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Abstract

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STUDY OF ROUTES FOR CONSTRUCTING THE BA RING SYSTEM OF TETRACYCLINES

Previously ([1]) we described the synthesis of ketols of the hydroanthracene series, two rings of which are similar in their structure to rings D and C of tetracycline (I), while the third ring, corresponding to ring B, contains functional groupings that make it possible to carry out the construction of ring A of tetracyclines.

(I)

Before proceeding to the next stage—the construction of the fourth ring—we studied possible routes for this on simpler examples, namely on cyclohexane derivatives. By ethynylation of cyclohexanone-2-acetic ester (II), followed by hydration of the triple bond and cyclization of the oxo keto ester, cis-decalol-9-dione-1,3 (III) was obtained, and its carboxamidation led to cis-2-carboxamidodecalol-9-dione-1,3 (IV), the right-hand ring of which contains all the functional groupings of ring A of tetracyclines, with the exception of the dimethylamino group ([2]).

(II) $\longrightarrow$ (III) $\longrightarrow$ (IV)

The aim of the present work was to study the possibility of constructing the complete BA ring system of tetracyclines. On the basis of the results of previous investigations, it seemed expedient first of all to study routes for the synthesis of compounds of type (V), where X is an acylated amino group and Y is a substituent that can be converted at later stages of the synthesis into a carbonyl group. Key compounds of this kind could serve as the basis for subsequently constructing the complete ring system of tetracycline (I). In this connection, for the synthesis of compounds of type (V) we chose 1,2-dibromocyclohexane as a model substance, since the previously described dibromide of a tricyclic ketol ([1]) can be used to create the tetracyclic DCBA system. As the first representative of compounds of type (V), we synthesized the methyl ester of 3-bromo-2-ketocyclohexylacetic acid (VI).

On condensation of 1,2-dibromocyclohexane with acetamidomalonic ester in the presence of two moles of sodium ethylate ([3]), 2-cyclohexenylacetamidomalonic ester (IXa) was obtained in 52% yield. The same compound was obtained in 62% yield by condensation of acetamidomalonic ester with

3-bromocyclohexene in the presence of one mole of sodium ethoxide. Saponification of the diester (XIa) with one equivalent of a 1 N solution of caustic potash in methanol at room temperature led, in 70% yield, to the acid ester of 2-cyclohexenylacetamidomalonic acid (IXb), whereas saponification of the diester (XIa) under the same conditions with two equivalents of caustic potash gave 2-cyclohexenylacetic acid (X) in 97% yield.

Bromination of the acid ester (IXb) in chloroform at −10° led to the carboxybromolactone (XIII), whose saponification with subsequent decarboxylation gave the bromolactone (XIIa). On bromination of 2-cyclohexenylacetic acid (X) in acetic acid solution at 5–10°, bromolactone (XIIa) (yield 37%) and dibromo acid (XIa) (yield 35%) were obtained. Subsequently it proved more convenient to carry out the bromination of 2-cyclohexenylacetic acid (X) in an aqueous solution of sodium carbonate (4, 5). Under these conditions bromolactone (XIIa) and bromooxy acid (XIb) were obtained in yields of 52 and 36%, respectively. On iodolactonization (6) of acid (X) in an aqueous solution of sodium bicarbonate, iodolactone (XIIb) was formed in 98% yield.

[[chemical scheme: compounds V–XVI]]

Bromooxy acid (XIb), bromolactone (XIIa), and iodolactone (XIIb) were used by us to obtain the bromoketo ester (VI).

Methylation of bromooxy acid (XIb) with diazomethane in dioxane gave the methyl ester of bromooxy acid (XIc). This ester was also synthesized by another route. By the action of methyl iodide on the silver salt of 2-cyclohexenylacetic acid (X), its methyl ester (XIV) was obtained; this was oxidized with perbenzoic acid to the α-oxide (XV), and the latter, on heating with pyridine hydrobromide in absolute ethanol, gave the methyl ester of bromooxy acid (XIc). On oxidation of it with chromic anhydride in 80% acetic acid at room temperature, the methyl ester of bromoketo acid (VI) was obtained in 78% yield. The same bromoketo ester was obtained by us in the following way. On treating bromolactone (XIIa) or iodolactone (XIIb) with one equivalent of a 0.5 N solution of caustic potash in absolute methanol at room temperature, the methyl ester of β-oxido acid (VIIIb) was formed in almost quantitative yield. The latter, on heating with pyridine hydrobromide in absolute ethanol, was converted into the ester of bromooxy acid (VII), which is

stereoisomer of ester (XIc). Oxidation of the bromoxy acid ester (VII) with chromic anhydride in acetic acid gave the bromo keto ester (VI) (yield 74%).

The structures of the compounds obtained were established as follows. Upon lactonization of the bromoxy acid (XIb) by boiling in 0.1 N sulfuric acid, bromolactone (XVIa) was formed in 78% yield; catalytic dehalogenation of it over pal-

ladium oxide or Raney nickel in the presence of diethylamine led to the lactone of threo-trans-2-oxycyclohexylacetic acid (XVIb), in turn obtained by acetylation of the previously described (7) lactone of threo-trans-2-oxycyclohexylglycine. Thus, the bromoxy acid (XIb), with respect to the asymmetric centers C_α and C_1, belongs to the threo series, and the hydroxyl group at C_2 is in the trans position to the N-acetylglycine residue.

Investigation of the IR spectrum of bromolactone (XIIa) showed that it is a γ-lactone ($\nu_{CO} = 1793$ cm^{-1}). The cis fusion of the lactone and cyclohexane rings in (XIIa) and (XIIb) was established on the basis of the following data. Catalytic dehalogenation of bromolactone (XIIa) and iodolactone (XIIb) gave one and the same lactone, isomeric with the lactone of threo-trans-2-oxycyclohexylacetic acid (XVIb). Since the formation of these two halolactones took place under conditions in which epimerization should not occur (4, 8), both of them, like the bromoxy acid (XIb), must belong to the threo series with respect to the centers C_α and C_1. Consequently, the lactone formed upon catalytic dehalogenation of the halolactones (XIIa) and (XIIb) must also have the threo configuration, differing from the isomeric lactone (XVIb) only in the configuration of the asymmetric center C_2; hence it may be assigned the structure of the lactone of threo-cis-2-oxycyclohexylacetic acid (XIIe).

The structure of the methyl ester of β-oxide acid (VIIIb) was established as follows. On saponification with 10% aqueous potassium hydroxide solution at room temperature, it gives the oxide acid (VIIIa); treatment of this acid with 1 N sulfuric acid (20°, 12 h) led to the oxylactone (XIIc). The same compound was formed in 38% yield upon hydroxylation of 2-cyclohexenylacetic acid (X) with performic acid. The cis fusion of the lactone and cyclohexane rings in (XIIa) determines the β-configuration of the oxide (VIIIb).

Table 1

Compound	Mp, °C	Solvent	Found, % C	Found, % H	Found, % N	Found, % Br (I)	Calculated, % C	Calculated, % H	Calculated, % N	Calculated, % Br (I)
VI	134–135	AcOEt	43,02	5,34	4,41	26,83	43,15	5,27	4,57	26,10
VII	137–138	20% EtOH	43,18	5,86	4,37	25,71	42,87	5,89	4,55	25,93
VIIIb	100–101	C_6H_6-hexane	58,32	7,76	6,21	–	58,13	7,54	6,16	–
IXa	48–49	Et_2O	60,37	7,97	4,68	–	60,59	7,80	4,71	–

Compound	Mp, °C	Solvent	Found, % C	Found, % H	Found, % N	Found, % Br (I)	Calculated, % C	Calculated, % H	Calculated, % N	Calculated, % Br (I)
IXb	116 – 117	20% EtOH	58,02	7,27	5,29	–	57,98	7,11	5,20	–
X	178 – 179	EtOH	60,58	7,58	7,24	–	60,89	7,67	7,10	–
XIa	167 – 168	20% EtOH	33,76	4,28	3,87	44,31	33,63	4,23	3,92	44,76
XIb	168 – 169	20% EtOH	40,69	5,38	4,82	27,36	40,83	5,48	4,76	27,17
XIc	134 – 135	AcOEt–hexane	43,13	5,98	4,58	25,83	42,87	5,89	4,55	25,93
XIIa	178 – 179	20% EtOH	43,53	5,20	5,02	29,11	43,49	5,11	5,07	28,97
XIIb	163 – 164	H_2O	37,12	4,42	4,29	39,23	37,17	4,37	4,33	39,28
XIIc	192 – 193	AcOEt	56,43	7,15	6,68	–	56,32	7,09	6,57	–
XIId	129 – 130	C_6H_6-hexane	56,52	6,65	5,51	–	56,46	6,71	5,49	–
XIIe	174 – 175	AcOEt	60,61	7,58	6,85	–	60,89	7,67	7,10	–
XIII	138 – 139	20% EtOH	44,76	5,08	4,03	22,80	44,83	5,21	4,04	22,95
XIV	102 – 103	C_6H_6-hexane	62,61	8,27	6,44	–	62,54	8,11	6,63	–
XV	100	C_6H_6-hexane	58,42	7,60	6,02	–	58,13	7,54	6,16	–
XVIa	172 – 173	20% EtOH	43,36	5,17	4,68	28,82	43,49	5,11	5,07	28,97

Compound	Mp, °C	Solvent	Found, % C	Found, % H	Found, % N	Found, % Br (I)	Calculated, % C	Calculated, % H	Calculated, % N	Calculated, % Br (I)
XVIa	148 – 149	AcOEt	60,91	7,57	6,74	–	60,89	7,67	7,10	–

In the ester of bromoxy acid (VII), obtained from the β-oxido ester (VIIIb), the hydroxyl group at C_2 is in the cis-position relative to the acetic-acid residue, since treatment of ester (VII) with a 10% solution of hydrogen bromide in acetic acid gave the bromolactone (XIIa). The formation of one and the same bromoketo ester (VI) upon oxidation of the stereoisomeric bromoxy esters (XIc) and (VII) serves as additional confirmation of the structure of the latter.

The bromoketo ester (VI), oxylactone (XIIc), its acetate (XIId) (obtained from (XIIc) by the action of acetic anhydride in pyridine), and also the stereoisomeric oxido esters (VIIIb) and (XV) synthesized by us may be used for constructing the BA ring system of the tetracyclines.

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