TETRACYCLINES

COMMUNICATION 33. SYNTHESIS OF 8-CHLORO-5-METHOXY-3,10-DIOXO-1,2,3,4,4a,9,9a,10-OCTAHYDROANTHRACENE [5-CHLORO-1,3,4,4a,9a,10-HEXAHYDRO-8-METHOXY-2,9-ANTHRACENEDIONE]*

(UDC 542.91+615.779.931)

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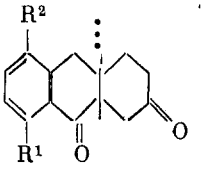
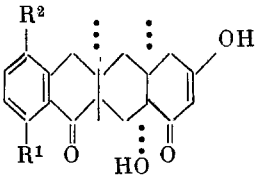
We have recently described the synthesis of the tricyclic compound (Ia) and its conversion into the hydronaphthacene hydroxy triketone (IIa), which has some of the characteristic functional groups of tetracycline antibiotics [1, 2]. To obtain the closer analog of tetracyclines (IIb), which, like aureomycin, have a chlorine atom and a hydroxy group in ring D, we have now synthesized the chloro methoxy diketone (Ib).



(Ia) : $R^1 = R^2 = H$
(Ib) : $R^1 = OMe$, $R^2 = Cl$



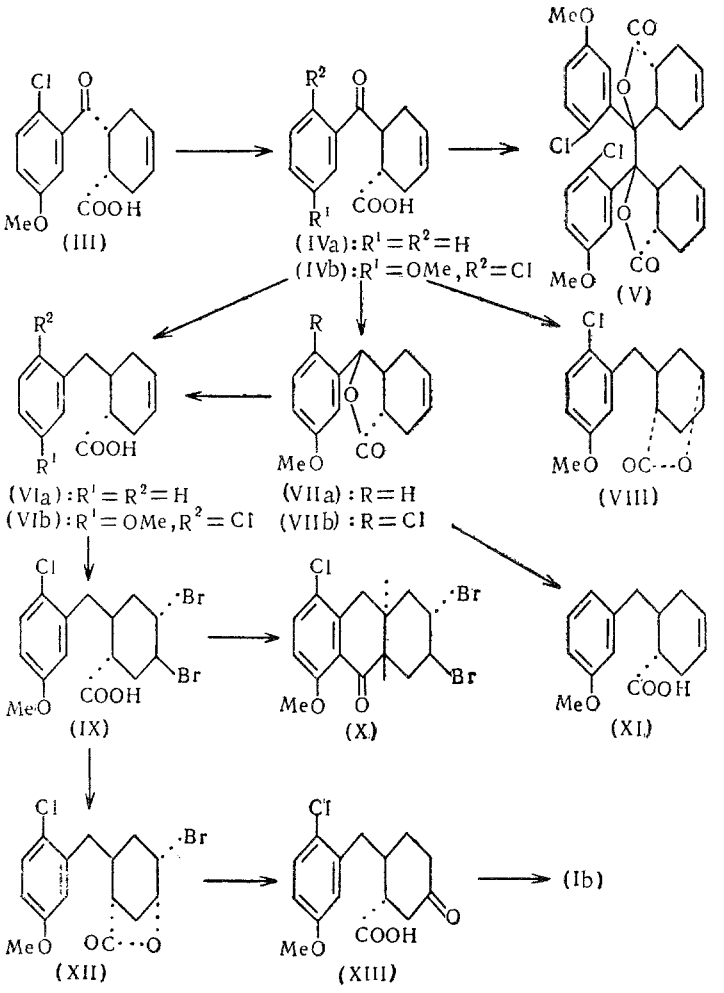
(IIa) : $R^1 = R^2 = H$
(IIb) : $R^1 = OH$, $R^2 = Cl$

(Ib) was synthesized by a method similar to that used [2] for the preparation of the simplest analog (Ia). By the condensation of cis-4-cyclohexene-1,2-dicarboxylic anhydride with 2-chloro-4-methoxyphenylmagnesium iodide or bromide we obtained the cis keto acid (III), which by the action of 0.5 N NaOH was isomerized into the trans keto acid (IVb). Unlike the keto acid (IVa), which is readily reduced to (VIa) by a modified Clemmensen method [2], the chloro methoxy keto acid (IVb) is reduced with considerable difficulty because of the presence of a chlorine atom in the ortho position relative to the keto group. When the keto acid (IVb) was heated with amalgamated zinc in an acid medium for a long time, a complex mixture of compounds was formed, from which we could isolate the desired acid (VIb) in a yield of only about 5%. From the neutral fraction, containing the bulk of the product, we isolated the dilactone (V). Judging from the chromatographic and spectral characteristics of the mixture of substances obtained, other reduction products were probably the δ-lactone (VIII) [ν(CO) about 1740 cm^{-1}] and the γ-lactone (VIIb) [ν(CO) 1780 cm^{-1}]. (See the structure at the top of the next page.)

In view of the low yield of the acid (VIb) in the direct Clemmensen reduction of the keto acid (IVb) we attempted to conduct this process in stages: (IVb) → (VIIb) → (VIb). By the action of excess of $NaBH_4$ on the keto acid (IVb) in aqueous alkali at 65° we obtained a high yield of (VIIb),† but the subsequent reduction of this with Zn + HCl went unsatisfactorily, and when sodium in liquid ammonia was used as reducing agent the lactone (VIIa) and the acid (XI) were formed, from which it follows that under these conditions the hydrogenolysis of the lactonized hydroxyl precedes the dechlorination of the aromatic ring.

*For preceding communication see [1].

†It must be mentioned that this lactone is very readily hydrolyzed, for example in crystallization from aqueous alcohol.



The further synthesis of the tricyclic diketone (Ib) was readily effected in accordance with the scheme developed earlier [2]. By the bromination of the unsaturated acid (VIb) we obtained the dibromo acid (IX),* which by treatment with hot alkali was converted in the high yield into the γ-keto acid (XIII); the position of the ketonic carbonyl in the last compound was determined from the size of the lactone ring in the intermediate γ-lactone (XII) [ν(CO) 1787 cm^{-1}], which we succeeded in isolating when the dehydrobromination of the dibromo acid (IX) was effected not with caustic alkali, but with sodium carbonate solution at 50°. Finally, the cyclization of the keto acid (XIII) with anhydrous HF at 20° led in good yield to the hydroanthracene diketone (Ib).

EXPERIMENTAL

4-Chloro-2-nitroanisole. A diazo solution, prepared from 101 g of 2-nitro-p-anisidine in 400 ml of 20% HCl and 42 g of $NaNO_2$ in 120 ml of water, was added to a stirred solution of CuCl (freshly prepared from 188 g of $CuSO_4 \cdot 5H_2O$) in 270 ml of 28% HCl at 0°. The mixture was stirred for 2 h at 2-5° and was then heated gradually and steam-distilled. We obtained 91 g (81%) of 4-chloro-3-nitroanisole, m. p. 42° (from 60% alcohol) (cf. [3]).

3-Bromo- and 3-Iodo-4-chloroanisoles. a) 95 g of 4-chloro-3-nitroanisole was added to a solution of 340 g of $SnCl_2 \cdot 2H_2O$ in 450 ml of concentrated HBr. The suspension was heated until an exothermic reaction set in (about 50°), and during the reaction the temperature was kept in the range 90-95°; the mixture was then cooled to 5°. The precipitate of 6-chloro-m-anisidine hydrobromide was filtered off, washed with alcohol, dissolved in 600 ml of concentrated HBr, and diazotized in the usual way with 32 g of $NaNO_2$ in 100 ml of water. The resulting diazo solution was poured with stirring into a solution of CuBr (freshly prepared from 143 g of $CuSO_4 \cdot 5H_2O$ and 68 g of NaBr) in 300 ml of concentrated HBr at 75°. The mixture was stirred for 1 h at 75° and then steam-distilled; the

* The acid chloride of this acid is cyclized smoothly under the action of $SnCl_4$ at 0° into the ketone (X).

distillate was extracted with ether, and the extract was washed with 10% sulfuric acid and then water, dried with $MgSO_4$, and distilled. The yield of 3-bromo-4-chloroanisole was 65 g (57%); b. p. 91-93° (2 mm); n_D^{15} 1.5853 (cf. [3]).

b) A diazo solution prepared as in the preceding experiment was poured into a solution of 85 g of KI in 100 ml of water at 0°. The mixture was left for 12 h at 20°, heated to 60°, cooled, and then extracted with chloroform. The extract was washed with 40% $NaHSO_3$ solution and then water, made alkaline with 20% NaOH, and steam-distilled. We obtained 63 g (46%) of 4-chloro-3-iodoanisole; b. p. 87-89° (1.5 mm); n_D^{20} 1.6261; d_4^{20} 1.8961. Found: C 31.66; H 2.30; Hal 60.26%. C_7H_6ClIO. Calculated: C 31.31; H 2.29; Hal 60.46%.

cis-6-(2-Chloro-5-methoxybenzoyl)-3-cyclohexene-1-carboxylic Acid (III). a) A solution of 125 g of 4-chloro-3-iodoanisole in 300 ml of dry ether was added in the course of 3.5 h to 11.25 g of magnesium in 30 ml of dry ether. The mixture was then heated for 30 min, after which it was added gradually to a stirred solution of 64 g of cis-4-cyclohexene-1,2-dicarboxylic anhydride in one liter of dry benzene. After 1 h the reaction mixture was decomposed at 0° with 250 ml of 20% HCl and extracted with saturated $NaHCO_3$ solution; the bicarbonate extract was clarified by prolonged shaking with charcoal and then acidified to Congo Red with 20% HCl. The substance which separated was crystallized from 50% methanol. The yield of the keto acid (III) was 56 g (45%); m. p. 116-117°; λ_{max}* 214, 291 mμ (log ε 4.23, 3.26); ν_{max} 1593, 1682, 1698, 3040 cm^{-1}. Found: C 60.79; H 5.09; Cl 12.33%. $C_{15}H_{15}ClO_4$. Calculated: C 61.11; H 5.14; Cl 12.03%.

b) A solution of 7.3 g dibromoethane in 40 ml of dry ether was added in the course of 4 h to a suspension of 1.35 g of magnesium in a boiling solution of 4.1 g of 3-bromo-4-chloroanisole in 20 ml of dry ether. The mixture was heated until solution occurred and then added gradually to a stirred solution of 2.6 g of cis-4-cyclohexene-1,2-dicarboxylic anhydride in 40 ml of benzene at 20°. After 1 h the reaction mixture was decomposed with 35 ml of 20% HCl at 0° and then treated as in Expt. (a). The yield of the keto acid (III) was 1.7 g (34%).

trans-6-(2-Chloro-5-methoxybenzoyl)-3-cyclohexene-1-carboxylic Acid (IVb). 5 g of the cis keto acid (III) was dissolved in 70 ml of 0.5 N NaOH, and the solution was heated for 2 h at 100°, cooled, and acidified with 20% HCl. The yield of the trans keto acid (IVb) was 4 g (80%); m. p. 137-139° (from 50% methanol); λ_{max} 216, 300 mμ (log ε 4.21, 3.21); ν_{max} 1605, 1691, 1704, 3040 cm^{-1}. Found: C 60.95; H 5.23; Cl 12.33%. $C_{15}H_{15}ClO_4$. Calculated: C 61.11; H 5.14; Cl 12.03%.

Reaction of the Keto Acid (IVb). a) A mixture of 20.65 g of the keto acid (IVb), 150 g of amalgamated zinc, 10 ml of acetic acid, 30 ml of toluene, and 50 ml of 20%HCL-was boiled for 8 h with the addition of 15 ml of concentrated HCl after every 3 h. The mixture was cooled, the toluene layer was separated, and the aqueous solution was extracted with ether. The combined extract was evaporated, the residue was dissolved in 80 ml of 10% NaOH, and 15 ml of dimethyl sulfate was added. The mixture was shaken for 15 min at 50°, boiled for 1 h, cooled, filtered, and acidified to Congo Red with 20% HCl. The oil that separated was extracted with ether, the extract was washed with 8% $NaHCO_3$ solution, and by acidification of the bicarbonate solution we isolated 1.7 g of trans-6-(2-chloro-5-methoxybenzyl)-3-cyclohexene-1-carboxylic acid (VIb); m. p. 119-121° (from 50% methanol); λ_{max} 204, 273, 280 mμ (log ε 4.39, 3.39, 3.06); ν_{max} 1711, 3030 cm^{-1}. Found: C 63.99; H 6.17%. $C_{15}H_{17}ClO_3$. Calculated: C 64.16; H 6.11%. By the evaporation of the ether extract and by rubbing out the neutral fraction (16.3 g) with ether we isolated 1.7 g of 3,3'-bi[3-(2-chloro-5-methoxyphenyl)-trans-3a,4,7,7a-tetrahydrophthalide] (V); m. p. 152-153° (from ethyl acetate); λ_{max} 205, 230, 284 mμ (log ε 4.75, 4.34, 3.64); ν_{max} 1780 cm^{-1}. Found: C 64.68; H 5.47; Cl 12.82%; mol. wt. 534.† $C_{30}H_{28}Cl_2O_6$. Calculated: C 64.87; H 5.08; Cl 12.77%; mol. wt. 555. Chromatography of the residue on 230 g of acidic alumina (activity III; elution with a 2:1 mixture of chloroform and heptane) gave 14.2 g of an oily substance having ν(CO) = about 1740 (s), 1780 (w) cm^{-1}, evidently the δ-lactone (VIII) contaminated with the γ-lactone (VIIb).

b) 5 g of the keto acid (IVb) was reduced as a solution in 40 ml of 0.5 N NaOH with 3 g of $NaBH_4$ over a period of 1 h at 60-65°. The mixture was decomposed with acetic acid. After extraction with ethyl acetate, distillation gave 3 g (63%) of trans-6-(2-chloro-α-hydroxy-5-methoxybenzyl)-3-cyclohexene-1-carboxylic acid γ-lactone (VIIb); b. p. 180-184 (0.5 mm); m. p. 126-127° (from a 1:9 mixture of heptane and toluene); λ_{max} 207, 230, 283 mμ (log ε 4.37, 3.99, 3.26); ν_{max} 1780 cm^{-1}. Found: C 64.48; H 5.44; Cl 12.64%. $C_{15}H_{15}ClO_3$. Calculated: C 64.63; H 5.42; Cl 12.72%.

* All ultraviolet spectra were determined in 95% alcohol; infrared spectra were determined in mineral oil.
† The molecular weight was determined in acetone by the isothermal distillation method.

Reduction of the Lactone (VIIb). a) A mixture of 1.53 g of the lactone (VIIb), 10 g of zinc turnings (amalgamated with 0.36 g of $HgBr_2$ in 2.5 ml of concentrated HCl and 5 ml of water), 5 ml of toluene, 1 ml of acetic acid, and 5 ml of 20% HCl was boiled for 8 h and then treated as described in Expt. (a) on the reduction of the keto acid (IVb). We obtained 40 mg (2.6%) of the acid (VIb) and isolated simultaneously 1.44 g (93.5%) of unchanged lactone (VIIb).

b) 3.9 g of sodium was added in the course of 40 min to a solution of 15.3 g of the lactone (VIIb) in 1800 ml of liquid ammonia at its boiling point, and after 2 h the mixture was decomposed with 10 g of NH_4Cl. After similar treatment we obtained 14 g of the lactone (VIIa), m. p. 78-80° (from 59% alcohol); λ_{max} 206, 275, 281 mμ (log ε 4.08, 3.35, 3.32); ν_{max} 1770 cm^{-1}. Found: H 6.72%. $C_{15}H_{16}O_3$. Calculated: C 73.75; H 6.60%. By acidification of the bicarbonate extract we obtained 0.5 g of the acid (XI), m. p. 117-118° (from 50% methanol); λ_{max} 208, 280, 286 mμ (log ε 4.32, 3.50, 3.45); ν_{max} 1699, 3040 cm^{-1}. Found: equiv. 240. $C_{15}H_{18}O_3$. Calculated: equiv. 246.

4α,5β-Dibromo-2β-(2-chloro-5-methoxybenzyl)cyclohexane-1α-carboxylic Acid (IX). A solution of 2.72 g of bromine in 25 ml of methylene chloride was added gradually to 4.8 g of the acid (VIb) in 125 ml of methylene chloride at −60°, and the reaction mixture was treated in the usual way. The yield of the dibromo acid (IX) was quantitative; m. p. 144-146° (from a mixture of chloroform and heptane); λ_{max} 282, 289 mμ (log ε 3.32; 3.28); ν_{max} 1709, 3020 cm^{-1}. Found: C 40.80; H 4.03%. $C_{15}H_{17}Br_2ClO_2$. Calculated: C 40.88; H 3.89%.

2α,3β-Dibromo-8-chloro-5-methoxy-10-oxo-1,2,3,4,4aβ,9aα,10-octahydroanthracene (X). By the action of 3.5 ml of thionyl chloride at 20°, 7.3 g of the dibromo acid (IX) in 15 ml of dry ether was converted into its acid chloride and then cyclized with the help of 3.75 ml of $SnCl_4$ in 4 ml of benzene (0-5°, 20 min). We obtained 6 g (86%) of the dibromo ketone (X), m. p. 158-159° (from ether); λ_{max} 254, 326 mμ (log ε 3.90, 3.65); ν_{max} 1694 cm^{-1}. Found: C 42.66; H 3.69%. $C_{15}H_{15}Br_2ClO_2$. Calculated: C 42.63; H 3.58%.

4α-Bromo-2β-(2-chloro-5-methoxybenzyl)-5α-hydroxycyclohexanecarboxylic Acid γ-Lactone (XII). A solution of 1.12 g of dibromo acid (IX) in 17.5 ml of 5% sodium carbonate solution was heated for 2 h at 50° and left for 12 h at 20°. The precipitated crystals were washed with water; after recrystallization from a 2:1 mixture of chloroform and hexane we obtained 270 mg (29%) of the lactone (XII), m. p. 156-158°; λ_{max} 207, 230, 282, 290 mμ (log ε 4.34, 4.00, 3.22, 3.19); ν_{max} 1787 cm^{-1}. Found: C 49.92; H 4.37; Hal 32.16%. $C_{15}H_{16}BrClO_3$. Calculated: C 50.09; H 4.48; Hal 32.08%.

2β-(2-Chloro-5-methoxybenzyl)-5-oxocyclohexane-1α-carboxylic Acid (XIII). a) A solution of 120 mg of the bromo lactone (XII) in 5 ml of 2% NaOH was boiled for 2 h and then acidified with 20% H_2SO_4. The precipitated oil was extracted with chloroform. Crystallization from a 2:1 mixture of hexane and acetone gave 60 mg (61%) of the keto acid (XIII), m. p. 107-109°; λ_{max} 229, 282, 289 mμ (log ε 4.02, 3,31, 3,26); ν_{max} 1710 cm^{-1}. Found: Cl 12.01%. $C_{15}H_{17}ClO_4$. Calculated: Cl 11.95%.

b) A solution of 1.5 g of the dibromo acid (IX) in 20 ml of 1 N KOH was boiled for 90 min; after acidification to Congo Red with 10% HCl we obtained 0.91 g (90%) of the keto acid (XIII) described in the preceding experiment.

8-Chloro-5-methoxy-3,10-dioxo-1,2,3,4,4aβ,9,9aα,10-octahydroanthracene (Ib) was prepared by treating 400 mg of the keto acid (XIII) with 150 ml of anhydrous HF for 4 h at 20°. After chromatography on 4 g of acidic alumina (activity III, elution with chloroform) and crystallization from toluene the yield of the diketone (Ib) was 225 mg (60%), m. p. 160°; λ_{max} 223, 255, 323 mμ (log ε 4.34, 3.86, 3.58); ν_{max} 1573, 1682, 1724 cm^{-1}. Found: Cl 12.77%. $C_{15}H_{15}ClO_3$. Calculated: Cl 12.72%.

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SUMMARY

8-Chloro-5-methoxy-3,10-dioxo-1,2,3,4,4aβ,9,9aα,10-octahydroanthracene (Ib) was synthesized; this can serve as an intermediary in the preparation of the tetracyclic analog (IIb) of aureomycin.

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