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Abstract

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STRUCTURAL AND SPATIAL DIRECTION OF THE ALUMINOHYDRIDE REDUCTION REACTION OF 1,4,4a,9a-TETRAHYDROANTHRAQUINONES

Previously we ([1]), and also Inhoffen et al. ([2]), synthesized hydroanthracene compounds of type (I, $R = \mathrm{Me}$), analogous to tetracycline antibiotics (II, $R = \mathrm{Me}$) with respect to the structure of their rings D and C. In continuing these studies we undertook the synthesis of tricyclic ketols of type (I, $R = \mathrm{H}$), which are of interest as possible intermediates for obtaining natural 6-demethyltetracyclines (II, $R = \mathrm{H}$) and related compounds. The first stage of such a synthesis, according to the scheme developed by us earlier ([3]), is the selective stereodirected reduction of the 9-keto group of 1,4,4a,9a-tetrahydroanthraquinones (III), to which the present communication is devoted.*

[[chemical structures (I) and (II)]]

On treatment of unsubstituted tetrahydroanthraquinone (IIIa) with 0.3 mole of $LiAlH_4$ in ethereal solution at 0°, one of the keto groups of the starting compound is reduced and ketol (IVa) is formed in 70% yield. The reactions of partial reduction with $LiAlH_4$ of acetoxydiketone (III), as well as of benzyloxydiketone (III), carried out in tetrahydrofuran or methylal at −60°, proceed analogously and lead, respectively, to acetoxyketol (IV) (70% yield) and benzyloxyketol (IV) (35% yield). The structure of acetoxyketol (IV) was proved by saponification of this compound with 0.05 N aqueous methanolic KOH (20°, 1 h) to the corresponding ketodiol (IV) (85% yield), in which the presence of a strong chelate structure was established spectroscopically (ν_{CO}1628 cm^{-1}), possible only when the keto group is in the peri-position relative to the phenolic hydroxyl. As for benzyloxyketol (IV), its structure was elucidated as a result of hydrogenolysis (Pd black, 20°) and subsequent acetylation (Ac_2O in Py, 20°, 2 days) to the saturated diacetoxyketone (V), also obtained from acetoxyketol (IV) through the unsaturated diacetate (IVe), which was then reduced in the presence of PdO.

Concerning the spatial structure of ketols (IVa)–(IV), it could be assumed that these compounds have a cis,cis arrangement of the H atoms at C_{4a}, C_{9a}, and C_9, since the starting naphthoquinone-butadiene adducts (III), according to Alder' s rule ([5]), have cis fusion of rings B and C, while reduction of ketones with $LiAlH_4$ usually proceeds by addition of the hydride ion from the least screened

side of the CO group and is not accompanied by epimerization of asymmetric centers in the α-position to the carbonyl being reduced (cf., for example, ([6])). The correctness of this assumption was confirmed by us using ketol (IVa) as an example in the following way. By the action of Ac_2O in pyridine (20°, 2 days)

* The synthesis of the starting diketones (IIIa)–(III) has already been described earlier ([1,4]). Compound (III) was obtained by us by benzylation of oxydiketone (III) with $PhCH_2Br$ and Ag_2O in chloroform (20°, 4 h; yield 75%), and also by condensation of 5-benzyloxynaphthoquinone with butadiene in benzene at 100° (yield 35%).

ketol (IVa) was converted into acetate (IVd) (yield 90%), which was then oxidized with BzO_2H in chloroform (20°, 24 h) to 2,3-epoxyketoacetate (VI) (yield 80%). The latter, on heating with an alcoholic solution of EtONa (80°, 4 h), underwent alcoholysis of the acetoxy group and intramolecular opening of the 2,3-oxide ring with formation of 3,9-epoxyketol (VII) (yield 50%; ν_{CO} 1696 cm^{-1}, ν_{OH} 3420 cm^{-1}). The structure of the epoxy ketol obtained was proved by its oxidation with CrO_3 in acetic acid (30°, 1 h) to epoxydiketone (VIII) (yield 75%; ν_{CO} 1695 and 1735 cm^{-1}), which, on condensation with MeMgI and subsequent dehydration with H_3PO_4, gave 3,9-dimethylanthracene, identified by thin-layer chromatography on Al_2O_3. As consideration of molecular models of compounds (VI)–(VIII) shows, formation of the 3,9-oxide bridge is possible only with cis,cis orientation of the hydrogen atoms in positions 4a, 9, 9a and anti configuration of the 2,3-epoxy group; hence follow the spatial formulas of all the substances obtained.

Further reduction of compounds of type (IV), or direct reduction of the starting diketones (III) with excess $LiAlH_4$, gives the corresponding glycols in good yield. Thus, on treatment of tetrahydroanthraquinone (IIIa) with 1 mole of $LiAlH_4$ in tetrahydrofuran (20°, 17 h), two stereoisomeric diols (IX) and (X) are formed (total yield 60%) in an approximate ratio of 2 : 1. The configuration of these diols was established on the basis of the equivalence of both OH groups in the molecule of the cis-diol (IX), which is a completely compensated meso form, and the stereochemical nonequivalence of these hydroxyls in the trans isomer (X), which was proved as follows. Acetoxyketone (IVd) was reduced with 1 equiv. of $LiAlH_4$ in tetrahydrofuran (−60°, 2.5 h) to oxyacetate (XIIa) (yield 80%), which has the same configuration as glycol (IX), since it can be saponified to it with 1 N alcoholic KOH (20°, 24 h; yield 60%). This oxyacetate, by condensation with dihydropyran in the presence of $POCl_3$ (20°, 24 h), was converted into acetoxycetal (XIIb) (yield 65%), which was saponified with 1 N alcoholic KOH (20°, 3 days) to oxyacetal (XV) (yield 70%) and then oxidized with CrO_3 in pyridine (20°, 24 h) to ketoacetal (XVI) (yield 65%). The latter proved identical with ketoacetal (XIIIa), obtained directly from ketol (IVa) and dihydropyran in the presence of $POCl_3$ (20°, 6 h; yield 65%), whence follows the equivalence of the relative configurations (XIIIa) and (XVI), possible only with cis,cis,cis arrangement of 9H, 9aH, 4aH, 10H in the molecules of diol (IX) and its derivatives (XII) and (XV).

On the other hand, ketoacetal (XIIIa) was reduced with $LiAlH_4$ in tetrahydrofuran (20°, 3 h) to oxyacetal (XIa) (yield 80%), configurationally corresponding to glycol (X), since it is converted into it on hydrolysis with 0.5% aqueous-alcoholic HCl (50°, 2 h; yield 65%). From oxyacetal (XIa), by the action of α-naphthyl isocyanate in toluene in the presence of Et_3N (100°, 3 h), acetal urethane (XIb) was obtained (yield 75%), which was hydrolyzed with 0.5% aqueous-alcoholic HCl (3 h at 50°, then 2 days at 20°) to oxyurethane (XIV) (yield 65%), further oxidized with CrO_3 in acetic

acid (30°, 30 min) into ketourethane (XVII) (yield 40%). The substance obtained proved to be isomeric, but not identical, with ketourethane (XIIIb), formed upon acylation of the starting ketol (IVa) with α-naphthyl isocyanate in toluene in the presence of Et_3N (100°, 5 h, yield 65%). Since the sole reason for the nonidentity of ketourethanes (XIIIb) and (XVII) is the difference in the configuration of their asymmetric centers 9 (on the stability of the cis fusion of rings B and C, see below), these transformations prove the trans arrangement of the hydroxy groups in glycol (X), thereby confirming the conclusion made above concerning the cis configuration of (IX), the principal product of complete aluminum hydride reduction of diketone (IIIa).

[Reaction scheme shown with compounds (IX), (X), (XIa): R = H, (XIb): R = $CONHC_{10}H_7$, (XIIa): R = H, (XIIb): R = THP, (IVd): R = Ac, (XIIIa): R = THP, (XIIIb): R = $CONHC_{10}H_7$, (XIV), (XV), (XVI), and (XVII); the interconversion arrows are indicated in the scheme, with (IIIa) shown above the equilibrium between (IX) and (X).]

Thus, the first stage of aluminum hydride reduction of tetrahydroanthracenes (III) proceeds mainly according to Cram' s rule ([7]), whereas in the second stage of the reaction (conversion of ketols (IV) into the corresponding glycols) there is sometimes a considerable, or even predominant, formation of products of the "anomalous" addition of hydrogen from the more shielded side of the C=O bond. Apparently this is explained by the fact that, in the transiently formed alcoholate (XVIII), or in the corresponding coordination complex of the type $>C_9H\cdots O(R) \rightarrow Al(H)<$, the keto group can be reduced not only by an "external" hydride attacking in the direction of the least steric hindrance (reaction *a*), but also intramolecularly, as a result of addition of the alkoxyaluminum hydride H from the sterically hindered α region (reaction *b*). Similar complex formation of $LiAlH_4$ with an ether oxygen atom also exerts a substantial influence on the structural direction of the partial reduction of diketones of type (III, R = OAlk). It may be assumed that precisely this accounts for the low selectivity of reduction of 9-CO in the case of benzyloxydiketone (III) (see above), since here coordination of $LiAlH_4$ at the ether O atom facilitates the reaction of reduction of 10-CO, compensating the steric shielding.* For the same reason, in compounds of type (III, R = OMe), the carbonyl located peri to the methoxy group preferentially enters into the Grignard reaction ([1]). Such complex formation, however, loses its significance (or does not occur at all) in compounds containing, instead of a simple ether group, an ester grouping. Thus, in the

already mentioned reduction of acetoxyketone (IV), hydride ion adds from the less shielded side, while under the action of 1 equiv of $LiAlH_4$ on acetoxydiketone (III) or β-hydrojuglone acetate (XIX), selective reduction (up to 70%) of the sterically unhindered car-

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* The shielding of C_{10} is indicated, in particular, by the fact that, upon treatment of benzyloxydiketone (III) with aluminum isopropylate, which has a larger effective volume than $LiAlH_4$, predominantly the 9-CO group undergoes reduction and benzyloxyketol (IV) is formed in 55% yield.

bonyl without affecting the keto group adjacent to the acetoxyl. In this connection, the previously expressed hypothesis[2] concerning the activating influence of the 4-acetoxy group (through its coordination with $LiAlH_4$) on alumohydride reduction of 10-CO in compounds of type (XX) appears to be erroneous. In fact, in these compounds, in contrast to acetoxydiketones (IIIb) and (XIX), the OAc group is not coplanar with 10-CO, but is spatially brought close to C_9,

Table 1

Compound	M.p., °C	Solvent for crystallization	Found, % C	Found, % H	Calculated, % C	Calculated, % H
IIIg	116–117	EtOH	79.10	5.71	79.22	5.70
IVa	141–142	EtOH	78.47	6.77	78.48	6.59
IVb	138–139	EtOH	72.56	6.17	73.02	6.13
IVv	136–137	EtOH	70.25	5.74	70.57	5.92
IVg	160–161	PhMe	78.74	6.38	78.72	6.29
IVd	95–96	MeOH – C_6H_{14}	75.15	6.17	74.98	6.29
IVe	125–127	EtOH	68.74	5.84	68.78	5.78
V	95–97	EtOH	68.10	6.45	68.34	6.37
VI	117–118	EtOH	70.31	5.71	70.57	5.92
VII	122–124	C_6H_6	72.82	6.12	73.02	6.13
VIII	149–151	EtOH	73.36	5.14	73.67	5.30
IX	124–125	C_6H_6	77.55	7.52	77.75	7.46
X	240–241	Dioxane	77.75	7.52	77.75	7.46
XIa	101–103	Pr_2O	75.78	8.18	75.98	8.05
XIb	166–168	EtOH	76.48	6.63	76.73	6.65
XIIa	120–121	C_6H_6	74.42	7.02	74.39	7.02
XIIb	104–106	EtOH	73.39	7.71	73.66	7.66
XIIIa=XVII	134–137	EtOH	76.43	7.46	76.48	7.43

structures XVIII, XIX, XX

Figure 1: structures XVIII, XIX, XX

Compound	M.p., °C	Solvent for crystallization	Found, %	Found, %	Calculated, %	Calculated, %
XIIIb	146–148	EtOH	78.03	5.40	78.31	5.52
XIV	153–155	Pr_2O	78.02	6.01	77.90	6.01
XV	111–114	Pr_2O	75.90	8.01	75.97	8.05
XVII	156–158	EtOH	78.49	5.41	78.31	5.58

with C_9, as a result of which it seems more probable that not activation of 10-CO, but deactivation of 9-CO, occurs.

An interesting stereochemical feature of compounds (IV) is the high stability of their *cis* junction of rings *B* and *C* under conditions that provide the possibility of prototropic *cis* trans-*B/C* isomerization. Thus, the ketoacetal (XIIIa) does not epimerize upon boiling for 1 hour with a 5% EtONa solution (regeneration more than 70%), while the acetoxyketone (IVd) is smoothly saponified to the ketol (IVa) (yield 60%) under the action of 1% alcoholic KOH (20°, 24 hours). These data indicate the thermodynamic favorability of the 4a,9a-*cis* configuration (IV) as compared with the corresponding trans configuration, which is probably caused by interaction of 9a-OH(OR) with the double bond of ring *B*.

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Note: Figure translations are in progress. See original paper for figures.