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HYDROACRIDINES AND RELATED COMPOUNDS.

# 22.* SYNTHESIS OF COMPOUND WITH 2,6-EPIDIOXYPIPERIDINE STRUCTURE

S. A. Shumakov, V. A. Kaminskii, and M. N. Tilichenko

UDC 547.821.2'831.3'832.5:541.63

The addition of hydrogen peroxide to a series of 1,4-dihydropyridine derivatives proceeds with the formation of derivatives of 6,7-dioxa-8-azabicyclo[3.2.1]octane. Such compounds may be obtained by the reaction of alicyclic 1,5-diketones with amines and hydrogen peroxide.

The nucleophilic addition to protonated 1,4-dihydropyridines (DHP) has been reported by Kuthan et al. [2, 3] but the addition of bifunctional nucleophiles to these compounds has been described only for the reaction of hydrogen peroxide to two DHP derivatives [4]. In the present work, this reaction is examined in detail.

Compounds Ia-k which are derivatives of 1,2,3,4,5,6,7,8,9,10-decahydroacridine, 1,4,5,6,7,8-hexahydroquinoline and their analogs were used as the DHP. Compounds Ic,d,f,i-k, which are reported for the first time, were obtained by the reaction of the corresponding pyridinium salts IIa-f with benzylmagnesium chloride or phenylmagnesium bromide (salt IIe which has not been described previously was prepared by the oxidation of Id using $CCl_4$). The reaction of the pyridinium salts with Grignard reagents may occur at C-2 or C-4 of the pyridinium structure [2, 3]. In our cases, this reaction proceeds only at C-4. In particular, the reaction of perchlorate IIa with phenylmagnesium bromide gave the known compound Ia, while the reaction of 1,5-diketone III with aniline gave Ih. (Formula, top, following page.)

The IR spectra of the newly synthesized DHP has C=C group bands at 1635-1645 and 1675-1685 $cm^{-1}$. This is in accord with the reported data for Ia,b, e, g. The PMR spectra of the new DHP lack signals for vinyl protons. The signals for the benzyl group protons at C-9 are at 2.68 ppm for Ii, 3.28 for Ij, and 2.85 ppm (4H) for Ik. The signal for these protons in the spectrum of Ic gives a doublet at 3.80 ppm. These findings indicate the symmetrical nature of the hydroacridine structure related to these benzyl groups. The protons at C-4 of the DHP ring in the spectra of 4-phenylsubstituted DHP If and Ih gives singlets at about 3.5 ppm (1H).

Hydrogen peroxide adds to Ia-h in the presence of acetic acid. The reaction does not proceed in the absence of this acid. The addition of sodium acetate facilitates the reaction. The role of this salt may lie in the generation of the highly nucleophilic hydroperoxide anion. The products of the reaction are cyclic aminoperoxides IVa-h, which are derivatives of 4a,10a-epidioxyperhydroacridine, 2,8a-epidioxyperhydroquinoline and their analogs. The yields of aminoperoxides IV are mostly preparative and only IVd is formed in low yield. The products of the addition of $H_2O_2$ could not be isolated in the case of DHP Ii-k and complex mixtures are formed, possibly as a result is related to the lower stability of the perhydroacridine structure with a benzyl group at C-9; this structure has definite repulsion of the hydrogen atoms in the benzyl groups and at positions 1 and 8 of hydroacridine. The instability is greater when there is a second substituent at C-9 as in Ii-k. The cyanide anion in acetic acid could be added to Ii and Ik with the formation of the corresponding derivatives of 4a,10a-dicyanoperhydroacridine Va and Vb. Cyanide ion does not add to Ij.

*For Communication 21, see [1].

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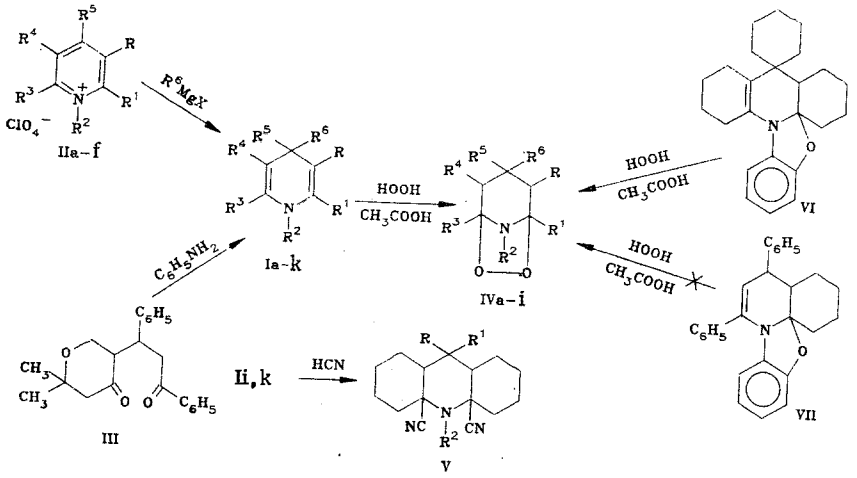


I, IV a – e R+R¹=R³+R⁴=(CH₂)₄; a R²=R⁵=C₆H₅, R⁶=H; b R²=CH₂C₆H₅, R⁵=C₆H₅, R⁶=H; c R²=C₆H₅, R⁵=CH₂C₆H₅; R⁶=H; d R²=R⁵=CH₂C₆H₅, R⁶=H; e R²=C₆H₅, R⁵+R⁶=(CH₂)₅; f R+R¹=(CH₂)₃, R³+R⁴=(CH₂)₄, R²=R⁵=C₆H₅, R⁶=H; g, h R=R⁶=H, R¹=R²=R⁵=C₆H₅; g R³+R⁴=(CH₂)₄; h R³+R⁴=CH₂C(CH₃)₂OCH₂; Ii–k R+R¹=R³+ +R⁴=(CH₂)₄; i R²=C₆H₅, R⁵=CH₃, R⁶=CH₂C₆H₅; J R²=R⁵=C₆H₅, R⁶=CH₂C₆H₅; k R²=R⁵=R⁶=CH₂C₆H₅; IIa–e R+R¹=R³+R⁴=(CH₂)₄; a R²=C₆H₅, R⁵=H; b R²=CH₂C₆H₅, R⁵=H; c R²=C₆H₅, R⁵=CH₃; d R²=R⁵=C₆H₅; e R²=R⁵=CH₂C₆H₅; f R+R¹=(CH₂)₃, R³+R⁴=(CH₂)₄, R²=C₆H₅, R⁵=H; IVi R+R¹=R³+R⁴=(CH₂)₄, R²=C₆H₄OH-*o*, R⁵+R⁶= =(CH₂)₅; V a R=CH₃, R¹=CH₂C₆H₅, R²=C₆H₅; b R=R¹=R²=CH₂C₆H₅

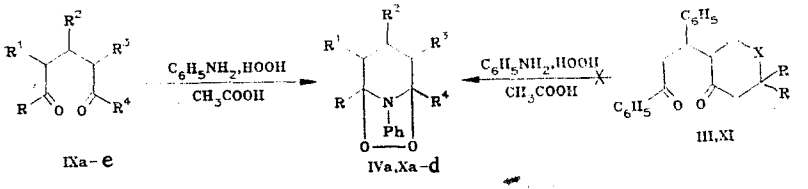
The benzoxazolinododecahydroacridine derivative VI adds $H_2O_2$ under the same conditions as Ia-h and forms aminoperoxide IVi. The benzoxazoline ring presumably initially opens up to form a DHP derivative, which is characteristic for such compounds [5]. The analogous hydroquinoline derivative VII does not react with $H_2O_2$ in accord with the greater difficulty in opening the oxazoline ring for such derivatives [5].

The reaction of DHP which are monosubstituted at C-4 with $H_2O_2$ gives the products of the oxidation of the DHP, namely, the corresponding pyridinium salts in addition to aminoperoxides IV. Salts IId and IIe were isolated as well 9-phenyl-10-benzyl- (VIIIa), 9-benzyl-10-phenyl-symm-octahydroacridinium (VIIIb), 1,4-diphenyl-2,3-trimethylene-5,6-tetramethylenepyridinium (VIIIc) and 1,2,4-triphenyl-5,6,7,8-tetrahydroquinolinium (VIIId) perchlorates in small amounts. The salt yield reached 36% only in the case of IIe.

9-Phenyl-substituted decahydroacridines Ia, Ib, and If at 35-40°C form IV almost exclusively with trans-syn-trans-perhydroacridine structure (α-IVa, α-IVb, and α-IVf). Stereoisomeric mixtures were formed upon lowering the temperature and reducing the acetic acid concentration and isomers of IVa and IVf were isolated with trans-anti-cis-perhydroacridine structure (β-IVa and β-IVf); at 10°C, the yield of these isomers reaches 60%. The second stereoisomer of IVb could not be isolated due to its instability. Isomers β-IVa and β-IVf are completely converted at 20°C in the presence of acetic acid to the corresponding α-isomers. The formation of the trans-syn-trans isomers of aminoperoxides IVa, IVb, and IVf is apparently the result of thermodynamic control, while the formation of the trans-anti-cis isomers is primarily due to kinetic control. 9-Benzyl-substituted decahydroacridine Ic under any conditions gives only one isomer of aminoperoxide IVb, which we assign trans-anti-cis configuration. An examination of the models shows that a conformation exists for this configuration with less repulsion of the hydrogen atoms of the benzyl groups at positions 1 and 8 of hydroacridine than for the trans-syn-trans configuration. Upon heating in the presence of acid, IVc is not converted. A 3:1 mixture of trans-syn-trans and trans-anti-cis aminoperoxides α-IVd and β-IVd is obtained from Id. This mixture yielded isomer β-IVd. 9,9-Pentamethylenehydroacridines Ie and VI form one stereoisomer of the corresponding aminoperoxide IVe and IVi. The configuration of these compounds was not determined by PMR spectral data but the trans-anti-cis configuration of 9,9-pentamethyleneperhydroacridine structure is known to be more stable than the trans-syn-trans structure [6]. Ig and Ih give one stereoisomer of aminoperoxides IVg and IVh. The configurations of these products were not determined.

In some cases, cyclic aminoperoxides may be obtained without isolation of the corresponding DHP by the reaction of alicyclic 1,5-diketones IXa, IXb, and IXe and their heteroanalogs IXc and IXd with primary amines (as shown for aniline) and hydrogen peroxide in the presence of acetic acid and sodium acetate (aminoperoxidation of 1,5-diketones). The aminoperoxidation

of diketone IXe gives IVa. In the other cases, aminoperoxides Xa-d are formed: these products are analogous to IV. The semicyclic 1,5-diketones III and XI do not enter this reaction since they virtually do not react with amines under mild conditions.



IXa-e IVa,Xa-d III,XI

IX, X a $R+R^1=(CH_2)_4$; a–d $R^2=H$; a, b, d $R^3+R^4=(CH_2)_4$; b $R+R^1=(CH_2)_3$; c, d $R+R^1=CH_2C(CH_3)_2OCH_2$; c $R^3+R^4=CH_2C(CH_3)_2OCH_2$; IXe $R+R^1=R^3+R^4=(CH_2)_4$, $R^2=C_6H_5$; XI R=H, X=$CH_2$

The aminoperoxidation of 1,5-diketones in some cases is preparatively more convenient than the use of DHP, especially since the separation of DHP from diketones IXa-d is often difficult. The aminoperoxidation of diketones IXa and IXe was previously carried out in the absence of acetic acid in water–ethanol [7, 8]. The reaction mechanism in this case is different than in the presence of acetic acid and most likely is analogous to that for the reaction of monoketones with hydrogen peroxide and ammonia [9] without the intermediate formation of DHP. In particular, this is indicated by the finding that Ii-k do not add $H_2O_2$ in water–ethanol in the absence of acetic acid.

The stereochemical results of the two types of aminoperoxidation are different. Thus, the reaction of diketone IXa with aniline and $H_2O_2$ in water–ethanol proceeds without affecting the chiral centers adjacent to the diketone carbonyl groups: the different stereoisomeric forms of the diketone (meso and racemic) give different stereoisomers of aminoperoxides Xa (α-Xa and β-Xa) [7]. On the other hand, in the presence of acetic acid, the result of the aminoperoxidation of both the pure racemic form of diketone IXa and a mixture of both forms is completely the same: the trans-syn-trans isomer α-Xa is formed predominantly under more vigorous conditions, while more of the trans-anti-cis isomer β-Xa is formed under milder conditions. This result is analogous to the synthesis considered above for IVa. The aminoperoxidation of diketone IXe in the presence of acetic acid leads to α-IVa and β-IVa with the same dependence on the reaction conditions as in the addition of $H_2O_2$ to Ia. The aminoperoxidation of this diketone in water–ethanol gives only isomer α-IVa [8].

The IR spectra of IV and X do not contain a band for C=C bonds above 1600 $cm^{-1}$. The spectrum of IVi has a band for the OH group at 3600 $cm^{-1}$. The spectra of IVa-h and of X lack the OH group band.

The PMR spectra of aminoperoxides α-IVa, α-IVb, and α-IVf have signals for the protons at C-9 as triplets (1H) with coupling constants close to 11 Hz at 2.67, 2.60, and 2.90 ppm, respectively, which indicates axial orientation of these protons and of the 8a-H and 9a-H protons which interact with these protons. Since the formation of the 2,6-dipiperidine structure is possible only for the cis-axial position of the oxygen atoms, this unequivocally indicates trans-syn-trans configuration of these compounds. On the other hand, the 9-H protons in the spectra of isomers β-IVa and β-IVf appear as quartets ($J_1$ = 12 and $J_2$ = 6 Hz) at 3.57 and 3.71 ppm, respectively, which indicates the nonequivalence of the 8a-H and 9a-H protons, the equatorial position of one of these protons, and, thus, trans, anti, cis configuration. The protons of the benzyl group at C-9 in the spectrum 1f IVc give separate signals, which indicates the asymmetry of the perhydroacridine structure related to the benzyl group, which should correspond to the trans, anti, cis configuration of this structure. One of these signals at 3.0 ppm (1H) is a quartet ($J_1$ = −14 and $J_2$ = 4 Hz) and the second signal at 2.37 ppm is also a quartet but not identical to the first signal ($J_1$ = −14 and $J_2$ = 12 Hz). The signals of the benzyl group protons at C-9 in the spectrum of aminoperoxide β-IVd give quartets at 2.97 and 2.35 ppm which are almost identical to those described above for IVc. The N-benzyl group protons gives doublets at 4.16 and 3.98 ppm with J = −16.5 Hz for each. In addition to the abovementioned signals for the trans,anti,cis configuration, the spectrum of a mixture of stereoisomers of IVd has a doublet (2H) at 2.78 ppm (J = 4.5 Hz) and singlet(2H) at 3.94 ppm which correspond to the benzyl group protons at C-9 and C-10, respectively, which are related to the symmetric perhydroacridine structure, i.e., have trans, syn,trans configuration.

The mass spectra of aminoperoxides α-IVa, IVb, IVh, Xc, and Xd have molecular ion peaks which correspond to the calculated molecular masses. Peaks are found with m/z M − 18 as well as very strong peaks with m/z M − 32. The IR spectra of dicyanides Va and Vb lack bands for the C=C group but have bands for the CN group at 2240 $cm^{-1}$.

## EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer for solutions in chloroform. The PMR spectra were taken on a Bruker WH-250 spectrometer with TMS as the internal standard. The mass spectra were taken on an LKB-9000 spectrometer with 70 eV ionization energy. The purity of the reagents and reaction course were monitored by thin-layer chromatography on Silufol plates. The characteristics of the compounds synthesized are given in Table 1.

Synthesis of Derivatives of 1,4-Dihydropyridine by the Reaction of Pyridinium Salts with Grignard Reactions. A sample of 100 mmoles finely ground crystalline perchlorate II was added in portions to a solution of Grignard reagent prepared from 330 mmoles magnesium and 300 mmoles $C_6H_5Br$ (A) or $C_6H_5CH_2Cl$ (B) in 400 ml abs. THF. The mixture was heated at reflux for 30 min until the perchlorate was dissolved, cooled, and 10% aq. $NH_4Cl$ was carefully added. The mixture was extracted with ether. The ethereal extract was washed with water and dried over $MgSO_4$. Ether was distilled off and the residue was recrystallized with mixtures of from 1:1 to 3:1 ethanol–ethyl acetate. Salt IIa + A gives Ia, IIa + B gives Ic, IIb + B gives Id, IIc + B gives Ii, IId + B gives Ij, IIe + B gives Ik, and IIf + A gives If. Compound Ia was identical in its IR spectrum to an authentic sample.

1,2,4-Triphenyl-7,7-dimethyl-6-oxa-1,4,5,6,7,8-hexahydroquinoline (Ih). A solution of 2 g (6 mmoles) diketone III, 1.5 g (20 mmoles) aniline, and 50 mg p-toluenesulfonic acid in 50 ml xylene was heated at reflux for 4 h until water was no longer liberated. The solvent was distilled off at reduced pressure and the residue was treated with 10 ml ethanol. The precipitate of 0.9 g unreacted diketone III was filtered off and Ih was precipitated upon maintaining the filtrate at −5°C.

Addition of Hydrogen Peroxide to 1,4-Dihydropyridine Derivatives. A. A solution of 7 g sodium acetate in 30 ml aq. $H_2O_2$ was added to a solution of 10 g I in 70 ml THF or THF–ethanol

TABLE 1. Characteristics of the Compounds Synthesized

| Compound | mp, °C | Found, % | | | Chemical formula | Calculated, % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | C | H | N | |
| Ic | 128—129 | 87,8 | 8,2 | 3,6 | $C_{26}H_{29}N$ | 87,8 | 8,2 | 3,9 | 91 |
| Id | 52—54 | 87,5 | 8,6 | 3,6 | $C_{27}H_{31}N$ | 87,8 | 3,5 | 3,8 | 57 |
| If | 72—73 | 88,1 | 8,0 | 4,5 | $C_{24}H_{25}N$ | 88,1 | 7,7 | 4,3 | 66 |
| Ih | 90—91 | 85,5 | 7,2 | 6,5 | $C_{28}H_{27}NO$ | 35,5 | 6,9 | 3,6 | 46[a] |
| Ii | 108—109 | 87,6 | 8,6 | 4,0 | $C_{27}H_{31}N$ | 87,8 | 8,5 | 3,8 | 70 |
| Ij | 169—171 | 88,7 | 8,1 | 3,2 | $C_{32}H_{33}N$ | 89,1 | 7,7 | 3,3 | 55 |
| Ik | 129—130 | 89,0 | 8,4 | 3,2 | $C_{34}H_{37}N$ | 88,8 | 8,1 | 3,1 | 63 |
| IIe | 210—211 | 69,5 | 6,7 | 3,1 | $C_{27}H_{30}ClNO_4$ | 69,3 | 6,5 | 3,0 | 72 |
| β-IVa | 152—153 | 79,7 | 7,8 | 3,8 | $C_{25}H_{29}NO_2$ | 80,0 | 7,8 | 3,7 | 60 |
| IVc | 129—130 | 80,4 | 8,1 | 3,8 | $C_{26}H_{31}NO_2$ | 80,2 | 8,0 | 3,6 | 73 |
| β-IVd | 164—166 | 80,6 | 8,1 | 3,4 | $C_{27}H_{33}NO_2$ | 80,4 | 8,2 | 3,5 | 15[b] |
| IVe | 165—166 | 78,2 | 9,1 | 3,6 | $C_{24}H_{33}NO_2$ | 78,4 | 9,1 | 3,8 | 57 |
| α-IVf | 143—144 | 79,6 | 7,6 | 4,1 | $C_{24}H_{27}NO_2$ | 79,8 | 7,5 | 3,9 | 55 |
| β-IVf | 149—150 | 79,9 | 7,9 | 3,9 | $C_{24}H_{27}NO_2$ | 79,8 | 7,5 | 3,9 | 63 |
| IVg | 118—119 | 81,3 | 6,5 | 3,9 | $C_{27}H_{27}NO_2$ | 81,6 | 6,8 | 3,5 | 87 |
| IVh | 164—165 | 79,2 | 7,2 | 3,6 | $C_{28}H_{29}NO_3$ | 78,7 | 6,8 | 3,3 | 52 |
| IVi | 166—167 | 75,4 | 8,5 | 3,9 | $C_{24}H_{33}NO_3$ | 75,2 | 8,7 | 3,7 | 30 |
| Va | 217—220 | 81,8 | 8,2 | 9,6 | $C_{29}H_{33}N_3$ | 82,2 | 7,9 | 9,9 | 78 |
| Vb | 242—245 | 84,1 | 7,8 | 8,6 | $C_{36}H_{39}N_3$ | 84,2 | 7,7 | 8,2 | 70 |
| VIIIb | 188—189 | 68,6 | 6,4 | 3,3 | $C_{26}H_{28}ClNO_4$ | 68,8 | 6,2 | 3,1 | 6[c] |
| VIIIc | 268—270 | 67,8 | 6,4 | 3,7 | $C_{24}H_{24}ClNO_4$ | 67,7 | 5,6 | 3,3 | 17[c] |
| VIIId | 211—213 | 70,2 | 5,3 | 2,9 | $C_{27}H_{24}ClNO_4$ | 70,2 | 5,2 | 3,0 | 8[c] |
| Xb | 97—98 | 76,3 | 8,4 | 4,9 | $C_{18}H_{23}NO_2$ | 75,8 | 8,1 | 4,9 | 79 |
| Xc | 122—123 | 70,2 | 8,1 | 4,1 | $C_{21}H_{29}NO_4$ | 70,4 | 8,3 | 3,9 | 81 |
| Xd | 98—99 | 73,4 | 8,3 | 4,3 | $C_{20}H_{27}NO_3$ | 73,0 | 8,2 | 4,3 | 69 |

[a]Relative to diketone III consumed. [b]Mixture of two stereoisomers. [c]As a side-product in the addition of $H_2O_2$ to the corresponding DHP.

and then 30 ml acetic acid (7 ml acetic acid in the case of β-IVa) was added. When necessary, the solution was cooled. Without cooling, the solution warms to 30-40°C. The mixture is maintained at −10°C for 20 h. In most cases, the corresponding aminoperoxide IV precipitates from the reaction mixture. The precipitate is filtered off, washed with water and recrystallized from ethanol. In order to separate β-IVa and IVc, the mixture is diluted with water and extracted with ether. The ethereal extract is washed with aq. $Na_2CO_3$ and water and dried over $MgSO_4$. Ether is distilled off and the residue is recrystallized from ethanol (IVc) or from ethanol–ethyl acetate (β-IVa). After separation of the aminoperoxides, the filtrate is diluted with water and extracted with ether. Aqueous $NH_4ClO_4$ is added to the aqueous layer and the corresponding pyridinium perchlorate is filtered off. The yields of salt were 10% (IId), 36% (IIe), and 11% (VIIIa). These compounds were identified by comparison of their IR spectra with those of authentic samples.

B. In order to obtain IVe and IVi, 10 g Ie or VI is dissolved in 60 ml hot acetic acid, cooled, and 50 ml THF is added. The mixture is cooled to −5°C and a solution of 6 g sodium acetate in 30 ml $H_2O_2$ was added. The mixture was maintained at −5°C for 15 h (in the case of Ie) or 30 h (in the case of VI). The aminoperoxide precipitate is filtered off and recrystallized from 3:1 ethanol–ethyl acetate.

Aminoperoxides α-IVa and IVb were identified by comparison of the IR spectra with those of authentic samples [8].

Aminoperoxidation of 1,5-Diketones. A sample of 5 g of a suitable 1,5-diketone was dissolved in 30 ml DMF and cooled to 5°C. The solution of 2.5 g aniline and 5 g sodium acetate in a mixture of 15 ml acetic acid and 20 ml 30% aq. $H_2O_2$ cooled to 5°C was added to the solution. In some cases, the mixing was carried out at −10°C with constant cooling; without cooling, the mixture warmed to 30°C. The mixture was maintained for 24 h at −5°C. The precipitated aminoperoxides IVa and Xa-c were filtered off and washed with water. In order to separate Xd, the mixture was diluted with water and the precipitated product was filtered off. Compound Xb was recrystallized from ethanol, while Xc and Xd were recrystallized from 3:2 ethanol–water. Compounds α-IVa and β-IVa were identified by comparion of their IR spectra with those of authentic samples. The comparison of products Xa obtained under various conditions with authentic samples of α-Xa and β-Xa [7] by thin-layer chromatography showed that α-Xa is formed predominantly at 20-30°C with a trace of β-Xa, while α-Xa appears as trace with the predominant formation of β-Xa at −10°C.

9,10-Dibenzyl-symm-octahydroacridinium Perchlorate (IIe). A solution of 1 g I in 10 ml $CCl_4$ was heated at reflux for 10 min, cooled and extracted with three 10-ml portions of water. The aqueous extract was extracted with ether. Aqueous $NH_4ClO_4$ was added to the transparent water layer and perchlorate IIe was filtered off.

9-R-o-$R^1$-10-$R^2$-4a,10a-Dicyanoperhydroacridines (Va and Vb). A solution of 0.4 g NaCN in a mixture of 1 ml water and 5 ml acetic acid was added to a solution of 1 g Ii-k in 10 ml dioxane. The mixture was heated on a water bath for 15 min. Dicyanide Vb precipitated out upon cooling. This product was filtered off, washed with water, and recrystallized from ethanol. In order to separate dicyanide Va, the mixture was diluted with water and extracted with ether. The ethereal extract was washed with water. Ether was distilled off and the residue was recrystallized from 5:1 ethanol–THF. In the case of Ij, the starting compound was recovered quantitatively after dilution of the reaction mixture with water.

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# SYNTHESIS OF 3-CYANO-4-ARYL-5-ETHOXYCARBONYL-6-METHYL-3,4-DIHYDROPYRIDINE-2-THIONES

A. A. Krauze, É. É. Liepin'sh, Yu. É. Pelcher, Z. A. Kalme, I. V. Dipan, and G. Ya. Dubur

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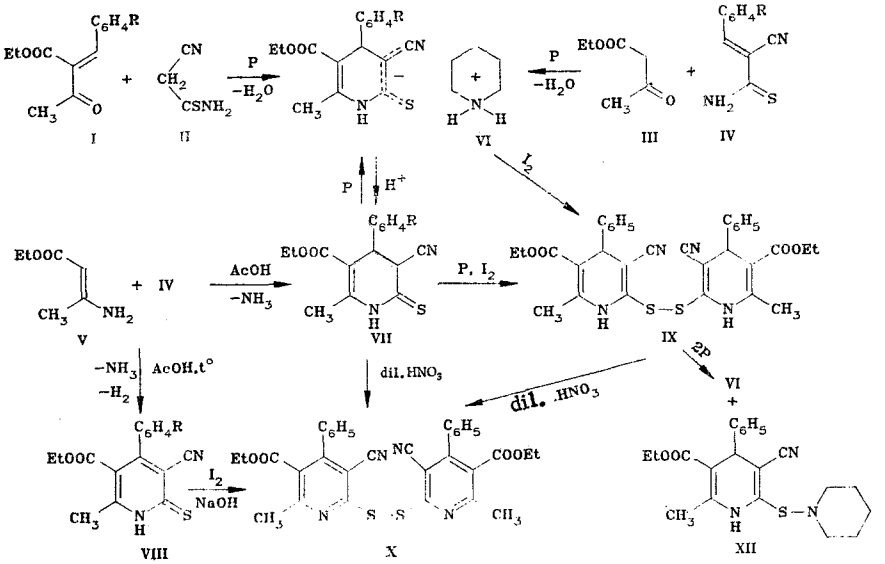
The condensation of ethyl arylidenacetoacetate with cyanothioacetamide and of arylidenecyanothioacetamides with ethyl acetoacetate or of arylidenecyanothioacetamides with ethyl β-aminocrotonate gave 3-cyano-4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones. PMR spectroscopy showed that the 3-cyano-4-aryl-3,4-dihydropyridine-2-thiones are formed as a mixture of cis and trans isomers.

In a continuation of studies on 3,4-dihydropyridine-2-thiones [1, 2], we synthesized a series of 5-ethoxycarbonyl-3,4-dihydropyridine-2-thiones. The introduction of electron-withdrawing substituents at C-3 and C-5 stabilizes 1,4-dihydropyridines, i.e., reduces their tendency to undergo oxidation to the corresponding pyridines [3]. In the present work, we sought methods of the synthesis of 3,4-dihydropyridine-2-thiones with an electron-withdrawing ethoxycarbonyl group at C-5 and the preparation of compounds more resistant toward oxidation than 3,4-dihydropyridine-2-thiones which are unsubstituted at C-5 [2].

The following methods were developed for the synthesis of 3-cyano-4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones: 1) condensation of ethyl arylidenacetoacetate I with cyanothioacetamide II, 2) condensation of ethyl acetoacetate III with arylidenecyanothioacetamide IV, and 3) condensation of ethyl β-aminocrotonate V with arylidencyanothioacetamide IV with subsequent intramolecular cyclization of the δ-keto- and δ-iminothioamides formed in the presence of bases and acids.



I, IV, VI—VIII a R=H, b R=4-$NO_2$, c R=4-Cl, d R=4-$OCH_3$, e R=4-$CH_3$, f R=4-$N(CH_3)_2$; P = piperidine

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