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HYDROBENZ[c]ACRIDINES AND THEIR ANALOGS BASED ON 1,5-DIKETONES*

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The reaction of 1,5-diketones containing an α-tetralone fragment with ammonia and primary amines gave hydrogenated benz[c]acridine and benzo[h]cyclopenta[b]quinoline derivatives, for which hydrocyanation, oxidation, and disproportionation reactions were studied.

Little study has been devoted to hydrogenated benz[c]acridines; biological activity has been noted for some of them [2]. Octa hydrobenz[c]acridines and derivatives with a higher degree of hydrogenation have not been described.

We have synthesized a number of derivatives of hydrobenz[c]acridines and their analogs by reaction of the accessible 1,5-diketones Ia-d and II [1] with ammonia and primary amines.

Pyridinization to give derivatives of 5,6,8,9,10,11-hexahydrobenz[c]acridine (IIIc, d) and 5,6,9,10-tetrahydro-8H-benzo[h]cyclopenta[b]quinoline (IIIa, b) occurs in the reaction of diketones Ia-d with ammonium acetate in acetic acid. Their IR spectra do not contain absorption bands in the multiple bond region.

The reaction of diketones Ia-d and II with primary aromatic amines (aniline, α-naphthylamine, and p-aminobenzoic acid) takes place more readily, since steric hindrance is absent. The IR spectra of the resulting 5,6,7,8,9,10,11,12-octahydrobenz[c]acridine derivatives (IVc-g), their oxa analog (IVh), and 5,6,7,9,10,11-hexahydro-8H-benzo[h]cyclopenta[b]quinoline derivatives (IVa, b) contain two characteristic bands at 1630-1650 (C = C conjugated with a benzene ring) and 1680-1695 cm^{-1} (unconjugated C = C). The C = O group in the spectra of IVe, g also absorbs at 1680 cm^{-1}.

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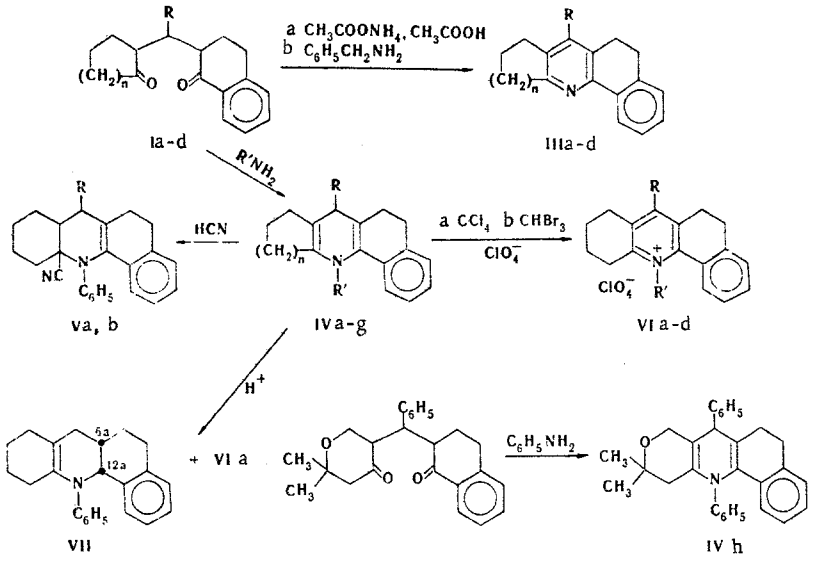
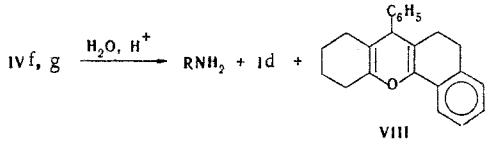


I, III a n=1, R=H; b n=1, R=C_6H_5; c n=2, R=H; d n=2, R=C_6H_5; IV a n=1, R=H, R' = α-naphthyl; e=1, R=R'=C_6H_5; c n=2, R=H, R=C_6H_5; d n=2, R=H, R'=α-naphthyl; e n=2, R=H, R'=*p*-C_6H_4COOH; f n=2, R=R'=C_6H_5; g n=2, R=C_6H_5, R'=*p*-C_6H_4COOH; V a R=H; b R=C_6H_5; VI a R=H, R'=C_6H_5; b R=H, R'=*p*-C_6H_4COOH; c R=R'=C_6H_5; d R=C_6H_5, R'=*p*-C_6H_4COOH

The PMR spectra of IV do not contain signals of vinyl protons; this provides evidence for the location of the double bonds. The spectra of IVb, f contain singlets (1H) at 4.14 and 3.79 ppm, respectively, which are related to a benzyl proton between double bonds. Signals of aromatic protons are found in the following intervals: 6.47-8.68 ppm for IVa, 6.62-8.70 ppm for IVd, 6.65-7.52 ppm for IVb, and 6.79-7.46 ppm for IVf.

The reaction of diketone Id with benzylamine is accompanied by aromatization with splitting out of toluene and leads to IIId; this is in agreement with the data in [3].

When IV are heated with aqueous solutions of acids they readily undergo decomposition to the starting diketone and amine; in the case of IVf, g, pyran derivative VIII is formed in addition to diketone Id [1].



In contrast to the previously investigated decahydroacridines (DHA) [4], IV add only one HCN molecule (in the case of IVc, f). The IR spectra of Va, b contain, in addition to absorption of a CN group at 2220 cm^{-1}, absorption of a conjugated C = C bond at 1640 cm^{-1}. Thus the conjugated double bond in IV is inactive in hydrocyanation; this can be explained both by a thermodynamic factor and by steric hindrance to the incorporation of a second cyano group.

The 1,4-dihydropyridine ring in IV is capable of undergoing oxidation by organic oxidizing agents. By determination of the time required for decolorization of methylene blue by IV, 9,10-diphenyldecahydroacridine (IXa), and 9-phenyl-10-(m-bromophenyl)decahydroacridine (IXb) we obtained the following order with respect to increasing decolorization time: IVa < IVd < IVc ≪ IVb < IXa < IXb < IVf. The introduction of a substituent in the 4 position of the dihydropyridine system to a great extent (by more than an order of magnitude) reduces the rate of decolorization (steric factor). Replacement of the six-membered ring condensed with this system by a five-membered ring facilitates oxidation.

Compounds IV are oxidized by carbon tetrachloride and bromoform as in the case of DHA [4] but under more severe conditions. The oxidation products – 7,12-disubstituted 5,6,8,9,10,11-hexahydrobenz[c]acridinium salts (VIa-d) – were also obtained by reaction of the corresponding diketones and amines in the presence of CCl_4 and $CHBr_3$. The IR spectra of salts VI do not contain absorption in the multiple bond region. The C = O absorption in the IR spectra of salts IVb and IVd is shifted to the 1720 cm^{-1} region due to the effect of a quaternary nitrogen atom. The signal of a benzyl proton at 3-4 ppm vanishes in the PMR spectrum of salt Vc. In general, the benz[c]acridine derivatives are oxidized with greater difficulty than DHA; this is due to the additional stabilization of the 1,4-dihydropyridine system by the benzene ring in the α position.

TABLE 1. Hydrobenz[c]acridines and Their Analogs

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IIIa[a]	236—240[b]	74,1	6,6	5,3	$C_{16}H_{16}NCl$	74,7	6,3	5,5	45
IIIb	129—130	88,9	7,1	4,9	$C_{22}H_{19}N$	88,9	6,4	4,7	60
IIIc[a]	194—195	75,1	6,8	6,0	$C_{17}H_{18}NCl$	75,3	6,6	5,2	42
IIId	151—153	88,4	6,9	4,7	$C_{23}H_{21}N$	88,7	6,8	4,5	95
IVa	155—160[b]	88,8	6,9	4,2	$C_{26}H_{24}N$	89,1	6,8	4,0	95
IVb	130—131	89,7	6,9	4,2	$C_{28}H_{25}N$	89,6	6,6	3,7	69
IVc	128—129	87,9	7,3	4,9	$C_{23}H_{23}N$	88,2	7,3	4,5	95
IVd	144—148	89,2	7,1	4,6	$C_{27}H_{25}N$	89,0	7,6	3,9	68
IVe	212—214[b]	80,2	6,5	3,8	$C_{24}H_{23}NO_2$	80,7	6,4	3,9	67
IVf	144—145	88,9	7,2	3,9	$C_{29}H_{27}N$	89,4	7,0	3,6	80
IVg	223—225	82,7	6,6	3,1	$C_{30}H_{27}NO_2$	83,1	6,3	3,2	70
IVh	161—163	84,8	7,0	3,9	$C_{30}H_{29}NO$	85,9	7,0	3,3	38
Va	173—174	84,7	7,0	8,2	$C_{24}H_{24}N_2$	85,5	7,4	8,8	64
Vb	228—229	85,7	6,9	6,8	$C_{30}H_{28}N_2$	86,5	6,8	6,7	31
VIa	241—242	66,3	5,5	3,7	$C_{23}H_{22}ClNO_4$	67,1	5,3	3,4	71
VIb	238—242[b]	63,3	5,5	3,3	$C_{24}H_{22}ClNO_6$	63,3	4,8	3,1	59
VIc	271[b]	70,8	5,5	3,3	$C_{29}H_{26}ClNO_4$	71,5	5,3	2,9	80
VId	328 b	69,6	4,9	2,6	$C_{30}H_{26}ClNO_6$	69,6	4,9	2,6	65
VII	102—103	86,9	8,3	4,9	$C_{29}H_{25}N$	87,6	7,9	4,4	18

[a]In the form of the hydrochloride. [b]With decomposition.

In the case of IVc we carried out the disproportionation of the 1,4-dihydropyridine ring. Disproportionation occurs when the compound is heated in dimethylformamide (DMF) saturated with dry HCl or when Ic is refluxed for a long time with aniline in acetic acid (with greater difficulty than in the case of DHA [4]). The reaction products are salt VIa and 12-phenyl-5,6,6a,7,8,9,10,11,12,12a-decahydrobenz[c]acridine (VII). The structure of VII is confirmed by the IR spectrum, which contains the absorption band of an unconjugated C = C bond at 1680 cm^{-1} but does not contain the absorption of a conjugated C = C bond at 1640-1650 cm^{-1}, and also by the PMR spectrum, which contains a doublet (1H) at 4.6 ppm (J = 4.8 Hz), which is related to 12a-H. The spin–spin coupling constant (SSCC) excludes a diaxial orientation of 6a-H and 12a-H and indicates cis ring fusion. Thus, in contrast to the hydrogenation of IV, the conjugated double bond reacts in this case; this indicates kinetic control of the disproportionation reaction. In attempts to carry out the disproportionation of IVf the principal product was pyran derivative VIII.

EXPERIMENTAL

The IR spectra of mineral oil and methylene chloride suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of deuterochloroform solutions of the compounds were recorded with a Brucker HX-90 spectrometer.

Reaction of Diketones Ia-d with Ammonium Acetate. A mixture of 5 mmole of diketone Ia-d, 40 mmole of ammonium acetate, and 10 ml of acetic acid was refluxed for 2 h, after which it was cooled and neutralized with sodium carbonate solution. In the case of diketone Id product IIId was removed by filtration and recrystallized from heptane. In the case of diketone Ib the solution was decanted from the liberated oil, and the latter was treated with ethanol. Reaction product IIIb was removed by filtration and recrystallized from acetone. In the case of diketones Ia, c the mixtures were extracted with ether, and the extract was dried, after which dry HCl was bubbled through it, and the hydrochlorides of IIIa, c were removed by filtration and recrystallized from dioxane.

Reaction of Diketones Ia-d and II with Primary Amines. A mixture of 20 mmole of the diketone, 25 mmole of the amine, 20 mg of p-toluenesulfonic acid, and 50 ml of xylene was refluxed in a flask equipped with a Dean–Stark trap (in an argon atmosphere in the case of the preparation of IVa, b, d, e) for 2-10 h until the liberation of water ceased. The xylene was then removed by evaporation at reduced pressure, and 20 ml of ethanol was added to the residue. Compounds IVa-h were removed by filtration. Reaction product IVe was recrystallized from absolute ethanol in a stream of argon, IVg was recrystallized from ethanol–water (3 : 1), and the remaining IV were recrystallized from ethanol.

Hydrocyanation of IVc, f. A solution of 1 g of IVc, f in 10 ml of dioxane was added with stirring in the course of 1 h to a solution of 1 g of KCN in a mixture of 10 ml of water and 10 ml of acetic acid, after which the mixture was stirred for 2 h in the case of IVc and 7 h in the case of IVf. It was then diluted with water, and the precipitated Va, b were removed by filtration and recrystallized from ethanol.

Reduction of Methylene Blue with IV and IX. The reduction was carried out at 20°C in DMF in an argon atmosphere at dihydropyridine–methylene blue molar ratios of 3:1 for IVa, c, d, 10:1 for IVa-d, and IXa, b, and 100:1 for IVf and IXa, b.

Oxidation of IV with Polyhalomethanes. A) A 0.5-g sample of IVc, f, g was refluxed in 10 ml of CCl_4 (with 5 ml of $CHCl_3$ in the case of IVg) for 2 h for IVc, 15 h for IVf, and 10 h for IVg, after which the mixture was cooled and extracted with water (three 5-ml portions), and the aqueous extract was washed with ether. Saturated NH_4ClO_4 solution was added to the aqueous extract, and the perchlorates of IVa, c, e were removed by filtration. Products VIa, c were recrystallized from ethanol, and VIe was recrystallized from acetone–petroleum ether (1:1).

B) A mixture of 0.5-g of IVf, 3 ml of CH_3COOH, and 1 ml of CCl_4 was heated on a water bath for 5 h, after which it was neutralized with sodium carbonate and extracted with ether. A saturated NH_4ClO_4 solution (1 ml) was added to the aqueous layer, and the perchlorate of VIc was removed by filtration. A better yield of VIc was obtained by this method than by method A.

C) A mixture of 1 g of diketone Ic, 0.5 g of p-aminobenzoic acid, 1 ml of bromoform, and 10 ml of xylene was refluxed for 4 h, after which it was cooled, and the yellow bromide was removed by filtration. It was then dissolved in water and converted to the perchlorate of VIb by treatment with a solution of $NHClO_4$; VIb was crystallized from methanol

Disproportionation of IVc. A) A mixture of 2 g of diketone Ic, 0.8 g of aniline, and 10 ml of acetic acid was heated in an argon atmosphere on a water bath for 6 h, after which it was cooled and diluted with 20 ml of 5% HCl. The mixture was extracted with ether, and the aqueous layer was made alkaline to pH 9 with sodium carbonate. The liberated oil was extracted with ether, and the ether extract was dried. The ether was evaporated, and the residue was triturated with 5 ml of ethanol. The mixture was filtered to remove VII. Treatment of the aqueous layer after extraction by the usual method gave perchlorate VIa in 42% yield.

B) A 1-g sample of IVc was heated in 15 ml of absolute DMF saturated with dry HCl on a water bath for 4 h, after which the mixture was cooled, diluted with water, and worked up as in method A to give VII in 6% yield and perchlorate VIa in 42% yield.

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