HYDROACRIDINES AND RELATED COMPOUNDS.

20.* REDUCTION OF ORGANIC COMPOUNDS BY 10-SUBSTITUTED DECAHYDROACRIDINES

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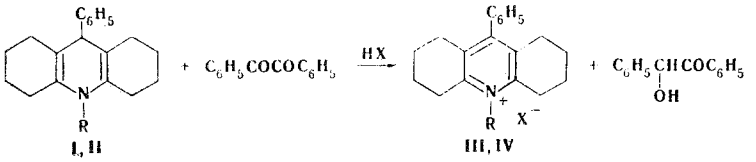
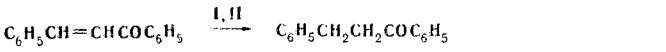
The reduction of benzil, chalcone, and acridine with 9-phenyl-10-benzyl- and 9,10-diphenyldecahydroacridines in acidic, neutral, and alkaline media was investigated. p-(10-Decahydroacridinyl)benzoic acid salts were obtained and were used to reduce a number of organic compounds under mild conditions in close-to-neutral media.

It has been shown [2] that several 10-substituted decahydroacridines reduce a number of organic compounds in the presence of strong acids, i.e., they are evidently hydride-ion donors in ionic hydrogenation. We have investigated the effect of the conditions and the structure of the decahydroacridine on the reduction and have also continued the search for convenient models of the reduced form of a redox coenzyme (NAD-H).

We studied the effect of the strength of the acid used on the reduction of benzil and chalcone by 9-phenyl-10-benzyldecahydroacridine (I) and 9,10-diphenyldecahydroacridine (II).



I, II — III, IV



I, III R = $CH_2C_6H_5$; II, IV R = C_6H_5

Compound I in the presence of HCl and CF_3COOH reduces benzil to benzoin, whereas only partial reduction is observed in the presence of CCl_3COOH, and reduction does not take place in the presence of $CH_2ClCOOH$. When CCl_3COOH was used and I was replaced by 9-unsubstituted 10-benzyldecahydroacridine, only partial reduction was observed, although it is known that 4-unsubstituted 1,4-dihydropyridines are reduced more rapidly than 4-substituted compounds [3, 4]. Equilibrium is probably reached when I is used.

Chalcone is reduced by I in the presence of HCl to benzylacetophenone; partial reduction is observed with CF_3COOH, while reduction does not take place in the presence of CCl_3COOH.

Compound II reduces benzil to benzoin only in the presence of HCl. Chalcone undergoes only partial reduction to benzylacetophenone by II when HCl is added, but it is not reduced in the presence of CF_3COOH. Thus the reductive activities of I and II decrease as the strength of the acid decreases, and I is a more active reducing agent than II. This is in agreement with the greater activity of 1-benzyl-substituted decahydroacridines as compared with the 10-phenyl-substituted compounds that was previously noted [4] in the reduction of organic dyes.

We were able to achieve partial reduction of a more easily reduced compound, viz., acridine, to acridan by means of I even in the absence of an acid; II does not reduce

*See [1] for Communication 19.

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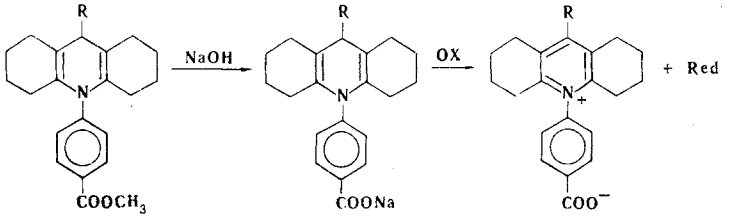
acridine under these conditions. The reductive activity of I and II is increased somewhat when an alkali is added; thus I reduces acridine completely to acridan, while II brings about partial reduction to the latter. This is possibly associated with the fact that pyridinium salts III and IV, which are formed in the oxidation of I and II, undergo further changes (ring opening) in an alkaline medium, and this shifts the equilibrium of the corresponding oxidation reaction to the right. However, the reductive activity of decahydroacridines is nevertheless considerably lower in an alkaline medium than in an acidic medium: I and II do not reduce benzalaniline, azobenzene, and nitrobenzene, which are readily reduced by II in the presence of HCl [2], in an alkaline medium. In contrast to acridine, indole is not reduced in an alkaline medium.

p-(10-Decahydroacridinyl)benzoic acid salts (VIa-c), which we obtained by alkaline hydrolysis of 9-substituted 10-(p-carbomethoxyphenyl)decahydroacridines (Va-c), proved to be considerably more convenient models of the coenzyme NAD-H than I and II.



V a-c VI a-c VII a-c

V–VII a R = H; b R = CH_3; c R = C_6H_5

Carboxylates VIa-c are considerably more active agents for the reduction of organic compounds at pH 5-9 than I and II; VIa and VIb are appreciably more active than VIc. Compounds VIa-c are soluble in water, and this makes it possible to carry out the reduction in aqueous solution. Some organic compounds are reduced by carboxylates VIa and VIb under milder conditions than in the case of the widely used model of a coenzyme, viz., the Hantzsch ester [5, 6].

The conditions and the results of the reduction of some organic substrates by VI are presented in Table 1.

Acridine and benzalaniline are reduced considerably more rapidly at pH 5-6 than at pH 8-9; on the other hand, chalcone is not reduced at pH 5-6. This is probably explained by the fact that at pH 5-6, on the one hand, the reductive activity is reduced as a consequence of conversion of the donor carboxylate group to an acceptor carboxy group (it has been shown [4] that donor groups accelerate reduction by decahydroacridines, while acceptor groups retard it); on the other hand, the reduction of benzalaniline and acridine, in contrast to the reduction of chalcone, is substantially facilitated by protonation.

In contrast to α,β-unsaturated ketones, α,β-unsaturated acids, viz., fumaric, maleic, cinnamic, and benzylidenemalonic acids, are not reduced by VI under the given conditions. We were also unable to reduce the carbonyl group in benzil and pyruvic acid.

The product of oxidation of VI are pyridinium betaines VIIa-c; we isolated betaine VIIa, the IR spectrum of which contains intense absorption at 1570 cm^{-1} (COO^-) but does not contain the absorption of a carbonyl group and double bonds at 1630-1750 cm^{-1}.

It was recently demonstrated [7, 8] that the reductive capacity of some of 1,4-dihydropyridines increases when Mg^{2+} ions and some other ions are added; the formation of a dihydropyridine—Mg^{2+}-substrate complex has been proposed [8]. We have shown that the addition of magnesium perchlorate does not affect the reductive activity of either I and II or carboxylates VI. This is possibly associated with the absence of electron-acceptor groups in the 3 and 5 positions of the dihydropyridine ring in the indicated compounds, in contrast to the examples described in the literature; such groups probably participate in the formation of the complex indicated above.

EXPERIMENTAL

The identification of the reduction products with authentic samples was carried out by mixed-melting-point determinations, by means of the IR spectra (with a UR-20 spectrometer), and by thin-layer chromatography (TLC) on Silufol in petroleum ether—ethyl acetate systems (from 10:1 to 2:1).

TABLE 1. Reduction of Organic Compounds by Carboxylates VI

Compound undergoing reduction	Reagent	Solvent*	T, °C	pH	Reduction product	Yield, %
Acridine	VIa	B	20	5—6	Acridan	60
Acridine	VIb	B	20	5—6	Acridan	70
Acridine	VIc	A	78	8—9	Acridan	—†
Chalcone	VIa	B	20	8—9	Benzylacetophenone	60
Chalcone	VIb	B	20	8—9	Benzylacetophenone	60
Chalcone	VIc	A	78	8—9	Benzylacetophenone	—†
Benzalaniline	VIa	B	20	5—6	Benzylaniline	41
Benzalaniline	VIb	B	20	5—6	Benzylaniline	75
p-Nitrosodimethylaniline	VIa	A	40	8—9	p-Phenylenediamine	—†
Benzalcyclohexanone	VIa	A	78	8—9	Benzylcyclohexanone	—†
Benzoylacrylic acid	VIa	C	100	7	Benzoylpropionic acid	70
Sodium benzoylacrylate	VIa	C	100	8—9	Benzoylpropionic acid	80

*Abbreviations: A is ethanol, B is ethanol—water, and C is water.

†According to the results of thin-layer chromatography, the substrate underwent complete reduction.

Reduction of Benzil by I and II. A 4-mmole sample of the appropriate acid (HCl, CF_3COOH, CCl_3COOH, or $CH_2ClCOOH$) and 2 mmole of I or II were added to a solution of 0.2 g (1 mmole) of benzil in 10 ml of dioxane, and the mixture was refluxed for 2 h, after which it was diluted with water, and the reaction product was liberated in the form of crystals or an oil. The crystals were identificed as benzoin when I was used in the presence of HCl or CF_3COOH and when II was used in the presence of HCl; the yields were 60, 32, and 25%, respectively. The crystals were identified as the starting benzil when I was used in the presence of $CH_2ClCOOH$ and when II was used in the presence of CF_3COOH. In the case of I and CCl_3COOH the liberated oil was identified as a mixture of benzil and benzoin from the results of thin-layer chromatography (TLC).

Reduction of Chalcone by I and II. The reduction was carried out as in the preceding method. In the case of I in the presence of HCl the reaction product was identified as benzylacetophenone in 64% yield. In the presence of CF_3COOH when both I and II were used, the product was identified as the starting chalcone. In the case of II in the presence of HCl the oily reaction product was identified as a mixture of benzylacetophenone and chalcone from TLC data.

Reduction in an Alkaline Medium. A) A mixture of 0.25 g (1.4 mmole) of acridine, 3 mmole of I or II, and 10 ml of a 10% solution of NaOH in propanol was refluxed for 2 h, after which it was diluted with water. Acridan was isolated in 80% yield in the case of I, while a mixture of acridine and acridan (from TLC data) was isolated in the case of II.

B) A mixture of 0.7 mmole of I or II, 1.4 mmole of the oxidizing agent (acridine, benzalaniline, azobenzene, nitrobenzene, or indole), and 10 ml of a 10% solution of NaOH in propanol was refluxed for 2 h, after which it was diluted with 30 ml of 10% HCl, and the mixture was extracted with ether (three 5-ml portions). A saturated solution of NH_4ClO_4 was added to the aqueous layer. In the case of acridine perchlorates III and IV precipitated in 80 and 48% yields, respectively (they were identical to genuine samples). Perchlorates were not precipitated in the case of the remaining oxidizing agents.

Reduction of Acridine in a Neutral Medium. The reduction was carried out as in method B in an alkaline medium without the addition of NaOH. Perchlorate III was isolated in 45% yield in the case of I, while perchlorate IV was not formed in the case of II.

9-Methyl-10-(p-carbomethoxyphenyl)decahydroacridine (Vb). This compound was obtained from 4-methyl-2,3-tetramethylenebicyclo[3.3.1]nonan-2-ol-9-one and methyl p-aminobenzoate as in the preparation of the previously described [2] Va and Vc. A product with mp 81-82°C (ethanol) was obtained in 68% yield. IR spectrum (in $CHCl_3$): 1660, 1690 (C=C); 1720 cm^{-1} (C=O). Found: C 78.1; H 8.1; N 4.4%. $C_{22}H_{27}NO_2$. Calculated: C 78.3; H 8.1; N 4.2%.

p-(10-Decahydroacridinyl)benzoic Acid Salts (VIa-c). A 1-g sample of Va, Vb, or Vc was dissolved in 15 ml of absolute ethanol, a strictly equivalent amount of a titrated (~1-2

N) solution of NaOH in absolute ethanol was added, and the mixture was refluxed for 2 h. The precipitated carboxylate was removed by filtration and washed with absolute ethanol, acetone, and ether. This procedure was used to obtain slightly yellowish powdery reaction products that were quite soluble in water. Compounds VIa-c were obtained in ~90% yields.

Reduction of Organic Substances by VI. A mixture of 1 mmole of the substrate and 2 mmoles of carboxylate VI in 10 ml of the appropriate solvent was maintained at the temperature and pH value indicated in Table 1 for 1-5 h (several drops of acetic acid were added to create pH 5-6). The acridan and benzylacetophenone were isolated by dilution of the reaction mixture with water. For the isolation of the benzylaniline, the reaction mixture was evaporated to 3 ml, and the concentrate was made alkaline with Na_2CO_3 solution and extracted with ether. The ether extract was chromatographed on Al_2O_3 (activity II); the benzylaniline was eluted with diethyl ether, the eluate was evaporated to 5-7 ml, HCl was bubbled through the concentrate, and the resulting precipitate was identified as benzylaniline hydrochloride. For the isolation of the benzoylpropionic acid, the reaction mixture was acidified with 10% HCl and extracted with ether (five 3-ml portions), the ether extract was evaporated, and the residue was identified as benzoylpropionic acid.

p-(10-sym-Octahydroacridinia)benzoate (VIIa). A 0.5-g (1.5 mmole) sample of carboxylate VIa and 0.55 g (3 mmole) of acridine were dissolved in 20 ml of ethanol, and the solution was refluxed for 2 h. It was then evaporated and chromatographed on Al_2O_3 (activity II). The acridan and excess acridine were eluted with acetone, after which betaine VIIa was eluted with ethanol–water (1:1) to give 0.26 g (56%) of a white crystalline substance that was readily soluble in ethanol but insoluble in ether, benzene, and DMF and had mp 262-264°C (from propanol). Found: C 78.2; N 7.2; N 4.4%. $C_{20}H_{21}NO_2$. Calculated: C 78.2; H 6.8; N 4.6%.

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