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Total Synthesis of Tetracyclines.[1] III.[2] Synthesis of a Tricyclic Model System

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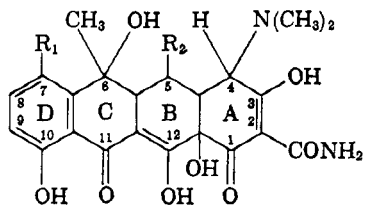
A synthesis of 5-chloro-8-hydroxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthramide, (VI), a three ring analog of the tetracyclines, is described. Starting with 4-chloro-3-methylanisole (VIII), a series of six steps gave 3-(2′-chloro-5′-methoxybenzyl)glutaric acid (XIV) which was cyclized with polyphosphoric acid to 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetic acids (XV). Condensation with malonic ester gave a tricyclic ester (XX) which was aminated and hydrolyzed to the desired compound.

The elucidation of the structures of oxytetracycline[3,4] (I), and chlortetracycline[5,6] (II), the first examples of closely related antibiotics which are grouped under the generic name of the parent "tetracycline"



I. R_1 = Cl, R_2 = H
II. R_1 = H, R_2 = OH
III. R_1 = R_2 = H

(III) system, gave impetus to synthetic efforts in this area. The complex array of functional groups in these molecules, together with the marked tendency of these systems toward acidic or alkaline degradation, presented immediate difficulties in attempts to achieve a wide range of selective structural modifications by direct chemical means. These same factors, moreover, provided a serious challenge with respect to an ultimate goal of total synthesis of biologically active tetracycline derivatives.

At the time total synthesis was first considered, it had already been observed that many small changes in chemical structure either drastically reduced or completely destroyed the antibacterial activity of these compounds. On the other hand, certain variations of substituents on carbons 5 and 7 were known which, while altering some properties, did not grossly affect the antibacterial activity. It seemed quite possible, therefore, that substituents on carbon 6 might also be varied within limits, while retaining the characteristic tetracycline antibiotic activity. During the course of the work reported here, this thesis was independently justified by the isolation of 6-demethyltetracyclines (IV)[7] and 6-deoxy-6-demethyltetracycline (V),[8] all of which possess the full biological activity of their

(1) Tetracycline and chlortetracycline are the generic names for which the American Cyanamid Company has the registered trademarks of Achromycin and Aureomycin respectively. Oxytetracycline is the generic name for which Chas. Pfizer & Co. has the registered trademark of Terramycin.

(2) The introductory paper in this series was a communication by J. H. Boothe, A. S. Kende, T. L. Fields, and R. G. Wilkinson, *J. Am. Chem. Soc.*, **81**, 1006 (1959).

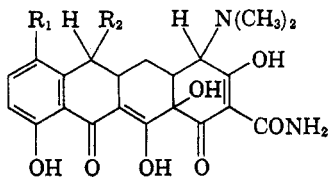
(3) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, K. J. Brunings, and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 3708 (1952).

(4) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings, and R. B. Woodward, *J. Am. Chem. Soc.*, **75**, 5455 (1953).

(5) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. A. Stein, C. F. Wolf, and J. H. Williams, *J. Am. Chem. Soc.*, **74**, 4981 (1952).

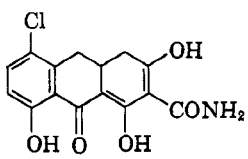
(6) C. R. Stevens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings, and R. B. Woodward, *J. Am. Chem. Soc.*, **76**, 3568 (1954).

precursors and in addition show greatly increased stability towards acids and bases. Thus the synthetic goal of a simpler tetracycline, *e.g.*, 6-demethyl-6-deoxy-tetracycline, was found to be justified.

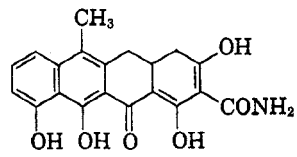


IV. R_1 = Cl or H, R_2 = OH
V. R_1 = R_2 = H

As the intact tricarbonylmethane system of the A ring appeared to be essential for activity, our initial goal was the construction of a model tricyclic structure, VI, having the principal features of the A, B, and D rings of the tetracyclines. It

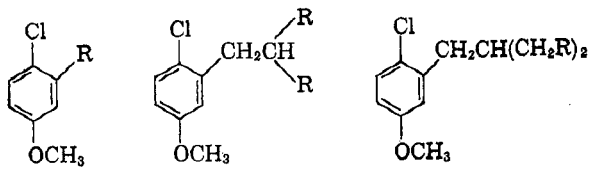


VI

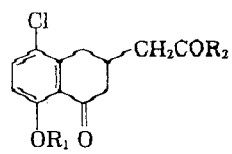


VII

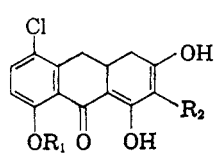
was of interest to see if such a simple compound might possess the minimal activity found in the tetracyclic analog, dedimethylamino-12*a*-deoxyanhydrochlortetracycline[6] (VII). Of more importance was the expectation that the techniques and synthetic intermediates so developed would be the basis for synthesis of tetracycline systems.



VIII. R = CH_3
IX. R = CH_2Br
X. R = $COOC_2H_5$
XI. R = CH_2OH
XII. R = $CH_2OSO_2CH_3$
XIII. R = CN
XIV. R = COOH



XV. R_1 = CH_3, R_2 = OH
XVI. R_1 = H, R_2 = OH
XVII. R_1 = CH_3, R_2 = Cl
XVIII. R_1 = CH_3, R_2 = $OCOOC_2H_5$
XIX. R_1 = CH_3, R_2 = $CH(COOC_2H_5)_2$



XX. R_1 = CH_3, R_2 = $COOC_2H_5$
XXI. R_1 = CH_3, R_2 = H
XXII. R_1 = H, R_2 = $COOC_2H_5$
XXIII. R_1 = CH_3, R_2 = $CONH_2$

The starting material for this total synthesis, 4-chloro-3-methylanisole (VIII)[9] was converted to 2-chloro-5-methoxybenzyl bromide (IX) in good yield by two methods. The longer route involved permanganate oxidation to 2-chloro-5-methoxybenzoic acid,[9] conversion to its methyl ester, lithium aluminum hydride reduction to the benzyl alcohol, and replacement of the hydroxyl group using phosphorus tribromide to give the benzyl bromide (IX),[10] a low melting solid with lachrymatory properties. The method of choice was the direct benzoyl peroxide catalyzed reaction of the 4-chloro-3-methylanisole (VIII) with *N*-bromosuccinimide to give the benzyl bromide (IX) directly.

This benzyl bromide was readily condensed with ethyl malonate and the resulting substituted malonic ester (X) homologated to 3-(2-chloro-5-methoxybenzyl) glutaric acid (XIV) in the following manner: Reduction with lithium aluminum hydride gave the 1,3-propanediol (XI)[11] from which the methanesulfonate and the *p*-toluenesulfonate esters were prepared in good yield. The former ester was the intermediate of choice and reacted smoothly with alkali cyanides to give 3-(2-chloro-5-methoxybenzyl)glutaronitrile (XIII). Little effort was expended in trying to isolate this intermediate since in the course of its formation some hydrolysis occurred and in one case some 3-(2′-chloro-5′-methoxybenzyl)-glutaric acid monoamide was isolated. In general, the reaction mixture was treated with aqueous sodium hydroxide and the alkaline hydrolysis to the 3-(2-chloro-5-methoxybenzyl)glutaric acid (XIV) was completed without difficulty.[12]

This glutaric acid when heated with acetic anhydride readily formed an anhydride. Either the acid or the anhydride, when gently warmed with polyphosphoric acid, cyclized to 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetic acid (XV) (referred to hereafter as the methoxy tetralone acetic acid.) This compound was resolved

(7) J. D. R. McCormick, N. O. Sjolander, U. Hirsch, E. R Jensen, and A. P. Doerschuk, *J. Am. Chem. Soc.*, 79, 4561 (1957).

(8) C. R. Stephens, K. Murai, H. H. Rennhard, L. H. Conover, and K. J. Brunnings, *J. Am. Chem. Soc.*, 80, 5324 (1958).

(9) A. Peratoner and G. B. Coronedi, *Gazz. chim. Ital.*, 28, I, 213 (1898).

(10) The corresponding benzyl chloride was prepared but was much less reactive in the succeeding condensation.

(11) Although the reaction of this diol with thionyl chloride readily gave the 1,3-dichloro compound, this was unreactive in the next step. Reaction with phosphorus tribromide gave the 1,3-dibromo compound which was quite reactive with sodium cyanide but the yield and purity of this dibromo derivative were not satisfactory. The 1,3-diiodo derivative was prepared by halogen exchange with the 1,3-dichloro compound and was readily purified and quite reactive with sodium cyanide.

(12) A similar route to a substituted glutaric acid was used by M. S. Newman and D. Lednicer, *J. Am. Chem. Soc.*, 78, 4765 (1958).

into its optical isomers but the succeeding steps were carried out on the racemic mixture.

Vigorous acid hydrolysis split the methyl ether to give the hydroxytetraloneacetic acid (XVI), a crystalline solid whose phenolic hydroxyl group could readily be benzylated or acetylated. The ultraviolet absorption spectrum of this phenolic ketone shows the characteristic bathochromic shift when the solvent is made basic.[13]

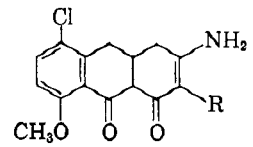
Treatment of the methoxytetraloneacetic acid (XV) with thionyl chloride resulted in a deep brown solution, whereas oxalyl chloride reacted to give a light yellow acid chloride (XVII) which could be crystallized from ether but was usually used as a gummy concentrate.[14]

The methoxytetraloneacetyl chloride (XVII) readily condensed with either sodio or magnesio malonic ester, but the resultant acyl malonate (XIX) was not generally isolated, as additional basic catalyst resulted directly in the cyclization to ethyl 5-chloro-8-methoxy-1,2,3,4,4a,9,9a,10-octahydro-1,3,4-trioxo-2-anthroate (XX).[15]

As might be expected the methoxy anthroate (XX) decarbethoxylated when subjected to 1*N* sodium hydroxide at 100° for six hours followed by acidification, but surprisingly the tricyclic system itself showed no apparent ring cleavage under these relatively vigorous conditions and 5-chloro-8-methoxy - 1,3,9 - trioxo - 1,2,3,4,4a,9,9a,10 - octahydroanthracene (XXI) was isolated in excellent yield.

Having in the former tricyclic system an arrangement of functional groups closely related to that in rings A, B and C of 4-dedimethylamino-12a-deoxy-6-demethyl anhydrotetracycline, which has some antibacterial activity *in vitro*, it was of interest to convert the carbethoxy group to a carboxamido group and to remove the blocking group on the phenolic oxygen to see whether the antibacterial activity of the anhydrotetracycline is dependent on the presence of the D ring.

Treatment of the methoxy anthroate (XX) with methanolic ammonia or concentrated ammonium hydroxide at room temperature does not affect the carbethoxy group but one of the carbonyl oxygens is replaced to give, according to the infrared spectrum (NH bands at 2.89 and 2.99 μ), a vinyl amine (XXIV).[16]



XXIV. R = $COOC_2H_5$
XXV. R = $CONH_2$

When methanolic ammonia was used in a sealed bomb at 80° for five hours, a compound containing two nitrogens was obtained. Analytical and spectral data indicate this product to be a carboxamide having a vinyl amine as in XXV. The vinyl amine group is readily hydrolyzed with 4*N* hydrochloric acid to give 5-chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthramide (XXIII).

The final step of hydrolysis of the methyl ether of the methoxy[17] anthramide (XXIII), using a mixture of 40% aqueous hydrobromic acid and glacial acetic acid at reflux temperature, failed to yield the desired product. This reaction was followed by the ultraviolet absorption spectra of the reaction mixture at various time intervals. The 375 mμ peak of the starting anthramide gradually shifted to 390 mμ with a shoulder at 410 mμ. On continued refluxing the long wave length peak decreased in intensity, shifting back to 340–345 mμ. This data indicated that the methyl ether was cleaved followed by cleavage of the ring system between C_1 and C_{9a} to give the hydroxy tetralone chromophore.

When this hydrolysis was carried out using 30% anhydrous hydrogen bromide in glacial acetic acid neither the above ring cleavage nor amide hydrolysis prevented recovery of the desired 5-chloro-8-hydroxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthramide (VI) in 53% yield. This product showed no antibacterial activity.

EXPERIMENTAL[18]

Methyl 2-chloro-5-methoxybenzoate. To a suspension of 87.0 g. (0.466 mole) of 2-chloro-5-methoxybenzoic acid[3] (m.p. 174–175°) in 300 ml. of dry benzene was added 3 drops of pyridine and then 72 ml. (1.0 mole) of thionyl chloride was added slowly with heating. When the vigorous reaction was over, the clear solution was refluxed for 10 min. before rapidly adding 100 ml. of absolute methanol. The mixture was refluxed for 2 hr., concentrated by distilling most of the benzene and excess methanol, washed with 1*N* sodium bicarbonate solution, and the product extracted with ether. The ether layer was washed with water, dried over magne-

(13) E. A. Braude, *Ann. Repts. Chem. Soc.* **42**, 105 (1945).

(14) This crude acid chloride was characterized by treatment with anhydrous ammonia to give the methoxytetraloneacetamide in almost quantitative yield. The same amide could be prepared by ring closure of the previously mentioned benzyl glutaric acid monoamide using polyphosphoric acid.

(15) Alternate routes which were investigated include the use of a mixed carboxylic- carbonic anhydride in place of the acid chloride, and phenolic blocking groups such as benzyl or acetyl instead of methyl. The acyl malonic esters in each case could be isolated as their crystalline copper chelates. The acetoxy derivative could not be cyclized to a tricyclic intermediate under the conditions used for the methoxy and benzyloxy compounds.

(16) Positioning of this vinyl amine group on carbon 3 as in XXIV is a likely possibility but the evidence does not make a clear distinction between the 1, 3 and 9 positions.

(17) The benzyl blocking group had been carried to this point despite the extra steps involved, in case the methyl ether might be too difficult to split selectively. As expected, the removal of the benzyl group by catalytic reduction was quite successful and ethyl 5-chloro-8-hydroxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthroate (XXII) was readily isolated.

(18) All boiling points and melting points are uncorrected

sium sulfate, and concentrated to a brown oil. Distillation at 0.2 mm. gave 92.2 g. (98%) of colorless oil at 108–110°.

2-Chloro-5-methoxybenzyl alcohol. A solution of 92.2 g. (0.460 mole) of methyl 2-chloro-5-methoxybenzoate in 100 ml. of dry ether was added slowly with stirring to a solution of 12.1 g. (0.318 mole) of lithium aluminum hydride in 300 ml. of dry ether. After the addition was complete, the reaction mixture was stirred for 1 hr. and let stand for 1.5 hr. The excess lithium aluminum hydride was decomposed with ethyl acetate and then by adding hydrochloric acid slowly. The acidic aqueous layer was separated and the ether layer was washed with 1*N* hydrochloric acid before drying. After concentration, the residual light yellow oil was distilled at 0.5 mm. yielding 78.3 g. (99%) of colorless oil between 110–116°.

2-Chloro-5-methoxybenzyl bromide (IX). Method A. To a solution of 78.3 g. (0.454 mole) of 2-chloro-5-methoxybenzyl alcohol in 300 ml. of dry benzene was added 15.2 ml. (0.16 mole) of phosphorus tribromide in 60 ml. of benzene. The mixture was refluxed for 1 hr. and let stand 1 hr. before washing with water. The organic layer was dried and concentrated to drive off almost all of the benzene. The residue crystallized from 100 ml. of petroleum ether (b.p. 20–40°) as white needles. The total yield was 104.7 g. (98%); m.p., 55.5–57.5°.

Anal. Calcd. for C_8H_8OClBr: C, 40.8; H, 3.42; Cl, 15.07; Br, 33.95. Found: C, 40.59; H, 3.66; Cl, 14.88; Br, 33.97.

Similarly, reaction with thionyl chloride gave the corresponding benzyl chloride which distilled at 60°/0.2 mm. to give a low yield of solid melting at 36–39°. Although analysis and infrared spectrum indicated only slight contamination, this halide was unreactive in the next step and was not further investigated.

Method B. A mixture of 2-chloro-5-methoxytoluene (VII) (94.0 g., 0.6 mole), 600 ml. reagent grade carbon tetrachloride, *N*-bromosuccinimide (117.4 g., 0.66 mole), and 0.1 g. of benzoyl peroxide was stirred at reflux temperature and additional 0.1-g. quantities of benzoyl peroxide were added after 1.5 and 18 hr. After refluxing 21 hr. the volume of solvent was reduced to approximately 250 ml. and the succinimide filtered off. The filtrate was washed with three 200-ml. portions of water, dried, concentrated, and the residual oil crystallized on standing overnight; yield of crude 2-chloro-5-methoxybenzyl bromide (IX) was 131.0 g. (93%). This material was used without further purification for the condensation with diethyl malonate. It could be recrystallized as above to yield material of analytical purity.

Diethyl 2-chloro-5-methoxybenzylmalonate (X). To a refluxing solution of 5.3 g. (0.230 g.-atom) of sodium in 200 ml. of absolute ethanol was added 60 ml. (0.305 mole) of freshly distilled diethyl malonate and then a warm solution of 47.0 g. of pure 2-chloro-5-methoxybenzyl bromide (0.200 mole) in 200 ml. of absolute ethanol was added at a rate which kept the reaction under control. White solid formed almost immediately and the mixture was refluxed for 2.5 hr. After distilling the alcohol and acidifying with 6*N* hydrochloric acid, the product was extracted with ether, followed by washes with water, dilute sodium bicarbonate, and water. The ether layer was dried and concentrated to a yellow oil. Distillation at 0.3 mm. yielded 54.6 g. (87%) of colorless oil at 147–155°, n_D^{25} 1.5030.

Anal. Calcd. for $C_{15}H_{19}O_5Cl$: C, 57.2; H, 6.08; Cl, 11.27. Found: C, 57.38; H, 6.32; Cl, 11.09.

2-(2′-Chloro-5′-methoxybenzyl)-1,3-propanediol (XI). A solution of 105 g. (0.33 mole) of diethyl 2-chloro-5-methoxybenzylmalonate in 360 ml. of dry ether was added slowly with stirring to 19.5 g. (0.513 mole) of lithium aluminum hydride dissolved in 700 ml. of dry ether. The mixture was stirred and refluxed for 4.5 hr. before decomposing the excess hydride with ethyl acetate. The mixture was acidified with 6*N* hydrochloric acid, washed with water, and let stand over 70 ml. of 5*N* sodium hydroxide over the weekend. The ether layer was washed with water, dried, and concentrated to an almost colorless viscous oil which turned to a semisolid on seeding. Distillation at 0.1 mm. gave 64 g. (84%) of a colorless oil at 160–175° with a small forerun at 130–160°. On seeding, the main fraction gave a white solid, m.p. 41–46°.

Anal. Calcd. for $C_{11}H_{15}O_3Cl$: C, 57.2; H, 6.54; Cl, 15.4. Found: C, 57.53; H, 6.66; Cl, 15.35.

2-(2′-Chloro-5′-methoxybenzyl)-1,3-propanediol, bismethanesulfonate (XII). A solution of 2-(2′-chloro-5′-methoxybenzyl)-1,3-propanediol (100.0 g., 0.435 mole) in 500 ml. of benzene and 95 g. of pyridine (1.2 moles) was cooled to 5°. Methanesulfonyl chloride (114 g., 1.0 mole) was added over a 30-min. period, the temperature of the reaction mixture being maintained between 5–15°. The reaction mixture was stored at 5° for 16 hr., and precipitated white crystals were collected on a filter and washed thoroughly with five 100-ml. portions of benzene. The combined washings and filtrate were washed with 250 ml. of 1*N* sodium bicarbonate, then with 200 ml. of water. The benzene layer was treated with charcoal, dried, and the volatile solvent removed *in vacuo*. The yield of crude 2-(2′-chloro-5′-methoxybenzyl)-1,3-propanediol, bismethanesulfonate was 172.3 g. Recrystallization of 148 g. of the crude material from 300 ml. 1-butanol yielded 135.0 g. of white crystals; m.p., 75–77° (93.7%).

Anal. Calcd. for $C_{13}H_{19}ClS_2O_7$: C, 40.4; H, 4.95; Cl, 9.19; S, 16.6. Found: C, 40.59; H, 5.09; Cl, 9.03; S, 16.58.

2-(2′-Chloro-5′-methoxybenzyl)-1,3-propanediol, bis-p-toluenesulfonate. To a solution of 2.30 g. (0.010 mole) of 2-(2′-chloro-5′-methoxybenzyl)-1,3-propanediol in 16 ml. of pyridine was added 4.40 g. (0.023 mole) of *p*-toluenesulfonyl chloride to get a clear warm solution. After standing at room temperature for 17 hr., the mixture, containing some white crystals, was concentrated to a gum. This was dissolved in ethyl acetate and washed with water. From the ethyl acetate layer on concentration a yellow oil was obtained which in part crystallized from an ethanol water mixture to give 0.15 g. (3%) of white needles, m.p. 89–94°.

Anal. Calcd. for $C_{25}H_{27}O_7S_2Cl$: C, 55.70; H, 5.05; S, 11.90; Cl, 6.58. Found: C, 56.98; H, 5.38; S, 10.32; Cl, 5.75.

2-(2′-Chloro-5′-methoxybenzyl)-1,3-dihalopropanes. (a) *Dichloro.* To a solution of 23.06 g. (0.100 mole) of 2-(2′-chloro-5′-methoxybenzyl)propane-1,3-diol in 100 ml. of dry benzene was added 24.0 ml. (0.35 mole) of thionyl chloride. This mixture stood at room temperature for 18 hr. and was then refluxed for 6 hr. Methanol was added slowly to react with the excess thionyl chloride. The reaction mixture was washed with 2*N* sodium hydroxide until alkaline, then with water until neutral, dried, and concentrated to a yellow oil. Attempts to purify this compound by crystallization from ether gave only a low yield of somewhat impure solid melting about room temperature.

(b) *Diiodo.* To the above crude oil was added a solution of 45 g. (0.34 mole) of sodium iodide in 350 ml. of acetone. There was an immediate blackening of the solution which was refluxed for 5 days with intermittent filtration removing 9.9 g. of sodium chloride. The mixture was then concentrated, water added, and the product extracted with ether. Evaporation of the ether gave an almost black oil from which only small yields of crude product could be obtained by crystallization from ethanol. However, evaporative distillation at 0.1 mm. gave a yellow forerun at about 130°, and a yellow gum from 130 to 150°, which crystallized readily from ethanol to give 16.2 g. of white needles; m.p., 67–69°. Additional material was recovered by redistillation of the forerun and the residues, yielding 7.2 g. of material melting from 58 to 68°; total yield, 23.4 g. (52%). Recrystallization from ethanol raised the melting point to 68–69.5°.

Anal. Calcd. for $C_{11}H_{13}OCII_2$: C, 29.35; H, 2.92; Cl, 7.88; I, 56.4. Found: C, 29.72; H, 3.12; Cl, 8.23; I, 56.10.

(c) *Dibromo.* The dibromo analog prepared from the diol using phosphorus tribromide was isolated in poor yield by distillation at 160–175°/0.5 mm. as a colorless oil with a poor analysis. This crude material, however, gave the desired product in the succeeding step.

β-(2-Chloro-5-methoxybenzyl)glutaric acid (XIV). A solution of potassium cyanide (47.7 g., 0.765 mole) in 230 ml. water was added to a solution of 2-(2′-chloro-5′-methoxy-

benzyl)-1,3-propanediol, bismethane-sulfonate (135.0 g., 0.348 mole) in 690 ml. of ethanol. The mixture was refluxed on a steam bath for 4.5 hr., during which time it changed from light yellow to dark green. A 230-ml. portion of 10*N* sodium hydroxide was then added and refluxing was continued for an additional 16 hr. At the end of this period the solution had completely lost its green color and was amber. The solution was concentrated to approximately 600 ml. by distillation at atmospheric pressure and then extracted with three 300-ml. portions of ether. The aqueous layer was treated with charcoal and acidified at 10° by the slow addition of 200 ml. of concentrated hydrochloric acid. The white solid which precipitated was collected on a filter and then dissolved in 350 ml. of 1*N* sodium bicarbonate. This yellow solution was slowly poured into 200 ml. of 6*N* hydrochloric acid and the β-(2-chloro-5-methoxybenzyl)glutaric acid separated as a tan oil which solidified upon cooling in an ice bath. It was collected on a filter and dried *in vacuo* over phosphorus pentoxide; yield, 69.0 g. (70%); m.p., 102–109°. On dissolving 200 mg. in 15 ml. of water and 2 ml. of acetone at the boiling point, decolorizing, and cooling, white crystals were obtained, m.p., 117–118°.

Anal. Calcd. for $C_{13}H_{15}O_5Cl$: C, 54.3; H, 5.27; Cl, 12.37; neut. equiv., 143.3. Found: C, 54.25; H, 5.53; Cl, 12.65; neut. equiv., 150.

The corresponding dibromo-, diiodo-, and bistoluenesulfonyl derivates were similarly treated with sodium or potassium cyanide followed by hydrolysis to give the substituted glutaric acid in good yield. The dichloro derivative, however, under similar reaction conditions was recovered unchanged.

Isolation of the dinitrile (XIII) before alkaline hydrolysis offered no advantages as far as yield or purification was concerned. In one preparation the β-(2-chloro-5-methoxybenzyl)glutaronitrile was isolated by removing the ethanol and extraction with ether. Distillation at 120–130°/3 mm. gave a colorless oil in poor yield and the analysis was not satisfactory. It did, however, show the characteristic infrared peaks at 4.45 μ and 4.50 μ.

Also, from the reaction mixture before the alkaline hydrolysis some β-(2-chloro-5-methoxy benzyl)glutaric acid monoamide could be isolated in 6.6% yield from an aqueous alkaline extract by acidification. Crystallization from ethyl acetate gave white plates; m.p., 143.5–145°.

Anal. Calcd. for $C_{13}H_{16}NClO_4$: C, 54.7; H, 5.66; Cl, 12.4. Found: C, 54.5; H, 5.73; Cl, 12.56.

β-(2-Chloro-5-methoxybenzyl)glutaric anhydride. A solution of β-(2-chloro-5-methoxybenzyl)glutaric acid (1.0 g.) in 25 ml. of acetic anhydride was refluxed for 1 hr. and the reaction mixture concentrated by distillation at 1 mm. The residual tan oil crystallized upon standing at room temperature. The crude β-(2-chloro-5-methoxybenzyl)glutaric anhydride was recrystallized from carbon tetrachloride, yielding 360 mg. (38.8%) of white platelets, m.p., 109–110.5°. Recrystallization from a benzene-heptane mixture did not raise the melting point. (Mixed m.p. with the acid, 92–100°).

Anal. Calcd. for $C_{13}H_{13}ClO_4$: C, 58.1; H, 4.87; Cl, 13.21. Found: C, 58.2; H, 5.24; Cl, 13.5.

8-Chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetic acid (XV). Polyphosphoric acid (600.0 g.) was poured onto β-(2-chloro-5-methoxybenzyl)glutaric acid (60.0 g., 0.21 mole) contained in a 1-l. beaker. The reactants were thoroughly mixed at room temperature and then heated at 50–60° for 2 hr. with intermittent stirring. The reaction mixture turned light yellow almost immediately, gradually darkening to a tannish yellow. After 2 hr. the reaction mixture was slowly poured into 6 l. of cool water with vigorous stirring. After storing at 5° for 14 hr. the white crystals were collected on a filter, washed with water (4 × 250 ml.) and dried *in vacuo;* weight of crude 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetic acid, 50.0 g.; m.p. 186–191°; yield, 88.5%. The crude material was dissolved in 450 ml. of refluxing ethanol, decolorized, and the light yellow filtrate allowed to stand at room temperature 2 days. The white crystals which separated were collected on a filter and dried *in vacuo;* yield of pure material, 41.4 g. (73.3%); m.p., 193–6°; $\lambda_{max}^{0.1N\ HCl}$ 225, 259, and 330 mμ, ε 22,400, 8600, 3900 and $\lambda_{max}^{0.1N\ NaOH}$ 220, 259, and 330 mμ, ε 25,200, 8475, and 3900, λ_{max}^{KBr} 5.82, 5.95 μ.

Anal. Calcd. for $C_{13}H_{13}ClO_4$: C, 58.1; H, 4.87; Cl, 13.21. Found: C, 57.69; H, 4.98; Cl, 13.25.

The corresponding glutaric anhydride was similarly cyclized with polyphosphoric acid to the same product. Similarly cyclization of β-(2-chloro-5-methoxybenzyl)glutaric acid monoamide with polyphosphoric acid gave 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthalene-acetamide in high yield as white crystals from ethanol, m.p. 237–239°.

Anal. Calcd. for $C_{13}H_{14}NClO_5$: C, 58.2; H, 5.29; N, 5.24; Cl, 13.31. Found: C, 57.68; H, 5.45; N, 5.20; Cl, 13.32.

This same amide could be obtained from the above 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthalene acetic acid by first treating with oxalyl chloride and then with anhydrous ammonia.

Resolution of 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthalene acetic acid (XV). To 1.60 g. (5.95 mmoles) of the acid in 50 ml. of absolute ethanol was added 1.95 g. of quinine base (6.0 mmoles). The mixture was warmed to get a clear solution which after being decolorized with charcoal was cooled in a refrigerator overnight. The long white needles which had formed were filtered off and washed with 20 ml. absolute ethanol. After drying, this solid weighed 2.78 g.; m.p., 180–182° and is called fraction A; $[\alpha]_D^{25}$ −65.7°. The ethanolic filtrate on concentration gave a gum which crystallized from acetone as white needles; yield, 1.03 g. of m.p. 172–174°, called fraction B; $[\alpha]_D^{25}$ −59.8°.

Fraction A on recrystallizing twice from ethanol yielded 1.57 g. m.p., 184.5–185.5°. When 1.0 g. of this was converted back to the acid and the acid recrystallized from methanol and water, a yield of 0.31 g. of white crystals was obtained, m.p. 194–196°; $[\alpha]_D^{25}$ −3.2° (methanol).

When fraction B (0.88 g.) was converted to the free acid, it also had a m.p. of 196–197° but a specific rotation of +3.1° in methanol.

8-Chloro-1,2,3,4-tetrahydro-5-hydroxy-4-oxo-2-naphthaleneacetic acid (XVI). A solution of 2.17 g. of the *dl* acid in 10 ml. of glacial acetic acid and 25 ml. of 48% hydrobromic acid was refluxed for 2 hr. and concentrated to a gum which was dissolved in sodium bicarbonate. Acidification gave a brown gum which crystallized from ethyl acetate to yield 1.37 g. (66%) of white crystals m.p. 144–145°; $\lambda_{max}^{0.1N\ HCl}$ 223, 260, and 343 mμ, ε 20,100; 10,200 and 3,950; $\lambda_{max}^{CH_3OH}$ 223, 257, and 343 mμ, ε 19,500, 7,800, and 3,700; $\lambda_{max}^{0.1N\ NaOH}$ 237, 260, and 376 mμ, ε 21,700, 7,000, and 6,550; λ_{max}^{KBr} 5.83 and 6.07 μ.

Anal. Calcd. for $C_{13}H_{11}O_4Cl.5H_2O$: C, 54.66; H, 4.59; Cl, 13.44. Found: C, 54.83; H. 4.07; Cl, 13.05.

5-Acetoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthaleneacetic acid. A solution of 8-chloro-1,2,3,4-tetrahydro-5-hydroxy-4-oxo-2-naphthaleneacetic acid (3.0 g., 0.01176 mole) in 40 ml. of acetic anhydride and 3 drops of concentrated sulfuric acid was allowed to stand at room temperature for 30 min. with occasional shaking. The reaction mixture was then diluted with 180 ml. of water and shaken mechanically for 1 hr. This aqueous solution was extracted with chloroform (3 × 40 ml.) and the combined chloroform extracts washed with water (3 × 40 ml.). The chloroform layer was dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo.* The crude acetoxy derivative thus obtained gave a negative ferric chloride test. Recrystallization from a methanol-water mixture yielded 2.86 g. (81.6%) of pure 5-acetoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthaleneacetic acid; m.p., 142–144°.

Anal. Calcd. for $C_{14}H_{13}O_5Cl$: C, 56.6; H, 4.41; Cl, 11.96. Found: C, 57.02; H, 4.57; Cl, 12.30.

5-Benzyloxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthaleneacetic acid. To a solution of 8-chloro-1,2,3,4-tetrahydro-5-hydroxy-4-oxo-2-naphthaleneacetic acid (1.0 g., 0.00392 mole) in 25 ml. of 1*N* sodium hydroxide was added benzyl

chloride (2.0 g., 0.0158 mole) and the mixture was refluxed under nitrogen for 2 hr. The reaction mixture was diluted with 175 ml. of water, cooled, and acidified with concd. hydrochloric acid. The white flocculent precipitate was collected on a filter, washed with water, and dried *in vacuo* over phosphorus pentoxide and sodium hydroxide pellets. The material was recrystallized from an ethanol-water mixture to yield 1.1 g. (85.2%) of 5-benzyloxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthaleneacetic acid, m.p. 173.5–175°.

Anal. Calcd. for $C_{19}H_{17}ClO_4$: C, 65.99; H, 4.97. Found: C, 65.55; H, 5.18.

8-Chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetyl chloride (XVIII). A solution of 5 ml. of oxalyl chloride in 50 ml. of dry benzene was added dropwise over a 30-min. period to a refluxing suspension of 5.4 g. (0.02 mole) of 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthalene acetic acid in 50 ml. of benzene. The reaction mixture was refluxed an additional 30-min. and the resultant solution concentrated to a dark brown oil *in vacuo*. A portion of this crude acid chloride was taken up in 40 ml. of ether and concentrated *in vacuo* to a dark yellow solid. The solid was slurried in 50 ml. of ether, collected on a filter, and washed three times with ether. The yield of acid chloride was 1.6 g. m.p. 80–82°.

Anal. Calcd. for $C_{13}H_{12}Cl_2O_3$: C, 54.4; H, 4.22; Cl, 24.68; OMe, 10.8. Found: C, 54.60; H, 4.54; Cl, 23.29; OMe, 10.74.

Ethyl 5-chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydroanthroate (XX). Crude 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetyl chloride was prepared as above from 10.8 g. (0.040 mole) of the acid and dissolved in 100 ml. of sodium dried toluene.

The magnesium salt of diethyl malonate[19] was prepared from magnesium metal (972.8 mg., 0.040 g.-atom), carbon tetrachloride (0.3 ml.), absolute ethanol (7.28 ml.), and diethyl malonate (6.08 ml., 0.040 mole). The mixture was heated intermittently on a steam bath for 15 min., then 100 ml. of sodium dried ether added and refluxed with stirring until all of the magnesium had dissolved (approximately 2 hr.). The ethereal solution of magnesio malonic ester was cooled to room temperature and the toluene solution of the acid chloride added dropwise, with stirring, over a 30-min. period. After 10 min. the magnesium salt of the acylated malonic ester began separating as a yellow gum. The reaction mixture was refluxed for 20 min. after the addition of the acid chloride, cooled to room temperature, and sodium hydride added (4.0 g., 0.160 mole). An additional 200 ml. of sodium dried toluene was added and the ether removed by distillation. The reaction mixture was then refluxed for 17 hr. The dark brown suspension was cooled to room temperature and 10 ml. of absolute ethanol added to decompose the excess sodium hydride. The reaction mixture was mechanically shaken for 1 hr. with 200 ml. of 1*N* hydrochloric acid, the toluene layer separated, washed twice with water, dried over anhydrous magnesium sulfate, and filtered. The ultraviolet absorption of an aliquot portion indicated 52% conversion. The filtrate was concentrated under reduced pressure to a sirupy residue and 50 ml. of absolute ethanol added. The mixture was heated on a steam bath and allowed to slowly cool to room temperature. Brownish yellow crystals of crude product deposited; yield, 4.97 g. (34%), m.p. 159–64°. A 4.68-g. sample of the crude was recrystallized from 200 ml. of absolute ethanol and 20 ml. of dimethyl formamide, yielding 3.72 grams of pure product (26.7%), m.p. 164–167°; λ_{max}^{KBr} 6.09, 6.27 μ; $\lambda_{max}^{0.1N\ HCl}$ 230 and 375 mμ, ϵ 18,800, 19,200 and $\lambda_{max}^{0.1N\ NaOH}$ 217, 270, and 385 mμ, ϵ 36,000, 15,050, and 10,500.

Anal. Calcd. for $C_{18}H_{17}ClO_6$: C, 59.26; H, 4.70; Cl, 9.72. Found: C, 59.39; H, 4.69; Cl, 9.76.

When the acid chloride in benzene solution was treated with a mixture of 3 moles of diethylsodiomalonate and 3 moles of sodium ethoxide with a 2.5-hr. reflux time the yield was only 11%.

(19) H. Lund and A. Voigt, *Org. Syntheses*, Coll. Vol. II, 594 (1943).

A study of the condensation conditions with variations in the diethyl malonate salt, the cyclization catalyst, the time, and the solvent showed the following effects on the yield of product.

Malonic Salt	Catalyst	Solvent	Time, Hr.	% Yield[a]
Sodio	Sodium ethoxide	Benzene	2.5	11
Sodio	Sodium methoxide	Benzene	20	24
Sodio	Sodium ethoxide	Benzene	20	20
Sodio	Sodium hydride	Benzene	20	20
Sodio	Sodium hydride	Toluene	20	29
Magnesio	Sodium hydride	Toluene	20	40–54
Magnesio	Sodium hydride	Xylene	20	13
Magnesio	Sodium hydride	Ether	20	0

[a] The yields except in the first case were based on the ultraviolet absorption maximum at 375 mμ.

A zinc dust distillation on 5.0 mg. of ethyl-5-chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthroate using 100 mg. of electrolytic zinc gave a yellowish condensate whose ultraviolet maxima at 308, 323, 339, 356, and 375 mμ were identical with those of anthracene.

Diethyl 8-chloro-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-acetyl malonate, copper salt. To a solution of 270 mg. (0.001 mole) of 8-chloro-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-acetic acid in 15 ml. of dry tetrahydrofuran was added 101 mg. (0.14 ml., 0.001 mole) of triethylamine. To the solution cooled in an ice-alcohol bath to −10 to −12° was added 108.5 mg. (0.095 ml., 0.001 mole) of ethyl chloroformate, and then 0.001 mole of diethyl magnesiomalonate dissolved in 20 ml. of dry ether. After standing at room temperature for 2 days, the mixture was evaporated to dryness *in vacuo* and the residue taken up in 20 ml. of ether and 20 ml. of 0.05*N* hydrochloric acid. The ether layer was washed three times with water and then 10 ml. of an aqueous solution of cupric acetate was mixed well with the ether. A blue solid formed slowly and after several hours was centrifuged, washed with water and ether, and dried; weight, 270 mg. A suspension of 150 mg. of this product in 3 ml. of water was heated on the steam bath and methanol was added slowly until nearly all was in solution (about 7 ml. of methanol). After filtering and cooling, a blue crystalline solid deposited slowly, was filtered off, washed well, and dried at 60° for 6 hr. *in vacuo;* weight, 90 mg.; m.p., shrinks and slowly melts at 77–100°.

Anal. Calcd. for $C_{20}H_{20}O_7ClCu_2$: Cl, 8.06; Cu, 7.25; OCH_3, 21.2. Found: Cl, 8.18; Cu, 7.27; OCH_3, 22.10.

Diethyl (5-benzyloxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthylacetyl)malonate, copper salt. This was prepared in the same manner as above using 5-benzyloxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthaleneacetic acid (329 mg., 0.00095 mole). The impure copper derivative was recrystallized from a chloroform-hexane mixture to yield 220 mg. of pure copper salt of diethyl (5-benzyloxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthylacetyl)malonate; m.p., 175–178°.

Anal. Calcd. for $C_{28}H_{26}ClO_7Cu/2$: C, 60.31; H, 5.06; Cl, 6.85; Cu, 6.14. Found: C, 60.20; H, 5.09; Cl, 7.27; Cu, 6.07.

Diethyl (5-acetoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthylacetyl)malonate, copper salt. Using the above procedure with 5-acetoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthaleneacetic acid (297 mg., 0.001 mole) the yield of copper salt of diethyl (5-acetoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-

2-naphthylacetyl)malonate was 160 mg. A small quantity was recrystallized from a toluene-hexane mixture for analysis; m.p., 180–198°.

Anal. Calcd. for $C_{21}H_{22}ClO_8Cu/2$: C, 53.64; H, 4.76; Cl, 7.58; Cu, 6.80. Found: C, 53.81; H, 5.02; Cl, 7.60; Cu, 7.27.

Ethyl 8-benzyloxy-5-chloro-1,2,3,4,4a,9,9a,10-octahydro-1,3,9-trioxo-2-anthroate. To a suspension of 5-benzyloxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthaleneacetic acid (1.3 g., 0.004 mole) in 40 ml. of dry toluene at −12° was added triethylamine (0.56 ml., 0.004 mole). Ethyl chloroformate (0.38 ml., 0.004 mole) was added to the clear solution and after stirring at −12° for 10 min., diethyl magnesiomalonate (0.004 mole in 20 ml. of toluene) was added, the ice bath removed, and the mixture stirred at room temperature for 3 hr. The reaction mixture was then washed with 20 ml. of 1*N* hydrochloric acid and three 15-ml. portions of water. The toluene layer was dried and refluxed using a Stark-Dean trap to remove any residual water. The thoroughly dried toluene solution was refluxed with sodium hydride (386 mg., 0.016 mole) for 1.5 hr., during which time a dark brown color developed. The reaction was then cooled, 5 ml. of ethanol added to decompose any residual sodium hydride and shaken with 20 ml. of 6*N* hydrochloric acid. The aqueous layer was extracted with toluene (3 × 10 ml.) and the toluene washed with water (3 × 15 ml.), dried and concentrated to a dark brown oil *in vacuo*. Upon the addition of 10 ml. of ether, light yellow crystals deposited which were washed thoroughly with several portions of ether and air dried; yield of ethyl 8-benzyloxy-5-chloro-1,2,3,4,4a,9,9a,10-octahydro-1,3,9-trioxo-2-anthroate, 640 mg. (36.2%), m.p. 149–152°. Recrystallization of a small amount from ethanol raised the m.p. to 150–152°.

Anal. Calcd. for $C_{24}H_{21}ClO_6$: C, 65.5; H, 4.80; Cl, 8.06. Found: C, 65.72; H, 5.08; Cl, 8.23.

Ethyl 5-chloro-1,2,3,4,4a,9,9a,10-octahydro-8-hydroxy-1,3,9-trioxo-2-anthroate (XXII). A solution of ethyl 8-benzyloxy-5-chloro-1,2,3,4,4a,9,9a,10-octahydro-1,3,9-trioxo-2-anthroate (220 mg., 0.0005 mole) in 20 ml. of 2-methoxy ethanol was added to a suspension of prereduced platinum oxide (22 mg.) in 25 ml. of 2-methoxy ethanol and 1 drop of glacial acetic acid. The mixture was reduced with hydrogen at atmospheric pressure. After 2.5 hr., 2 equivalents of hydrogen had been absorbed and the reaction had slowed appreciably. The catalyst was removed by filtration and the solution concentrated to dryness *in vacuo*. The crude product was recrystallized from 7 ml. of ethanol; yield of pure ethyl 5-chloro-1,2,3,4,4a,9,9a,10-octahydro-8-hydroxy-1,3,9-trioxo-2-anthroate was 115 mg. (72.7%), bright yellow crystals, m.p. 142–144°; $\lambda_{max}^{CH_3OH}$ 220, 267, 405 mμ (ε 17,900, 10,200, 25,950).

Anal. Calcd. for $C_{17}H_{15}O_6Cl$: C, 58.2; H, 4.31; Cl, 10.13. Found: C, 58.54; H, 4.67; Cl, 10.12.

5-Chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydroanthracene (XXI). A solution of ethyl 5-chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthroate (XX) (900 mg., 0.0025 mole) in 50 ml. of 1*N* sodium hydroxide was heated on a steam bath for 6 hr. in an atmosphere of nitrogen. The reaction mixture was then cooled and acidified to *p*H 1 with 4*N* hydrochloric acid. The yellow crystals which precipitated were collected on a filter and dried; yield of crude XXI, 615 mg. (88.6%). Recrystallization of 100 mg. from 2 ml. of 95% ethanol gave 40 mg. of pure 5-chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydroanthracene; m.p., 168–173° dec.; $\lambda_{max}^{CH_3OH}$ 250, 373 mμ (ε 8,200, 19,000); λ_{max}^{KBr} 5.81, 6.30 μ.

Anal. Calcd. for $C_{15}H_{13}O_4Cl$: C, 61.55; H, 4.48; Cl, 12.11. Found: C, 61.43; H, 4.92; Cl, 12.03.

Ethyl 3(?)-amino-5-chloro-8-methoxy-1,9-dioxo-1,4,4a,9,9a,10-hexahydro-2-anthroate (XXIV). A suspension of ethyl 5-chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthroate (100 mg., 0.000276 mole) in 10 ml. of absolute methanol contained in a stainless steel bomb was cooled to 0° and saturated with anhydrous ammonia. The bomb was sealed and allowed to stand at room temperature for 4 days after which it was opened and the brown solution evaporated to near dryness with an air jet at room temperature. The residue was shaken thoroughly with 5 ml. of water and the *p*H adjusted to 4.5 with acetic acid. The precipitated yellow micro-crystals were collected on a filter and dried in vacuum; yield, 80 mg., m.p., turns red at 80° and dec. at 95°.

Anal. Calcd. for $C_{18}H_{18}NO_5Cl$: C, 59.42; H, 4.99; N, 3.85; Cl, 9.75; OMe, 17.06. Found: C, 58.44; H, 4.99; N, 4.05; Cl, 10.10; OMe, 15.45.

3-(?)-Amino-5-chloro-8-methoxy-1,9-dioxo-1,4,4a,9,9a,10-hexahydro-2-anthramide (XXV). A suspension of ethyl-5-chloro-8-methoxy-1,3,9-trioxo-1,2,3,4,4a,9,9a,10-octahydro-2-anthroate (1.0 g., 0.00276 mole) in 25 ml. of absolute methanol saturated at 0° with ammonia was sealed in a stainless steel bomb, heated at 80° for 5 hr., and then allowed to stand at room temperature overnight. The methanol was evaporated under an air jet at room temperature and the residue slurried in 10 ml. of 1*N* sodium hydroxide. The tan solid was collected on a filter and heated in 10 ml. of ethanol. The insoluble portion was collected and dried *in vacuo* to yield 350 mg. of crude product. A 150-mg. sample of this material was heated on a steam bath for 10 min. with 15 ml. of 4*N* hydrochloric acid and the yellow crystals were collected and recrystallized from a dimethyl formamide water mixture, yielding 65 mg.; m.p., 194–197° dec.

Anal. Calcd. for $C_{16}H_{15}N_2ClO_4$: C, 57.39; H, 4.52; Cl, 10.59; OMe, 9.26. Found: C, 57.03; H, 4.76; Cl, 10.48; OMe, 8.69.

5-Chloro-8-methoxy-1,2,3,4,4a,9,9a,10-octahydro-1,3,9-trioxo-2-anthramide (XXIII). The above crude product (XXV) (100 mg.) was heated on a steam bath with 5 ml. of 4*N* hydrochloric acid for 3 hr. and then allowed to stand at room temperature for an additional 3 hr. The reaction mixture was filtered and the crude amide recrystallized from a dimethyl formamide ethanol mixture, yielding 55 mg. of pure XXIII, m.p. 239–241° dec.

Anal. Calcd. for $C_{16}H_{14}NClO_5$: C, 57.24; H, 4.20; N, 4.17; Cl, 10.56. Found: C, 57.32; H, 4.54; N, 4.39; Cl, 10.59.

5-Chloro-1,2,3,4,4a,9,9a,10-octahydro-8-hydroxy-1,3,9-trioxo-2-anthramide (VI). A suspension of 5-chloro-1,2,3,4,4a,9,9a,10-octahydro-8-methoxy-1,3,9-trioxo-2-anthramide (XXIII) (460 mg., 0.00137 mole) in 25 ml. of anhydrous 30% hydrobromic acid in glacial acetic acid was refluxed for 1.5 hr. and then concentrated to dryness *in vacuo*. The residual dark green solid was washed with water until the washings gave a negative silver nitrate test. The crude demethylated product (400 mg.) was dissolved in 40 ml. of hot 2-methoxyethanol, treated with decolorizing carbon and filtered. The filtrate was concentrated to 25 ml. and 10 drops of water added. Upon cooling light yellow crystals precipitated, were collected on a filter, and dried *in vacuo* at 100°; yield of 5-chloro-1,2,3,4,4a,9,9a,10-octahydro-8-hydroxy-1,3,9-trioxo-2-anthramide, 180 mg., m.p. 230–233°. Upon standing overnight at 5° the filtrate yielded an additional 54 mg. of the demethylated compound; total yield, 234 mg. (53%); $\lambda_{max}^{CH_3OH}$ 220, 263, 390, 410 (shoulder) mμ (ε 17,400, 12,900, 19,300, 15,300); λ_{max}^{KBr} 2.95, 3.10, 6.02, 6.28 μ.

Anal. Calcd. for $C_{15}H_{12}O_5ClN$: C, 56.0; H, 3.77; Cl, 11.05; N, 4.36. Found: C, 56.29; H, 4.08; Cl, 10.98; N, 4.76.

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