TETRACYCLINES

COMMUNICATION 20. CONFIGURATION OF 2- AND 3-SUBSTITUTED 10-KETO-9-HYDROXY-1,2,3,4,4a,9,9a,10-OCTAHYDROANTHRACENES [1,2,3,4,4a,9a-HEXAHYDRO-10-HYDROXYANTHRONES], AND THE STEREOCHEMISTRY OF THE REDUCTION OF NAPHTHOQUINONE-BUTADIENE ADDUCTS WITH LITHIUM ALUMINUM HYDRIDE

(UDC 542.19 + 615.779.931)

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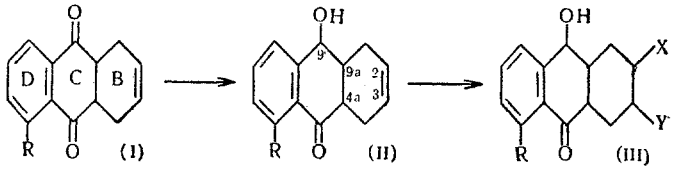
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 492-501, March, 1964
Original article submitted October 4, 1962

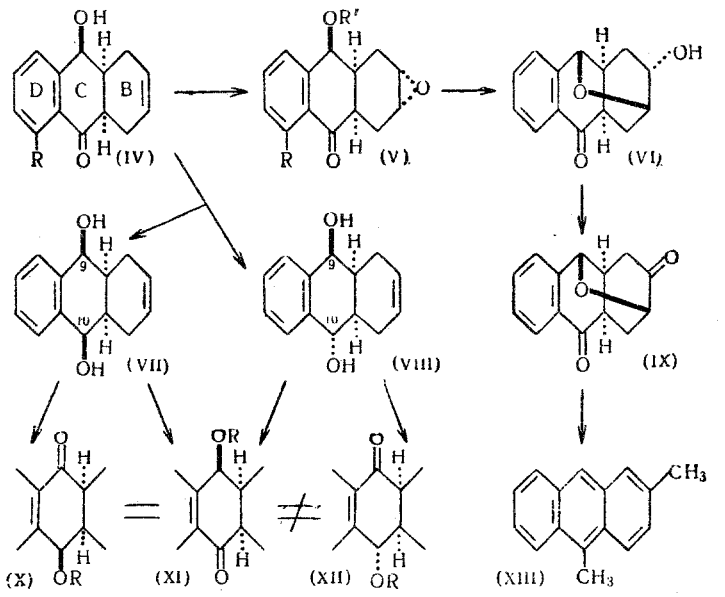
In the course of a search for ways of synthesizing substances allied to 6-demethyltetracyclines we carried out the selective reduction of naphthoquinone-butadiene adducts (I) with lithium aluminum hydride into the hydroxy ketones (II) and the conversion of the latter into various compounds of general formula (III). It was shown also that the configurations of all the substances obtained can be deduced if the steric structure is known for the 2,3-epoxides (III; X + Y = O <), which are formed by the oxidation of the hydroxy ketones (II) with peroxybenzoic acid [1]. Hence, to resolve the question of the steric structures of the compounds synthesized it was necessary to prove the configuration of these epoxides.



R = H, OH, OAc, OCH_2Ph ; X and (or) Y = H, Hal, OH, O=, O<

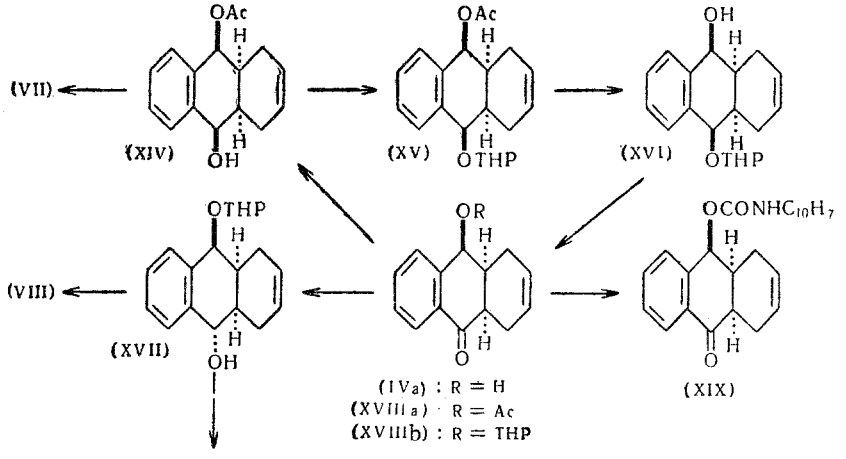
On the basis of the method of synthesizing the epoxides (III; X + Y = O <), it could be supposed that they have a cis,cis-arrangement of the 4a-, 9a-, and 9-hydrogen atoms and an anti orientation of the epoxy ring. The original adducts (I), in agreement with the known rule for the diene synthesis, should have cis-fusion of the B and C rings, and the reduction of ketones with $LiAlH_4$ usually proceeds by the addition of a hydride ion from the less screened side of the keto group and is not accompanied by the epimerization of asymmetric centers (cf., e.g., [2]), as a result of which the hydroxy ketones (II) may be assigned the steric formula (IV). The epoxidation of the hydroxy ketones (IV) goes highly stereospecifically, from which it follows that one side of their 2,3-double bond is strongly screened; since this screening is brought about by the groups of the C-ring disposed in the β-region, it seemed very probable that the oxidant adds from the α-region and the reaction product has the configuration (V).

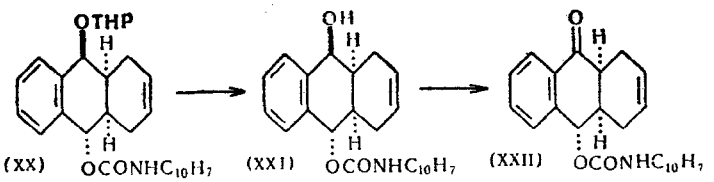
The correctness of this conclusion was confirmed for the case of the acetoxy epoxide (V; R = H, R' = Ac) by converting it into the 3,9-epoxy hydroxy ketone (VI) by heating it with alcoholic EtONa. The presence of a 3,9-epoxy bridge in (VI) was established by its oxidation to the epoxy diketone (IX), whose structure was proved spectroscopically and also by condensation with MeMgI followed by dehydration with H_3PO_4 into 3,9-dimethylanthracene (XIII). The rigid ring structure of (VI) and (IX) permits only one configuration of the angular asymmetric centers, a cis,cis,cis-arrangement of the 3-, 4a-, 9a-, and 9-H atoms, and the character of the reaction leading to the formation of (VI) (alcoholysis of the 9β-acetoxy group and intramolecular nucleophilic opening of the 2,3-epoxy ring) shows that in (V) the epoxy ring is the trans-position to the 9β-O atom, i.e., has the 2,3α-configuration.



The hydroxy ketones (IV) are the products of the first stage of the reduction of the diketones (I) with lithium aluminum hydride. Under the further action of $LiAlH_4$ they are converted into the corresponding diols, and the determination of the configuration of these presents interest for the study of the stereochemistry of reduction with $LiAlH_4$ in this series of compounds. In view of this we investigated the two stereoisomeric diols (VII) and (VIII) which are formed in approximately 2 : 1 proportions in the further reduction of the hydroxy ketone (IV; R = H) or, more simply, in the complete reduction of the diketone (I; R = H) with $LiAlH_4$. The determination of the configuration of these diols was based on the fact that the first of them (VII) is a fully compensated meso form, whereas in the second (VIII) the hydroxy groups are stereochemically nonequivalent, so that protection of 9-OH and oxidation of 10-OH and, on the other hand, protection of 10-OH and oxidation of 9-OH should lead in the case of the cis isomer (VII) to the same substituted-hydroxy ketone (X) = (XI), whereas in the case of the trans isomer (VIII) it should lead to two different compounds (XI) ≠ (XII). The experimental proof of the configurations of the diols (VII) and (VIII) was carried out as follows.

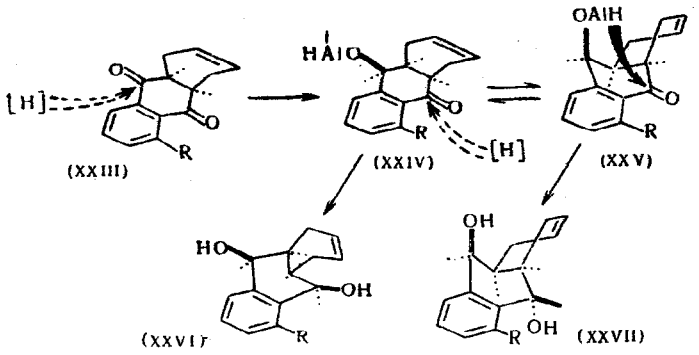
The acetoxy ketone (XVIIIa), prepared from the hydroxy ketone (IVa) by the action of Ac_2O in pyridine [1], was reduced with one equivalent of $LiAlH_4$ to the acetoxy alcohol (XIV), which has the same configuration as the diol (VII) since it is converted into (VII) by hydrolysis with 1 N KOH. By condensation with dihydropyran in presence of $POCl_3$ this acetoxy alcohol was converted into the acetoxy acetal (XV), which was then hydrolyzed with alkali to the hydroxy acetal (XVI). Oxidation of the latter with CrO_3 in pyridine gave the keto acetal (XVIIIb), which was obtained previously by the condensation of the hydroxy ketone (IVa) with hydropyran [1], from which it follows that the diol has a completely cis configuration.





On the other hand, by the reduction of the keto acetal (XVIIIb) with excess of $LiAlH_4$ we obtained the hydroxy acetal (XVII), which corresponds configuratively to the diol (VIII) since it is converted into it by hydrolysis with 0.5% HCl. Acylation of the hydroxy acetal (XVII) with 1-naphthyl isocyanate in presence of triethylamine led to the acetal urethan (XX), which was then hydrolyzed with aqueous-alcoholic HCl to the hydroxy urethan (XXI). On oxidation of this hydroxy urethan we obtained the keto urethan (XXII), which was found to be isomeric to the keto urethan (XIX) formed by the acylation of the hydroxy ketone (IVa) with 1-naphthyl isocyanate. Since the only source of the nonidentity of the keto urethans (XIX) and (XXII) is the difference in the configurations of their asymmetric centers, which are attached to the acylated hydroxy group (with regard to the stability of the cis-fusion of the B and C rings see below), these transformations prove the trans-arrangement of the OH groups in the diol (VIII) and so confirm the conclusion reached above regarding the cis-configuration of the diol (VII), which is the main product of the complete reduction of the diketone (I; R = H) with lithium aluminum hydride.

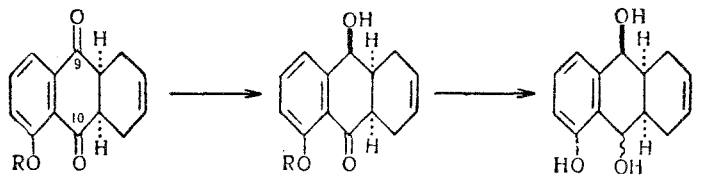
Hence, the first stage of the reduction of the adducts (I) with lithium aluminum hydride goes mainly* by Cram's rule [3] – by the addition of the hydride ion from the side of the angular H atoms – whereas in the further reduction of the hydroxy ketone (IVa) a considerable amount is formed of the product of abnormal addition of hydrogen from the more screened side of the molecule. This is probably to be explained on the view that the reduction of the alkoxide (XXIV) that is formed at first may proceed by two mechanisms: 1) by the addition of "external" hydride, attacking from the α-region from the least sterically hindered side [the reaction (XXIV) → (XXVI), analogous to (XXIII) → (XXIV)], which leads to the normal reduction product – the cis-diol (VII) = (XXVI) – and 2) intramolecularly – by the conversion of the C ring and the addition of alkoxyaluminum hydride H from the sterically hindered β-region [(XXIV) → (XXV) → (XXVII)], as a result of which the trans-diol (VIII) = (XXVII) is formed.



This hypothesis enables us also to explain the steric orientation which holds in the $LiAlH_4$ reduction of O_9-derivatives of the hydroxy ketone (IVa) – its acetate (XVIIIa) and tetrahydropyranyl derivative (XVIIIb). As already stated, the first of these reactions leads to the monoacetate of the cis-diol (XIV) (80% yield) and therefore goes similarly to the conversion (XXIV) → (XXVI). In the second reaction, on the other hand, an 80% yield is obtained of the derivative of the trans-diol (XVII), which is evidently brought about by the formation of a coordination complex of the type $\gtrdot C_9 - O(R) \cdots Al(H) \lessdot$ and by further intramolecular reduction, similar to (XXIV) → (XXV) → (XXVII).

The complex formation of $LiAlH_4$ with an ether oxygen atom has a substantial effect also on structural orientation in the partial reduction of the diketones (XXVIII; R = Alk). It may be supposed that it is just this which explains the lower selectivity of the reduction of 9-CO in the case of the benzyloxy diketone (XXVIIIa) [the yield of the hydroxy ketone (XXIXa) is 35%], because here the coordination of $LiAlH_4$ at the ether O atom facilitates the reduction

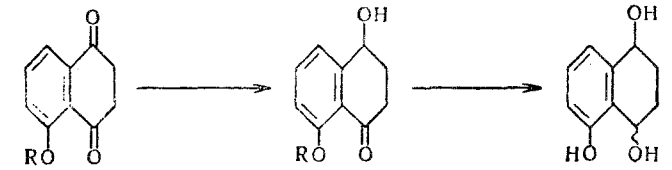
* The hydroxy ketones (IV; R = H) and (IV; R = OAc) are formed from the adducts (I; R = H) and (I; R = OAc) in about 70% yield.



(XXVIIIa) : R = CH_2Ph
(XXVIIIb) : R = Me
(XXVIIIc) : R = Ac

(XXIXa) : R = CH_2Ph
(XXIXb) : R = Ac

(XXX)



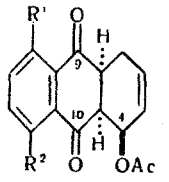
(XXXIa) : R = H
(XXXIb) : R = Ac

(XXXIIa) : R = H
(XXXIIb) : R = Ac

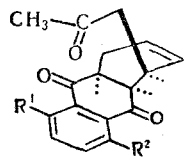
(XXXIII)

of the 10-keto group, compensating for its screening by the alkoxy group.* For this reason, in compounds of the type (XXVIIIb) it is the carbonyl in the peri position to the methoxy group that preferentially undergoes the Grignard reaction [4].

Such complex formation, however, loses its significance or does not occur at all in compounds with an ester in place of an ether grouping. Thus, in the reaction of $LiAlH_4$ with the acetoxy diketones (XXVIIIc) and (XXXIb) there first occurs the selective reduction of the sterically unhindered carbonyl with formation of the hydroxy ketones (XXIXb) [1] and (XXXIIb), and only with the further action of $LiAlH_4$ does the reduction occur of the keto group adjacent to the acetoxy group (which is then eliminated), resulting in the formation of the triols (XXX) and (XXXIII). In view of this the previously expressed view [5] of the activating effect of a 4β-acetoxy group (by its coordination with $LiAlH_4$) on the $LiAlH_4$ reduction of 10-CO in compounds of the type (XXXIV) would appear to be erroneous. In these compounds, unlike the acetoxy diketones (XXVIIIc) and (XXXIb), the acetoxy group is not coplanar with 10-CO, but is spatially close to the C-9 atom [cf. the conformation (XXXV)], so that here a deactivated 9-CO is more probable than an activated 10-CO.



(XXXIV)



(XXXV)

An interesting stereochemical peculiarity of hydroxy ketones of type (IV) and their $O_{(9)}$-derivatives is the high stability of the cis annelation of the B and C rings under conditions that ensure the possibility of prototropic cis ⇌ trans B–C isomerization. For example, the keto acetal (XVIIIb) is not epimerized when boiled with sodium ethoxide solution, but the acetoxy ketone (XVIIIa) is hydrolyzed smoothly into the hydroxy ketone (IVa) under the action of alcoholic KOH. Such behavior undoubtedly indicates the thermodynamic favorability of the 4a,9a-cis configuration of compounds of type (IV), as compared with the corresponding trans configuration, which distinguishes these substances sharply from most other alicyclic ketones, in which it is usually the trans isomers that are the more stable (cf. the classical example of the α-decalones). In the C ring of the hydroxy ketones (IV) there are three trigonal carbon atoms, so that the atoms of this ring, with the exception of C-9a, must be in the same, or almost the same, plane, like the C atoms of a five-membered ring. However, this conformational peculiarity is not the only factor determining the stability of the cis annelation of the B and C rings, for in compounds of analogous structure with no OR group in the 9β-position this reversal in the stability relation between cis and trans isomers is observed [6].

* The screening of 10-CO is evidenced, in particular, by the fact that when the benzyloxy diketone (XXVIIIa) is treated with $(i\text{-PrO})_3Al$, which has a greater effective volume than $LiAlH_4$, it is the 9-carbonyl that is reduced preferentially and the yield of the hydroxy ketone (XXIXa) is increased to 55%.

EXPERIMENTAL*

10-Keto-2α-hydroxy-3,9β-epoxy-1,2,3,4,4aα,9,9aα,10-octahydroanthracene (VI). 2.98 g of the 2,3-epoxy hydroxy ketone (V; R = H, R' = Ac) [1] in 22 ml of 0.5 N alcoholic EtONa was heated for 4 h at the boil, and then alcohol was driven off, and the residue was acidified with acetic acid, diluted with water, and extracted with chloroform. After the usual treatment the extract was evaporated, and the residue was dissolved in acetone, passed through a column of activated charcoal, and again evaporated. The yield of the 3,9-epoxy hydroxy ketone (VI) was 1.52 g (51%); m. p. 123-124° (from benzene); ν_{max} 1600, 1696, 3420 cm^{-1}. Found: C 72.84; H 6.12%. $C_{14}H_{14}O_3$. Calculated: C 73.02; H 6.13%.

Preparation of 2,10-diketo-3,9β-epoxy-1,2,3,4,4aα,9,9aα,10-octahydroanthracene (IX) and its conversion into 3,9-dimethylanthracene (XIII). a) 348 mg of CrO_3 in 4 ml of 50% acetic acid was added to a solution of 400 mg of the 3,9-epoxy hydroxy ketone (VI) in 2 ml of acetic acid at 30°. After 1 h the mixture was poured into water and extracted with chloroform. The yield of the 3,9-epoxy diketone (IX) was 340 mg (76%); m. p. 149-151° (from alcohol); ν_{max} 1695, 1735 cm^{-1}. Found: C 73.36; H 5.14%. $C_{14}H_{12}O_3$. Calculated: C 73.67; H 5.30%.

b) A solution of 46 mg of the 3,9-epoxy diketone (IX) in 5 ml of benzene was added to a Grignard reagent (from 24 mg of Mg and 0.14 g of MeI in 5 ml of ether) at 20°. The mixture was stirred for 2 h at 20° and for 2 h at the boil, and it was then decomposed with 5% HCl and extracted with benzene. The extract was washed with sodium bicarbonate solution and with water, and it was dried with $MgSO_4$ and evaporated. The oily residue was mixed with 1 ml of 85% H_3PO_4, and the mixture was heated at 130-135° for 2 h, cooled, and diluted with water. After extraction with benzene we obtained 36 mg of a substance which in thin-layer chromatography on unbound alumina had the following R_f values: in 2:1 methylcyclohexane-benzene, 0.40; in 4:1 heptane-benzene, 0.70 (samples of 2,9- and 3,9-(2,10-)dimethylanthracenes had respective R_f values of 0.51 and 0.40 in the first solvent system and 0.45 and 0.70 in the second).

9β,10β-Dihydroxy- and 9β,10α-dihydroxy-1,4,4aα,9,9aα,10-hexahydroanthracene (VII) and (VIII). A solution of 4.24 g of the diketone (I; R = H) [7] in 25 ml of tetrahydrofuran was added over a period of 4 h to 20 ml of a 1 M ethereal solution of $LiAlH_4$ at 20°. The mixture was stirred further for 13 h and decomposed by the addition of acetone and then a saturated solution of NH_4Cl. After the addition of anhydrous magnesium sulfate powder, the organic layer was rapidly separated, and the precipitate of the trans-diol (VIII) that formed was filtered off and crystallized from acetone and then from dioxane. Yield 0.84 g (19%); m. p. 240-241°; ν_{max} 1660, 3360 cm^{-1}. Found: C 77.75; H 7.52%. $C_{14}H_{16}O_2$. Calculated: C 77.75; H 7.46%. Its diacetate, prepared by the standard method with Ac_2O in pyridine (89% yield), had m. p. 134-135° (from alcohol). Found: C 72.12; H 7.07%. $C_{18}H_{20}O_4$. Calculated: C 71.98; H 6.71%.

From the ether-tetrahydrofuran solution, after the separation of the trans-diol (VIII), by evaporation we isolated the cis-diol (VII); yield 1.64 g (39%); m. p. 124-125° (from benzene); ν_{max} 1658, 3380 cm^{-1}. Found: C 77.55; H 7.52; H_{act} 0.95%. $C_{14}H_{16}O_2$. Calculated: C 77.75; H 7.46; H_{act} 0.93%.

The diacetate (yield 95%) had m. p. 103-104° (from petroleum ether). Found: C 71.88; H 6.80%. $C_{18}H_{20}O_4$. Calculated: C 71.98; H 6.71%.

10β-Hydroxy-9β-acetoxy-1,4,4aα,9,9aα,10-hexahydroanthracene (XIV). 1.55 ml of 1 M ethereal $LiAlH_4$ was added to a solution of 1.28 g of the acetoxy ketone (XVIIIa) [1] in 10 ml of tetrahydrofuran at −60°, after which the reaction mixture was stirred at −60° for a further 2 h and treated in the usual way. We obtained 1.06 g (82%) of the acetoxy alcohol (XIV); m. p. 119-120° (from benzene); ν_{max} 1718, 3550 cm^{-1}. Found: C 74.42; H 7.02%. $C_{16}H_{18}O_3$. Calculated: C 74.39; H 7.02%.

On hydrolysis of this acetoxy alcohol with 0.15 N alcoholic KOH (20°, 24 h) we obtained a 60% yield of the cis-diol (VII), m. p. 124-125° (from benzene), which we obtained in the preceding experiment.

10β-(Tetrahydropyranyloxy)-9β-acetoxy-1,4,4aα,9,9aα,10-hexahydroanthracene (XV). Three drops of $POCl_3$ were added to a solution of 774 mg of the acetoxy alcohol (XIV) in 3 ml of tetrahydrofuran and 1 ml of dihydropyran, and the mixture was left at 20° for 24 h. After the usual treatment we obtained 660 mg (65%) of the acetoxy acetal (XV); m. p. 104-106° (from alcohol); ν_{max} 1732 cm^{-1}. Found: C 73.40; H 7.64%. $C_{21}H_{26}O_4$. Calculated: C 73.66; H 7.66%.

* All ultraviolet spectra were run in 95% alcohol and all infrared spectra in mineral oil.

10β-(Tetrahydropyranyloxy)-9β-hydroxy-1,4,4aα,9,9aα,10-hexahydroanthracene (XVI). A suspension of 600 mg of the acetoxy acetal (XV) in 10 ml of alcohol and 1.1 ml of 2 N alcoholic KOH was shaken for 2 days at 20°. The solution formed was evaporated, water was added to the residue, and the mixture was acidified with acetic acid and extracted with chloroform. The yield of the hydroxy acetal (XVI) was 360 mg (69%); m. p. 111-114° (from dipropyl ether); ν_{max} 3340 cm^{-1}. Found: C 75.90; H 8.01%. $C_{19}H_{24}O_3$. Calculated: C 75.97; H 8.05%.

Oxidation of 100 mg of this hydroxy acetal with 100 mg of CrO_3 in 2.5 ml of pyridine (20°, 48 h) gave the previously described [1] keto acetal (XVIIIb); yield 64 mg (64%); m. p. 133-136° (from alcohol); ν_{max} 1600, 1690 cm^{-1}.

Preparation and hydrolysis of 10α-hydroxy-9β-(tetrahydropyranyloxy)-1,4,4aα,9,9aα,10-hexahydroanthracene (XVII). a) 4 ml of 1 M ethereal $LiAlH_4$ was added over a period of 1 h at 20° to a solution of 2.98 g of the keto acetal (XVIIIb) in 30 ml of tetrahydrofuran. The mixture was stirred further for 2 h and then treated in the usual way. We obtained 2.38 g (80%) of the hydroxy acetal (XVII); m. p. 101-103° (from dipropyl ether); ν_{max} 1655, 3450, 3590 cm^{-1}. Found: C 75.88; H 8.18%. $C_{19}H_{24}O_3$. Calculated: C 75.97; H 8.05%.

The acetate, prepared by the action of Ac_2O in pyridine at 20° (yield 99%), had m. p. 124-125° (from alcohol); ν_{max} 1737 cm^{-1}. Found: C 73.82; H 7.61%. $C_{21}H_{26}O_4$. Calculated: C 73.66; H 7.66%.

b) 100 mg of the hydroxy acetal (XVII) in 5 ml of alcohol was heated with 0.07 ml of concentrated HCl for 2 h at 50°. The solution was evaporated, diluted with ether, washed with sodium bicarbonate solution and with water, dried with $MgSO_4$, and again evaporated. We obtained 45 mg (63%) of the trans-diol (VIII), m. p. 240-241° (from dioxane), which has been described above in the experiment on the reduction of (I; R = H).

10α-(1-Naphthylcarbamoyloxy)-9β-(tetrahydropyranyloxy)-1,4,4aα,9,9aα,10-hexahydroanthracene (XX). A solution of 3.00 g of the hydroxy acetal (XVII), 1.86 g of 1-naphthyl isocyanate, and 0.1 ml of Et_3N in 20 ml of dry toluene was heated at 100° for 4 h and then vacuum-evaporated. The yield of the acetal urethan (XX) was 3.51 g (75%); m. p. 166-168° (from 2-methoxyethanol); ν_{max} 1600, 1699, 3245 cm^{-1}. Found: C 76.47; H 6.63%. $C_{30}H_{31}NO_4$. Calculated: C 76.73; H 6.65%.

10α-(1-Naphthylcarbamoyloxy)-9β-hydroxy-1,4,4aα,9,9aα,10-hexahydroanthracene (XXI). A suspension of 1.88 g of the acetal urethan (XX) in 70 ml of alcohol and 1 ml of concentrated HCl was heated for 3 h at 50° and then left for 1 day at room temperature. The solution was made alkaline with concentrated ammonia (to phenolphthalein), most of the solvent was vacuum-distilled off, and the hydroxy urethan (XXI) was extracted from the residue with chloroform. Yield 1.07 g (63%); m. p. 153-155° (from dipropyl ether); ν_{max} 1600, 1691, 3300, 3430 cm^{-1}. Found: C 77.95; H 5.99%. $C_{25}H_{23}NO_3$. Calculated: C 77.90; H 6.01%.

10α-(1-Naphthylcarbamoyloxy)-9-keto- and 9β-(1-Naphthylcarbamoyloxy)-10-keto-1,4,4aα,9,9aα,10-hexahydroanthracenes (XXII) and (XIX). a) 20 mg of CrO_3 in 2 ml of 50% acetic acid was added to a solution of 38.5 mg of the hydroxy urethan (XXI) in 2 ml of acetic acid, and the mixture was stirred for 30 min at 30°, poured into water, and extracted with chloroform. After the evaporation of the extract we obtained a dark-brown oil, which was purified with charcoal, as in the first experiment. The yield of the keto urethan (XXII) was 15 mg (40%); m. p. 156-158° (from alcohol); ν_{max} 1601, 1690, 3320 cm^{-1}. Found: C 78.49; H 5.41%. $C_{25}H_{21}NO_3$. Calculated: C 78.31; H 5.58%.

b) A solution of 214 mg of the hydroxy ketone (IVa), 186 mg of 1-naphthyl isocyanate, and 0.1 ml of Et_3N in 20 ml of dry toluene was heated for 5 h at 100°. On cooling, the precipitate of dinaphthylurea was filtered off, and by evaporation of the filtrate the keto urethan (XIX) was isolated. Yield 245 mg (65%); m. p. 146-148° (from alcohol); ν_{max} 1600, 1687, 3360 cm^{-1}. Found: C 78.03; H 5.40%. $C_{25}H_{21}NO_3$. Calculated: C 78.31; H 5.58%.

5,9β,10-Trihydroxy-1,4,4aα,9,9aα,10-hexahydroanthracene (XXX). 50 ml of 1 M ethereal $LiAlH_4$ was added over a period of 5 h to a vigorously stirred solution of 2.7 g of the acetoxy diketone (XXVIIIc) [4] in 250 ml of dry ether at 20°. The mixture was stirred further for 20 h and treated in the usual way. We obtained a dark-yellow oil, which crystallized partially when rubbed out with ether. The yield of the triol (XXX) was 270 mg (12%); m. p. 178-179° (from ethyl acetate); ν_{max} 1650, 3380, 3440 cm^{-1}. Found: C 72.23; H 6.87%. $C_{14}H_{16}O_3$. Calculated: C 72.39; H 6.94%.

The same triol was formed by the analogous reduction of the previously described [8] hydroxy diketone (XXVIII; R = H); yield 23%. The triacetate, prepared by the standard method by the action of Ac_2O in pyridine (yield 87%); had m. p. 136-137° (from alcohol); ν_{max} 1731, 1765 cm^{-1}. Found: C 66.98; H 6.00%. $C_{20}H_{22}O_6$. Calculated: C 67.02; H 6.19%.

From 0.5 g of the triol (XXX) dissolved in 8 ml of pyridine and 35 ml of chloroform by reaction with 3 g of $COCl_2$ in 12 ml of toluene (20°, 48 h) we obtained the carbonic ester of 5,10-dihydroxy-9-chloro-1,4,4aα,9,9aα,10-hexahydroanthracene. Yield 0.24 g (45%); m. p. 157-159° (from alcohol); ν_{max} 1600, 1778 cm^{-1}. Found: C 64.98; H 4.86; Cl 12.96%. $C_{15}H_{13}ClO_3$. Calculated: C 65.10; H 4.73; Cl 12.81%.

2,3-Dihydrojuglone (XXXIa) and its acetic ester (XXXIb). a) 15 g of zinc dust was gradually sprinkled into a shaken suspension of 50 g of juglone in 500 ml of ether and 600 ml of 2 N H_2SO_4. When the zinc had dissolved, the aqueous solution was replaced by a fresh 600 ml of 2 N H_2SO_4 and the addition of zinc dust was continued until the reaction mixture was decolorized. The ethereal solution was separated, washed with water, rapidly dried with $MgSO_4$, and evaporated. The residue was heated for 15 min at 160° (20 mm) and distilled at 160-170° (0.1 mm). The yield of 2,3-dihydrojuglone (XXXIa) was 48 g (96%). After crystallization from alcohol it had m. p. 97-98° (cf. [9]).

b) 15 ml of a 0.5% solution of H_2SO_4 in Ac_2O was added over a period of 15 min to a stirred suspension of 17.5 g of 2,3-dihydrojuglone (XXXIa) in 30 ml of Ac_2O at −5°. The mixture was stirred further for 20 min, and the precipitate was filtered off and washed with ether. The yield of 2,3-dihydrojuglone acetic ester (XXXIb) was 12.3 g (56%); m. p. 145-146° (from alcohol) (cf. [9]).

3,4-Dihydro-4,8-dihydroxy-1(2H)-naphthalenone (XXXIIa) and its acetic esters. a) 6.5 ml of 1 M ethereal $LiAlH_4$ was added to a solution of 5 g of the acetoxy diketone (XXXIb) in 400 ml of tetrahydrofuran at −60°. The mixture was stirred for 90 min at −60° and then poured into a saturated ammonium chloride solution; the ether-tetrahydrofuran solution was separated, and the aqueous layer was extracted with ethyl acetate. The combined extract was washed with NaCl solution, dried with $MgSO_4$, and evaporated. The residue was ground with ether, and the precipitate was filtered off and crystallized from toluene. We obtained 3.45 g (70%) of the 8-acetate of the dihydroxy ketone (XXXIIa); m. p. 111-112° (from alcohol); λ_{max} 247, 297 mμ (log ε 4.17, 3.26); ν_{max} 1686, 1749 cm^{-1}. Found: C 65.56; H 5.42%. $C_{12}H_{12}O_4$. Calculated: C 65.44; H 5.49%.

b) 0.5 g of the acetoxy hydroxy ketone (XXXIIb) prepared in the preceding experiment was hydrolyzed in 50 ml of alcohol with 80 ml of 0.1 N KOH (20°, 2 h), neutralized to phenolphthalein with 0.1 N HCl, and extracted with ethyl acetate. After the usual treatment the extract was evaporated, and from the residue 3,4-dihydro-4,8-dihydroxy-1(2H)-naphthalenone (XXXIIa) was extracted with boiling hexane. Yield 0.3 g (78%); m. p. 99-100° (from hexane); λ_{max} 257, 327 mμ (log ε 3.98, 3.55); ν_{max} 1640, 3245 cm^{-1}. Found: C 67.38; H 5.65%. $C_{10}H_{10}O_3$. Calculated: C 67.40; H 5.66%.

c) The 4-acetate of the dihydroxy ketone (XXXIIa) was prepared by acetylation with a standard Ac_2O—Py mixture for 2 h at 20°. Yield 99%; m. p. 64-65° (from methanol saturated with hexane); λ_{max} 259, 325 mμ (log ε 3.92, 3.49; ν_{max} 1640, 1740 cm^{-1}. Found: C 65.26; H 5.58%. $C_{12}H_{12}O_4$. Calculated: C 65.44; H 5.49%.

d) The 4,8-diacetate of the dihydroxy ketone (XXXIIa) was prepared by acetylation in the same way but for 20 h at 20°. Yield 80%; m. p. 124-125° (from alcohol); λ_{max} 247, 298 mμ (log ε 3.95, 3.31); ν_{max} 1690, 1742, 1760 cm^{-1}. Found: C 64.25; H 5.47%. $C_{14}H_{14}O_5$. Calculated: C 64.11; H 5.38%.

1,2,3,4-Tetrahydro-1,4,5-naphthalenetriol (XXXIII). A solution of 4.4 g of the acetoxy diketone (XXXIb) in 250 ml of tetrahydrofuran was added over a period of 3 h at 20° to 60 ml of 1 M ethereal $LiAlH_4$. The mixture was stirred further for 5 h, left overnight, and then poured into 500 ml of saturated ammonium chloride solution and treated as in the preceding experiment. The yield of the triol (XXXIII) was 2.56 g (71%); m. p. 123-125° (from ethyl acetate); λ_{max} 281, 283 mμ (log ε 3.35, 3.35); ν_{max} 3250, 3435 cm^{-1}. Found: C 66.53; H 6.62%. $C_{10}H_{12}O_3$. Calculated: C 66.65; H 6.71%.

Behavior of derivatives of 10-keto-9β-hydroxy-1,4,4aα,9,9aα,10-hexahydroanthracene (IVa) toward alkaline agents. a) A solution of 256 mg of the acetoxy ketone (XVIIIa) in 7 ml of 1% alcoholic KOH was heated for 1 h at the boil. Alcohol was driven off, and the residue was diluted with water, acidified with acetic acid, and extracted with ethyl acetate. We obtained 132 mg (62%) of the hydroxy ketone (IVa), m. p. 138-140°. The same hydroxy ketone (IVa) was obtained in 68% yield by the hydrolysis of the acetoxy ketone (XVIIIa) with 1% alcoholic KOH for 3 days at 20°.

b) A solution of 298 mg of the keto acetal (XVIIIb) in 15 ml of 5% alcoholic EtONa was heated for 1 h at the boil. After neutralization and evaporation we isolated 220 mg (74%) of the original substance, m. p. 133-135° (from alcohol).

The authors thank L. B. Senyavina of the Institute for the Chemistry of Natural Products of the Academy of Sciences of the USSR for the measurement of infrared spectra.

SUMMARY

1. The configurations of some hydroanthracene compounds, synthesized as possible intermediaries in the preparation of natural 6-demethyltetracyclines and their analogs, were established.

2. The causes of the structural and steric orientation observed in the reduction of some naphthoquinone-butadiene adducts with lithium aluminum hydride were discussed.

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