DISPROPORTIONATION OF N-R-DECAHYDROACRIDINES AND 14-CYANO-N-R-$\Delta^{11(12)}$-DODECAHYDROACRIDINES

V. A. Kaminskii, A. N. Saverchenko,
and M. N. Tilichenko

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N-R-Decahydroacridines, formed by the reaction of 2,2'-methylenedicyclohexanone with primary amines, disproportionate in acetic acid to form N-R-$\Delta^{11(12)}$-dodecahydroacridines and N-R-sym-octahydroacridinium salts. 14-Cyano-N-R-$\Delta^{11(12)}$-dodecahydroacridines, obtained by partial dehydrocyanation of 11,14-dicyano-N-R-perhydroacridines, undergo intermolecular redistribution of hydrogen cyanide under the same conditions.

We previously reported that 2,2'-methylenedicyclohexanone (I) reacts with aniline in acetic acid to give N-phenyl-$\Delta^{11(12)}$-dodecahydroacridine and an N-phenyl-sym-octahydroacridinium salt, and we expressed our assumption that this is the result of disproportionation of the intermediately formed N-phenyldecahydroacridine (A) [1]. We subsequently obtained the latter [2]. We subjected A to treatment with acetic acid and obtained the above-indicated disproportionation products, which confirmed our assumption. We subsequently reacted a number of other primary amines with I. In so doing, it was found that aromatic amines which do not contain electron-acceptor substituents react with I very readily at room temperature in 98% acetic acid, and the reaction proceeds like the reaction with aniline. The N-R-sym-octahydroacridinium salts were isolated as the perchlorates. Preparatively speaking, it was more convenient to isolate the products of addition of hydrogen cyanide to the N-R-$\Delta^{11(12)}$-dodecahydroacridines (II), viz., 11-cyano-N-R-perhydroacridines (IV), rather than the II themselves. Compounds IV, which were usually satisfactorily crystallized products, are isolated if aqueous NaCN is added after the reaction of the diketone with the amine. According to thin-layer chromatography, cyano compounds IV are pure substances, which serves as an indication of the stereospecificity of the disproportionation. The IR spectra of IV contain a peak at 2240 cm^{-1} ($C \equiv N$) but do not contain peaks in the double-bond absorption region. Hydrogen cyanide is split out to form the corresponding II when the cyano compounds are refluxed with 60% H_2SO_4. A peak at 1675-1680 cm^{-1} ($C=C$) appears in the IR spectrum of II. The position of the double bond was established (in the case of IIa, b) by the NMR spectra, in which vinyl proton signals are absent. The structure of IIa was also proved by hydrogenation to the known N-phenylperhydroacridine [1].

In the reaction of benzylamine with I, disproportionation occurs only on heating on a water bath. Perchlorate IIIe and nitrile IVe were also isolated here. The reaction of I with methylamine and ethanolamine gives appreciable amounts of the corresponding octahydroacridinium salts (IIIf, g) only on prolonged refluxing. However, II or IV could not be isolated in these cases since mixtures of products are formed, and resinification occurred on attempts to separate them by chromatography on Al_2O_3.

In our opinion, the more facile reaction with aromatic amines is explained by the increased stability of the N-aryl-sym-octahydroacridinium cation. However, p-nitroaniline reacts only with great difficulty with I, apparently due to its low basicity. (See scheme, top of page 1436.)

Several cases of disproportionation of nitrogen-unsubstituted 1,4-dihydropyridine derivatives to pyridine and tetrahydropyridine derivatives are known [3]. This sort of disproportionation was also noted for the reaction of I with ammonium acetate [4]. According to our data, such transformations have not. been described for N-substituted 1,4-dihydropyridine derivatives. As for the mechanism of the dispropor-

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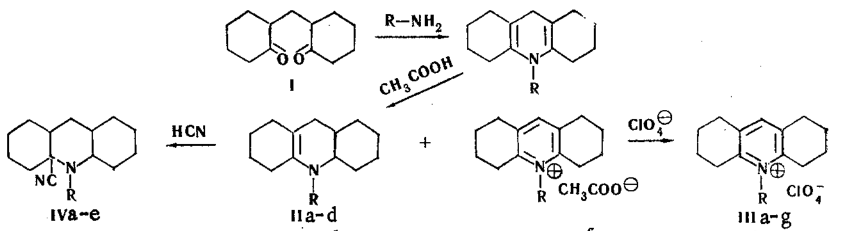
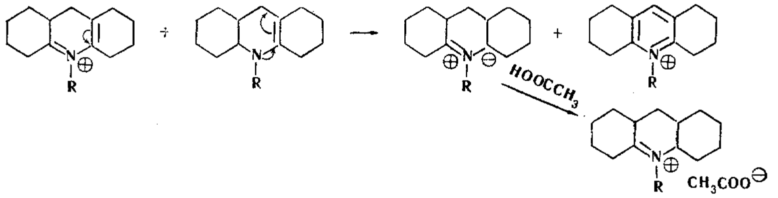


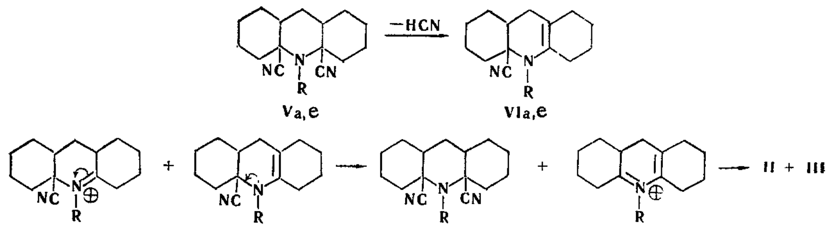
a $R=C_6H_5$; b $R=\alpha\text{-}C_{10}H_7$; c $R=\beta\text{-}C_{10}H_7$; d $R=p\text{-}CH_3OC_6H_4$; e $R=CH_2Ph$; f $R=CH_3$; g $R = HOCH_2CH_2$

tionation observed by us, we assume that, here, a hydride ion is transferred from the unprotonated form of the N-R-decahydroacridine to the protonated form.



The capacity of 1,4-dihydropyridine derivatives for hydride-ion transfer from the 4 position is well known [5]. In the given case, one can, for example, draw an analogy with reduction of α,β-unsaturated ketones by 1,4-dihydropyridine derivatives [6], where hydride-ion transfer is realized in the β position with respect to the carbonyl group.

Another transformation discovered by us – disproportionation of 14-cyano-N-R-$\Delta^{11(12)}$-dodecahydroacridines (VI) – is associated with the above-examined reaction. Compounds VI are obtained during partial dehydrocyanation of 11,14-dicyano-N-R-perhydroacridines (V) by the action of HCl in ether. Intermolecular redistribution of HCN occurs on treatment of VI with acetic acid. The reaction products are the corresponding dinitriles (V) and N-R-decahydroacridines, which, under the reaction conditions, slowly disproportionate as indicated above, so that II or IV and perchlorate III are isolated from the reaction mixture. Thus, the disproportionation reaction described for 14-cyano-$\Delta^{10(11)}$-dodecahydroacridines [7] also applies to its N-substituted derivatives. The reaction probably proceeds by cyanide-ion transfer from the unprotonated form (VI) to the protonated form.



Disproportionation of VIa also occurs in aqueous alcoholic HCl, during which diketone I and aniline are formed along with dicyano compound Va; this is apparently the result of hydrolysis of the N-phenyldecahydroacridine.

EXPERIMENTAL

Disproportionation of N-Phenyldecahydroacridine (A). Compound A (3.2 g) was dissolved at 45° in 20 ml of 98% acetic acid, and the solution was cooled and held at 20° for 2 h. It was then carefully neutralized with saturated sodium carbonate solution to pH 9, and the resulting oil was extracted with ether. The ether extract was evaporated, the residue was drenched with alcohol, and 0.9 g (56%) of crystallized IIa separated out after 1 day. Saturated NH_4ClO_4 solution was added to the aqueous layer after the extraction, and 2 g (91%) of IIIa separated out. The IIa and IIIa obtained were identical to known samples (mixed melting-point test).

Reaction of 2,2'-Methylenedicyclohexanone (I) with Primary Amines. Solutions of 0.025 mole of I in 10 ml of acetic acid and 0.030 mole of amine in 10 ml of acetic acid were mixed. Spontaneous heating of the mixture up to 10 to 15° was observed with aromatic amines, and up to 2 to 3° with benzylamine, while

TABLE 1. N-R-Hydroacridines and Cyano-N-R-hydroacridines (II-VI)

Compound	R	Mp, °C	Empirical formula	Found %			Calc. %			Yield, %
				C	H	N	C	H	N	
IIb	α-$C_{10}H_7$	113—114	$C_{23}H_{27}N$	87,1	8,7	4,7	87,1	8,5	4,4	72
IIc	β-$C_{10}H_7$	230—240 (0,1)*	$C_{23}H_{27}N$	87,1	8,7	4,6	87,1	8,5	4,4	84
IId	*p*-$CH_3OC_6H_4$	224 (0,1)*	$C_{20}H_{28}NO$	79,3	9,4	4,6	80,1	9,1	4,7	78
IIIf	CH_3	124—124,5	$C_{14}H_{20}ClNO_4$	55,8	6,5	4,6	55,6	6,6	4,6	68
IIIg	$HOCH_2CH_2$	108,5—109	$C_{15}H_{22}ClNO_5$	—	—	4,3	54,3	6,4	4,2	70
IVa	C_6H_5	112—113	$C_{20}H_{26}N_2$	81,8	8,8	10,0	81,9	8,5	9,7	96
IVb	α-$C_{10}H_7$	160—161	$C_{24}H_{28}N_2$	84,0	8,3	8,0	83,7	8,2	8,1	93
IVc	β-$C_{10}H_7$	191—192	$C_{24}H_{28}N_2$	83,7	8,5	8,0	83,7	8,2	8,1	93
IVd	*p*-$CH_3OC_6H_4$	130—131	$C_{21}H_{28}N_2O$	77,8	8,7	8,7	77,8	8,6	8,6	84
IVe	$C_6H_5CH_2$	119—120	$C_{21}H_{28}N_2$	81,9	9,3	9,4	81,8	9,1	9,1	80
Ve	$C_6H_5CH_2$	189—190	$C_{22}H_{27}N_3$	79,1	8,3	12,7	79,3	8,1	12,6	70
VIa	C_6H_5	75—76	$C_{20}H_{24}N_2$	82,3	8,3	9,7	82,2	8,2	9,6	81
VIe	$C_6H_5CH_2$	89—90	$C_{21}H_{26}N_2$	82,6	8,6	9,4	82,4	8.6	9,2	74

*bp (mm).

no spontaneous heating was observed with methylamine and ethanolamine. The mixture containing the aromatic amines was allowed to stand for 2 h at room temperature, that containing benzylamine was heated for 3 h on a water bath, while that containing methylamine or ethanolamine was refluxed for 10 h. A solution of 0.03 mole of NaCN in 7-8 ml of water was then added dropwise with water cooling and stirring. The precipitated nitriles (IVa-d) were filtered, washed with water, dried, and recrystallized from alcohol. IVe was isolated in the form of an oil; it was extracted with ether, HCl was passed through the solution, and the resulting precipitate of IVe hydrochloride was separated and dissolved in water, during which IVe crystallized out. IVa-e are white crystalline substances that are soluble in acetone and chloroform and slightly soluble in cold alcohol (Table 1). The filtrate after separation of nitriles IVa-e was made alkaline with sodium carbonate to pH 9, the slightly turbid mixture was extracted with ether, and an ammonium perchlorate solution was added to the aqueous layer. The slowly formed precipitates of perchlorates IIIa-e [8] were filtered, washed with cold water, and dried. The yields were 80-90%. In the case of methylamine and ethanolamine, where the nitriles do not precipitate, the entire reaction mixture was made alkaline with sodium carbonate, and IIIf, g (Table 1) were similarly isolated. Perchlorates IIIa-g are white, crystalline substances that are soluble in chloroform and acetone, less soluble in alcohol, and slightly soluble in water.

N-R-$\Delta^{11(12)}$-Dodecahydroacridines (IIa-d). Compound IVa-d (1 g) were refluxed with 20 ml of 60% hydrochloric acid for 2 h, the solution was cooled, the precipitate of nitrile was extracted with ether, and the aqueous layer was carefully neutralized with ammonia. Compound IIa, b crystallized out in the process and was filtered and recrystallized from alcohol. The yield of IIa (R = Ph) was 96%. Compounds IIc, d precipitated in the form of oils; these were extracted with ether and purified by vacuum distillation. They are viscous, uncrystallizable syrups that give one spot on a thin-layer chromatogram (Table 1).

14-Cyano-N-R-$\Delta^{11(12)}$-dodecahydroacridines (VIa, e) (Table 1). The starting dinitriles (Va, e) were obtained according to [2]. A mixture of 20 g of Va or Ve, 100 ml of ether, and 200 ml of concentrated HCl was refluxed for 5 h, 200 ml of water was added, and the mixture was neutralized with ammonium carbonate. The aqueous layer was decanted and the oil was drenched with 30-40 ml of alcohol. The solidified product was filtered and crystallized from alcohol. Compounds VIa and VIe are white, crystalline substances that are quite soluble in the usual organic solvents (except alcohol) and insoluble in water. The IR spectra (in CCl_4) contained peaks at 2240 ($C \equiv N$) and 1675 cm^{-1} ($C = C$).

Disproportionation of VIa and VIe. Weighed samples of Va and Ve were drenched with 2.5 wt. parts of 98% acetic acid, and the mixtures were heated for 40 min at 70-75° and cooled (a precipitate formed). A double volume of water was added, and Va (73%) or Ve (95%) was filtered. The filtrate was neutralized with sodium carbonate to pH 9, extracted with ether, and the ether was removed. The residue, in the case of VIa, was drenched with alcohol, and crystalline IIa (55%) was separated. In the case of VIe, IVe (60%) was isolated when the mixture was treated with sodium cyanide in acetic acid. Compounds IIa and IVe are identical to known samples (mixed melting-point test). A saturated ammonium perchlorate solution was added to the aqueous layer after extraction to give perchlorates IIIa (90%) or IIIe (72%).

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