band at 3400  $\text{cm}^{-1}$ , which corresponds to a secondary amino group. In the PMR spectra of compounds IIa and IIb there are no signals of vinyl protons, and this confirms the positions of the double bonds. In these spectra there is a broadened singlet (4 H) at 2.29 ppm, which can be assigned to the protons of the pentamethylene group which is located in the  $\alpha$  position relative to the dihydropyridine ring and partially deshielded by the double bonds. The mass spectra of compounds IIa and IIb provide masses of the molecular ions equal to 333 and 363, respectively. In both mass spectra there are splinter ions corresponding to M-28 and M-56, as well as m/e 28, indicating fragmentation of the two cyclohexane rings of the retrodiene type with the splitting off of two ethylene molecules.

The hydrocyanation of compounds IIa and IIb in an acetic acid-dioxane mixture at room temperature yields dicyano derivatives VIa and VIb. Under these conditions compound IIc yields unsaturated monocyanide VII, probably due to the low solubility of the latter. The hydrocyanation of IIc in an acetic acid-DMFA mixture at 80°C results in the formation of dicyanide VIc. The IR spectra of dicyanides VIa-VIc do not display absorption of double bonds, while there is absorption of cyanogen groups at 2240  $\text{cm}^{-1}$ . Monocyanide VII, on the other hand, displays absorption of a C=C bond at 1660  $\text{cm}^{-1}$ .

In accordance with their structure, compounds IIa-IIc are not oxidized by carbon tetrachloride, do not provide indigo carmine and methylene blue, and do not undergo disproportionation under the action of acids. In the last case, salts form, and stable perchlorates of IIa and IIb have been isolated from them. Their IR spectra contain absorption of  $\text{ClO}_4^-$  at 1100 and of double bonds at 1660  $\text{cm}^{-1}$ . When their solutions are alkalinized, the original compounds IIa and IIb are regenerated.

The water-soluble sodium salt VIII was obtained from IIc by alkaline hydrolysis. Along with absorption at 1630 and 1660  $\text{cm}^{-1}$  its IR spectrum has intense absorption of a carboxylate anion at 1560  $\text{cm}^{-1}$ , and the absorption of the esteric carbonyl at 1720  $\text{cm}^{-1}$ , which is present in the spectrum of IIc, is absent.

The reduction of IIa by a DMFA-conc. HCl mixture [9] produced a derivative of perhydroacridine (IX), and, as in the previously described cases [9], only one stereoisomer forms. The IR spectra of IX and its hydrochloride do not contain absorption of C=C bonds. In the PMR spectra of the compounds the 4a-H proton produces a signal in the form of a doublet of triplets with a center at 2.58 ppm, and the 10a-H proton produces a singlet at 3.37 ppm. This picture is completely analogous to the spectra of trans-anti-cis-perhydroacridine [10] and trans-anti-cis-9-methylperhydroacridine [11], allowing us to postulate the same configuration for IX. Thus, in this case, a stereoisomer different from that formed in the case of the reduction of 9-phenyldecahydroacridines under the same conditions [9], in which trans-syn-trans isomers were obtained, forms. An examination of models reveals that in the present case, the trans-anti-cis form is more stable than the trans-syn-trans form, since considerable repulsion between the hydrogen atoms of the pentamethylene group and the hydrogen atoms in positions 1 and 8 of the perhydroacridine system is observed in the latter.

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in liquid petrolatum and chloroform. The PMR spectra were obtained on a Bruker HE-90X instrument, and the internal reference was TMS. The mass spectra were measured on an MKh-1303 mass spectrometer with direct introduction of the sample into the ion source and an energy of the ionizing electrons equal to 30 eV. The purity of the preparations was monitored by TLC on Silufol in petroleum ether-ethyl acetate systems with ratios ranging from 10:1 to 2:1. The characteristics of the compounds synthesized are presented in Table 1.

Reaction of 8,8-Pentamethylenetricyclo[7,3,1,0<sup>2,7</sup>]tridecan-2-ol-13-one with Primary Amines. A mixture of 2 g of ketol I with a 10% molar excess of the corresponding amine and ~30 mg of p-toluenesulfonic acid in 30 ml of acid was boiled with a Dean-Stark trap to the cessation of the liberation of water (5-8 h). The xylene was driven off in a vacuum, the residue was crushed with 10 ml of ethanol, and compounds II-V were filtered off.

TABLE 1. 10-Substituted 9,9-Pentamethylenedehydroacridines

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIa	99-100	87.0	9.6	4.5	C <sub>24</sub> H <sub>31</sub> N	86.5	9.3	4.2	69
Perchlorate-IIa	171-173	66.6	7.5	3.2	C <sub>24</sub> H <sub>32</sub> NCIO <sub>4</sub>	66.4	7.4	3.3	62
IIb	114-115 <sup>a</sup>	82.9	9.0	4.4	C <sub>25</sub> H <sub>33</sub> NO	82.6	8.4	3.9	61
Perchlorate-IIb	131-132	65.4	7.5	2.9	C <sub>25</sub> H <sub>34</sub> NCIO <sub>5</sub>	65.7	7.4	3.0	77
IIc	121-122 <sup>a</sup>	79.6	8.1	4.0	C <sub>26</sub> H <sub>33</sub> NO <sub>2</sub>	79.8	8.4	3.6	47
III	66-67	79.8	10.5	4.9	C <sub>20</sub> H <sub>31</sub> NO	79.7	10.3	4.6	73
IV	135-136	82.6 <sup>b</sup>	—	4.7	C <sub>24</sub> H <sub>31</sub> NO	82.5	—	4.0	57
V	119-120	81.8	9.0	8.0	C <sub>24</sub> H <sub>32</sub> N <sub>2</sub>	82.7	9.2	8.1	24
VIa	200-202	80.0	9.0	10.7	C <sub>26</sub> H <sub>33</sub> N <sub>3</sub>	80.7	8.5	10.9	82
VIb	171-172	76.9	8.5	9.5	C <sub>27</sub> H <sub>35</sub> N <sub>3</sub> O	77.7	8.4	10.1	92
VIc	219-220 <sup>c</sup>	75.5	7.6	9.8	C <sub>28</sub> H <sub>35</sub> N <sub>3</sub> O <sub>2</sub>	75.5	7.9	9.4	67
VII	130-131	78.0	8.6	6.9	C <sub>27</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub>	77.5	8.4	6.7	60
VIII	260-261	75.6	7.8	3.8	C <sub>25</sub> H <sub>30</sub> NO <sub>2</sub> Na	75.2	7.5	3.5	59
IX	97-98	85.7	10.4	4.2	C <sub>24</sub> H <sub>35</sub> N	85.5	10.4	4.2	89

<sup>a</sup>From dimethylformamide. <sup>b</sup>Analysis by wet combustion. <sup>c</sup>From dioxane. The remaining compounds, except for the perchlorate of IIa, the perchlorate of IIb, and VIII, were recrystallized from ethanol.

Hydrocyanation of 9,9-Pentamethylenedehydroacridines. A. A solution of 7.6 mmole of KCN in 2 ml of water and 3 ml of acetic acid was given an addition of a solution of 1.3 mmole of IIa, IIb, or IIc in 6 ml of dioxane with stirring over the course of 1 h. The stirring was continued for 2 h, and VIa, VIb, and VII, respectively, were filtered off.

B. A solution of 7.6 mmole of KCN in 4 ml of water at 80°C was added to a solution of 2.4 mmole of IIc in a mixture of 12 ml of DMFA and 6 ml of acetic acid with stirring over the course of 30 min. The mixture was heated at this temperature for another 3 h 30 min and then cooled, and dicyanide VIc was filtered off.

Response of IIa-IIc to CCl<sub>4</sub>. A solution of 0.1 g of dehydroacridine in 1 ml of CCl<sub>4</sub> was boiled for 2 h and extracted twice with 1-ml portions of water. A solution of NH<sub>4</sub>ClO<sub>4</sub> was added to the aqueous extract. No precipitation of pyridinium perchlorates was observed.

Perchlorates of IIa and IIb. Hydrogen chloride was passed through a solution of 2 mmole of IIa or IIb in 10 ml of absolute ether, and the hygroscopic hydrochloride was filtered off, dissolved in 20 ml of water, and given an addition of a solution of NH<sub>4</sub>ClO<sub>4</sub>. The perchlorates were filtered off and purified by reprecipitation from an ethanolic solution with ethyl ether. The perchlorates indicated were also obtained after the boiling of solutions of the compounds of type II in acetic acid for 2 h (test for disproportionation) followed by dilution with water and the addition of a solution of NH<sub>4</sub>ClO<sub>4</sub>.

Sodium p-N-(9,9-Pentamethylenedehydroacridyl)benzoate (VIII). A 1-g portion (2.5 mmole) of IIc was boiled with 2.6 ml of a 0.94 N NaOH solution in absolute ethanol over the course of 2 h. The mixture was cooled, and salt VIII was filtered off and washed with absolute ethanol and ether.

10-Phenyl-9,9-pentamethyleneperyhydroacridine (IX). A mixture of 1.5 g of IIa, 9 ml of DMFA, and 3 ml of conc. HCl was heated for 10 h in an aqueous bath, cooled, and poured into 30 ml of water with stirring. After 3 h product IX was filtered off, the filtrate was alkalized with a solution of Na<sub>2</sub>CO<sub>3</sub> to pH 9, and an additional quantity of product IX was isolated.

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## HYDROACRIDINES AND RELATED COMPOUNDS.

### 18.\* N-SUBSTITUTED 2,3,5,6-BISTRIMETHYLENE PYRIDINES AND 2,3-TRIMETHYLENEHYDROQUINOLINES

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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 there is a single absorption band of a C=C bond at  $1670\text{ cm}^{-1}$  instead of the two characteristic of the dehydroacridines [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  $\text{ClO}_4^-$  at  $1100\text{ cm}^{-1}$ , but they do not contain absorption due to C=C bonds between  $1600$  and  $1700\text{ cm}^{-1}$ , and in the spectra of perchlorates IVb and IVe there is also absorption of an esteric carbonyl at  $1730\text{ cm}^{-1}$ .

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 dehydroacridine 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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