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Abstract

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STUDY OF ROUTES FOR CONSTRUCTING THE BA RING SYSTEM OF TETRACYCLINES

SYNTHESIS OF ESTERS OF SUBSTITUTED 2-KETOCYCLOHEXYLACETIC ACIDS

In connection with the problem of the total synthesis of tetracyclines (I), we undertook, on model compounds, a study of possible routes for the conversion of the previously described ([1]) hydroanthracene dibromides and epoxides (II) into tricyclic compounds of type (III), having such substituents X and Y that could subsequently be converted, respectively, into a dimethylamino group and a ketone carbonyl. For this purpose, from 1,2-dibromocyclohexane via an unsaturated acid (IV, X = NHAc) the first representative of compounds of type (V) was obtained—3-bromo-2-ketocyclohexylacetic ester (V, X = NHAc, Y = Br) ([2]). In continuation of these investigations, we have now carried out the synthesis of a number of other compounds of type (V), namely the keto esters (XIIIa)—(XIIIc) and (XVIIb), to which the present communication is devoted.

(I) tetracycline skeleton with rings D, C, B, A;
R = H, Cl or Br; R' = H or OH

(II) hydroanthracene derivative ⇢ (III) tricyclic keto ester derivative
$Z = Z'$ = Br or $Z + Z'$ = O

1,2-dibromocyclohexane ⟶ cyclohexenylacetic acid derivative (IV) ⟶ 2-ketocyclohexylacetic ester derivat

Epoxidation of ethyl 2-cyclohexenylacetic ester (VIc) by means of $PhCO_3H$ in chloroform solution gave, in 85% yield, 2,3-α-epoxycyclohexylacetic ester (VIIb). The stereoisomeric β-epoxy ester (XIIa) is formed in almost quantitative yield by the action of 0.5 N ethanolic KOH on the bromolactone (XIa), which in turn is obtained by bromination of 2-cyclohexenylacetic acid (VIa) in aqueous solution ([2,3]). Both isomeric epoxy esters—(VIIb) and (XIIa)—under the action of benzyl

Reaction scheme: compounds VIa-VIIf, VIIa-VIIc, VIIIa-VIIId, IXa-IXc, Xa-Xc, XIa-XId, XIIa-XIIb, XIIIa-XIIIc, XIV, XV, XVIa-XVIb, XVIIa-XVIIb

Figure 1: Reaction scheme: compounds VIa-VIIf, VIIa-VIIc, VIIIa-VIIId, IXa-IXc, Xa-Xc, XIa-XId, XIIa-XIIb, XIIIa-XIIIc, XIV, XV, XVIa-XVIb, XVIIa-XVIIb

alcohol in the presence of BF_3 at 20°, gave one and the same oxybenzyloxy ester (VIIIa). The latter, however, could not be isolated in the individual state, since it partially lactonized during distillation. Nevertheless, after saponification of this oxybenzyloxy ester, pure benzyloxylactone (IXa) was readily obtained in 70% yield; by treatment with methanolic KOH, and then with $AgNO_3$ and MeJ, it was converted into oxybenzyloxy ester (VIIIb) (yield 76%).

In an analogous manner, the epoxy esters (VIIc) and (XIIb), synthesized by us earlier from the unsaturated ester (VIf) and bromolactone (XIc) ([2]), were converted by the action of $PhCH_2OH$ in the presence of BF_3 or H_2SO_4 into the oxybenzyloxy ester (VIIId), purified through the lactone (IXc). Methanolysis of the same epoxy esters (VIIc) and (XIIb) gave, in yields of 94 and 80%, the oxymethoxy ester (VIIIc).

Oxidation of the oxalkoxy esters (VIII) to alkoxyketo esters (XIII) presented known difficulties owing to the considerable shielding of the hydroxyl group in the starting compounds and the pronounced tendency of the acyloin ethers formed to undergo hydrolysis under the influence of acids and bases. In this connection the reaction was first studied using trans-2-benzyloxycyclohexanol as an example, and it was found that the oxidation conditions recommended by Musseron ([4]) (H_2CrO_4 in sulfuric-acid solution) give unsatisfactory results (yield about 15%), whereas when CrO_3 in pyridine is used as the oxidizing agent (20°, 24 h) the yield of 2-benzyloxycyclohexanone, isolated as the semicarbazone, reaches 50%*. On oxidation by this method of the oxy esters (VIIIb)–(VIIId), the corresponding keto esters (XIIIa)–(XIIIc) were obtained in 60-80% yield.

VIa: X=H, R=H
VIb: X=H, R=Me
VIc: X=H, R=Et
VId: X=CO_2Et, R=Et
VIe: X=NHAc, R=H
VIf: X=NHAc, R=Me

VIIa: X=H, R=H
VIIb: X=H, R=Et
VIIc: X=NHAc, R=Me

VIIIa: X=H, R=Et, R′=CH_2Ph
VIIIb: X=H, R=Me, R′=CH_2Ph
VIIIc: X=NHAc, R=R′=Me
VIIId: X=NHAc, R=Me, R′=CH_2Ph

IXa: X=H, R=CH_2Ph
IXb: X=NHAc, R=Me
IXc: X=NHAc, R=CH_2Ph

Xa: X=H
Xb: X=CO_2H
Xc: X=NHAc

XIa: X=H, Y=Br
XIb: X=H, Y=OH
XIc: X=NHAc, Y=Br
XId: X=NHAc, Y=OH

XIIa: X=H, R=Et
XIIb: X=NHAc, R=Me

XIIIa: X=H, R=CH_2Ph
XIIIb: X=NHAc, R=Me
XIIIc: X=NHAc, R=CH_2Ph

(XIV)
(XV)

XVIa: R=H
XVIb: R=Me

XVIIa: R=H
XVIIb: R=Me

The synthesis of ketallactone (XV), necessary for obtaining the ketalketo ester (XVIIb), was carried out starting from 2-cyclohexenylmalonic ester (VId) according to the previously described scheme ([6]) through (Xb), (Xa), and (XIV); in this case, a modification of the procedure, consisting in decarboxylation of the intermediate carboxylactone (Xb) in boiling pyridine, made it possible for the first time to obtain trans-oxylactone (Xa) in crystalline form. Direct oxidation of ketallactone (XV) with $Mg(OBr)_2$ by the McRae method ([7]) led to the keto acid (XVIIa), but the yield of the latter, in contrast to Rosenmund' s data ([6]), did not exceed 15%. Therefore the lactone (XV) was first saponified to the corresponding oxy acid (XVIa), which was then converted by the action of CH_2N_2 or by methylation of its Ag salt by means of CH_3I

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* 2-Benzyloxycyclohexanone was also synthesized by us in 45% yield by esterifying adipoin with benzyl alcohol in the presence of HCl (cf. ([5])).

into the methyl ester (XVIb). Oxidation of this ester with di-*tert*-butyl chromate* led, in 55% yield, to the ketal keto ester (XVIIb), which was also obtained by methylation of the acid (XVIIa) with CH_2N_2.

The structure of the compounds described in the present article (their constants and analytical data are given in the table) was established as follows. In the

alcoholysis of the α-epoxy ester (VIIc) with methyl or benzyl alcohol in the presence of the corresponding alcoholates, there were obtained

Table 1

Compound	M.p. (decomp.), b.p., solvent for crystallization	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N
VIb	80–81°/10 mm	70,31	9,29		70,10	9,15	
VIc	85–86°/10 mm	71,22	9,72		71,39	9,59	
VIIa	S-benzylthiuronium salt: 153–154° (EtOH)	59,22	6,91		59,60	6,88	
VIIb	92–93°/1 mm	65,18	8,90		65,19	8,75	
VIIIb	165–167°/1 mm	69,37	7,81		69,04	7,97	
VIIIc	113–114° (AcOEt–Et_2O)	55,59	8,26	5,52	55,58	8,16	5,40
VIIId	41–42° (AcOEt–Et_2O)	64,28	7,47	4,23	64,46	7,51	4,18
IXa	173–175°/1 mm	72,92	7,43		73,14	7,37	
IXb	147–148° (AcOEt–MeOH)	57,92	7,55	6,01	58,13	7,54	6,16

Compound	M.p. (decomp.), b.p., solvent for crystallization	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N
IXc	68–69° (AcOEt–Et_2O)	67,29	7,06	4,66	67,31	6,98	4,62
Xa	39–40° (Et_2O)	61,23	7,74		61,52	7,75	
Xa	3,5-dinitrobenzoate: 112–113° (EtOH)	51,48	4,15		51,43	4,03	
Xc	167–168° (AcOEt)	56,32	7,14	6,66	56,32	7,09	6,57
Xc	3,5-dinitrobenzoate: 230–231° (EtOH)	49,84	4,32	10,15	50,12	4,21	10,32
XIa	58–59° (Et_2O–hexane)	43,85	5,06		44,06	5,15	
XIIa	87–88°/1 mm	64,93	8,75		65,19	8,75	
XIIIa	148–150°/0,5 mm	69,46	7,35		69,54	7,30	
XIIIa	Semicarbazone: 139–140° (MeOH)	60,98	6,97	12,95	61,24	6,95	12,61
XIIIb	71–73° (AcOEt–Et_2O)	55,88	7,41	5,71	56,02	7,44	5,44
XIIIc	59–60° (AcOEt)	65,19	7,19	4,25	64,85	6,95	4,20

Compound	M.p. (decomp.), b.p., solvent for crystallization	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N
XVIb	135–137°/1 mm	57,69	7,59		57,38	7,88	
XVIIb	63–64° (MeOH)	57,56	7,04		57,88	7,07	

the same oxyalkoxy esters (VIIIc) and (VIIId), which are formed in the interaction of the epoxy ester (VIIc) with MeOH or $PhCH_2OH$ under the influence of BF_3 or H_2SO_4. Meanwhile, it is known that base-catalyzed alcoholysis of epoxides is an SN2 reaction, whereas acid alcoholysis may also proceed by a carbonium mechanism ([9]). It therefore seemed likely that the oxyalkoxy esters (VIII) are obtained from the α-epoxides (VII) as a result of attack by the alkoxyl anion at the 3β position (the least screened), with retention of the configuration of C_2, whereas the formation of these same compounds from the β-epoxides (XII) is associated with inversion of asymmetric center 2. The validity of this assumption was then rigorously proved by hydrogenolysis of the benzyloxylactones (IXa) and (IXc) to the trans-oxylactones (Xa) and (Xc), which had been synthesized earlier ([2,6]), together with the corresponding cis isomers (XIb) and (XId), by hydroxylation of the unsaturated acids (VIa) and (VIe) with HCO_3H. Thus, the oxyalkoxy esters (VIII) possess a cis arrangement of substituents at asymmetric centers 1 and 3; moreover, these substituents apparently are in the thermodynamically most stable 1,3-cis-diequatorial conformation. Obviously, the same conformation must also be retained in the final keto esters, as a result of which the spatial structure (XIII) is the most probable for them.

* Contrary to the literature data ([8]), oxyketals of this type, for example ethylene ketal of adipoin, can be oxidized in satisfactory yield by the $CrO_3 \cdot 2Py$ complex. However, still better results are obtained when *tert*-Bu_2CrO_4 is used for the same purpose.

The structure and configuration of bromolactone (XIa) were proved by reductive dehalogenation of this compound in the presence of PdO or skeletal Ni to the previously known lactone of *cis*-2-oxycyclohexylacetic acid [10]; naturally, the *cis* fusion of the lactone and cyclohexane rings in compound (XIa) determines the β-configuration of the oxide ring in the epoxy ester (XIIa). As for the structure of the remaining compounds, it requires no special explanation.

Thus, we have carried out the synthesis of a series of new keto esters of type

(V), which may serve for the construction of the bicyclic BA system of tetracyclines by using various addition reactions at the ketone group (ethynylation, cyanohydrin synthesis, the Normant reaction, etc.).

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