priate solvent to give 250–500 μmoles of halide when a 5-ml aliquot was taken from the reaction mixture. After thermostating for several hours, the base and sample solutions were combined. Aliquots taken at appropriate intervals were quenched in a solution of 2 ml of acetone and 4 ml of nitric acid (0.25 M) and titrated potentiometrically.[26] The recorder chart units were tabulated and corrected for a blank.

Pseudo-first-order rate constants were obtained by plotting log $(N_\infty - N_t)$ *vs.* t, where N_∞ is the number of chart units at infinity and N_t is the number at time t. These plots were linear for more than four half-lives.

Titrimetric rate constants were determined in duplicate for $PhCH_2SO_2CHClPh$: $k = 2.58 \times 10^{-2}\ M^{-1}\ sec^{-1}$ at 25° in 40% (volume) dioxane–water. The spectrophotometric rate constant under the same conditions was $2.51 \times 10^{-2}\ M^{-1}\ sec^{-1}$.

Bis(α,α-dideuteriobenzyl) Sulfone. Benzyl sulfone (2.46 g, 9.97 mmoles), sodium hydroxide (0.20 g, 5.0 mmoles), deuterium oxide (9 ml, 500 mmoles, 99.77% deuterated), and dioxane (40 ml) were kept at 60° for 12 hr. The resulting solution was acidified with 1 ml of 12 N hydrochloric acid and concentrated. The yellow platelets obtained were washed with water and crystallized from absolute ethanol to give 2.35 g (9.39 mmoles, 94%) of colorless needles, mp 146.0–146.5°. The nmr spectrum showed 97% deuteration.

The rate of exchange was determined by dissolving sufficient sulfone in methanol to give 0.03 g/10-ml aliquot. This solution was thermostated and mixed at t_0 with a thermostated sample of methanolic sodium methoxide; the base concentration in the resulting solution was $1.60 \times 10^{-2}\ M$. Aliquots (10 ml) were removed at appropriate time intervals and quenched with 10 ml of 0.25 N nitric acid. The sulfone was collected on a sintered-glass filter and, after drying, transferred quantitatively to an nmr tube. Acetonitrile was used as a solvent; the same volume was used for each aliquot.

The instrument (Varian A-60) was tuned, and the aliquot samples were run, one after the other, without instrument readjustments. Each spectrum was integrated (relative to the phenyl hydrogens) eight to ten times. The reactions were allowed to continue for three to four half-lives. Rates were determined by plotting log $(A_\infty - A_t)$ *vs.* t, where A is the percentage of α,α′-hydrogens. The slope multiplied by 2.303 and divided by the base concentration gave the second-order rate constant. The values obtained (uncorrected for statistical or isotope effects) were: 8.9×10^{-3} and $9.5 \times 10^{-3}\ M^{-1}\ sec^{-1}$ at 0.2° and 2.0×10^{-1} and 2.2×10^{-1} at 25.1° (E_a = 20 kcal/mole; $\Delta S^{\pm} = +1$ eu).

Activation Parameters. The activation energy was calculated in each instance from the slope of the linear plot of log k *vs.* $1/T$ (three temperatures); $E_a = 4.576 \times$ slope. Activation entropies were obtained from the equation

$$\Delta S^{\pm} = 4.576[-10.7531 - \log T + \log k + (E_a/4.576\ T)]$$

Acknowledgment. We are grateful to the National Science Foundation for support of this work (GP 4208).

(26) H. A. Strobel, "Chemical Instrumentation," Addison-Wesley Inc., Reading, Mass., 1960, p 483.

The Total Synthesis of *dl*-6-Demethyl-6-deoxytetracycline[1]

J. J. Korst, J. David Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward

Contribution from the Medical Research Laboratories of Chas. Pfizer & Co., Inc., Groton, Connecticut 06340, and the Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts 02138. *Received September 5, 1967*

Abstract: The first total synthesis of the prototypic tetracycline antibiotic, *dl*-6-demethyl-6-deoxytetracycline (**7**), from methyl *m*-methoxybenzoate (**10**), is described.

Interest in the tetracyclines, a class of uniquely constituted hydronaphthacene derivatives characterized by the intricacy of their chemistry and notable for their utility in medical practice, had its origin in the announcement by Duggar in 1948 of the discovery of Aureomycin [(chlortetracycline (**1**)].[2] The molecular structures of Aureomycin and Terramycin[3] [oxytetracycline (**2**)] were elucidated in these laboratories in 1952,[4] two years after Finlay and his colleagues announced the preparation of the latter antibiotic[5] by fermentation of the actinomycete, *Streptomyces rimosus*. Production of tetracycline itself (**3**) by catalytic hydrogenolysis of Aureomycin was reported in 1953;[6a,b] subsequently, the preparation by this compound by cultivation of certain strains of *Streptomyces aureofaciens* was reported.[6c]

Since 1953 a prodigious number of investigations has been recorded, directed toward a definition and rationalization of the biogenetic origin and of the chemical, microbiological, pharmacological, and clinical properties of these polyoxygenated hydronaphthacenes,[7] while simultaneously a search for new mem-

(1) This work has been the subject of two preliminary reports: (a) L. H. Conover, K. Butler, J. D. Johnston, J. J. Korst, and R. B. Woodward, *J. Am. Chem. Soc.*, **84**, 3222 (1962); (b) R. B. Woodward, *Pure Appl. Chem.*, **6**, 561 (1963).

(2) B. M. Duggar, *Ann. N. Y. Acad. Sci.*, **51**, 177 (1948).

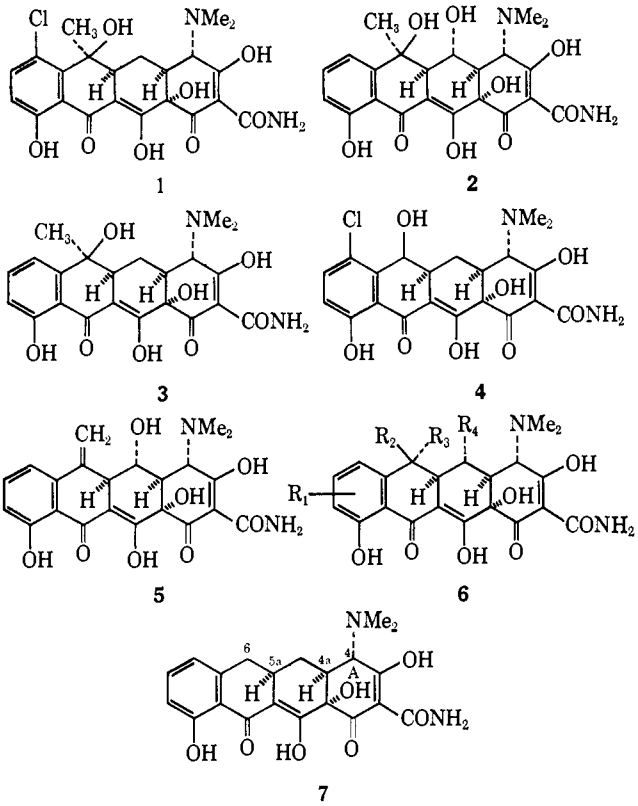
(3) Terramycin is a registered trademark of Chas. Pfizer & Co., Inc. Aureomycin is a registered trademark of Lederle Laboratories Division, American Cyanamid Co.

(4) (a) 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); 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, *ibid.*, **75**, 5455 (1953). *Cf.* also S. Hirakawa, Y. Okaya, F. M. Lovell, and R. Pepinsky, *Z. Krist.*, **112**, 439 (1959); (b) C. R. Stephens, L. H. Conover, F. A. Hochstein, P. P. Regna, F. J. Pilgrim, K. J. Brunings, and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 4976 (1952); C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings, and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

(5) A. C. Finlay, G. L. Hobby, S. Y. P'an, P. P. Regna, J. B. Routien, D. B. Seeley, G. M. Shull, B. A. Sobin, I. A. Solomons, J. W. Vinson, and J. H. Kane, *Science*, **111**, 85 (1950).

(6) (a) J. H. Boothe, J. Morton, II, J. P. Petisi, R. G. Wilkinson, and J. H. Williams, *J. Am. Chem. Soc.*, **75**, 4621 (1953); (b) L. H. Conover, W. T. Moreland, A. R. English, C. R. Stephens, and F. J. Pilgrim, *ibid.*, 4623 (1953); (c) P. P. Minieri, M. C. Firman, A. G. Mistretta, A. Abbey, C. E. Bricker, N. E. Rigler, and H. Sokol, "Antibiotics Annual 1953–1954," Medical Encyclopedia, Inc., New York, N. Y., 1953, pp 81–87.

(7) Some recent articles in which specialized aspects of the literature of the tetracyclines are reviewed are: (a, chemistry) G. C. Barrett, *J. Pharm. Sci.*, **52**, 309 (1963); H. Muxfeldt, *Angew. Chem. Intern. Ed. Engl.*, **1**, 372 (1962); H. Muxfeldt and R. Bangert, *Progr. Chem. Org.*

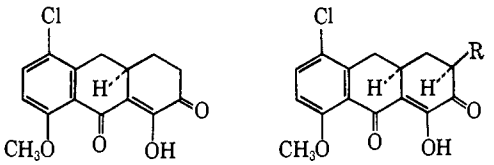


bers of the series has been pressed on a world-wide scale. As a consequence, the more recently discovered 6-demethylchlortetracycline[8] (**4**) and methacycline[9] (**5**) have joined chlortetracycline, oxytetracycline, and tetracycline in widespread application in clinical practice. All of these substances are characterized by their exceptional chemotherapeutic efficacy against bacteria, both gram negative and gram positive, rickettsia, and large viruses, such as members of the lymphogranuloma group. Most of the tetracycline antibiotics are produced by cultivation of strains of certain *Streptomyces* species. Methacycline is made by chemical modification of oxytetracycline and, as mentioned previously, tetracycline may be prepared either by partial synthesis or by fermentation.

Only a few of the large number of known tetracyclines possess the chemotherapeutic efficacy associated with the structures **1**–**4**. Analysis of the relationships between the molecular structures and the *in vivo* biological activities of such compounds led us and others[10] to conclude that the characteristic chemotherapeutic activity of the tetracycline antibiotics is dependent upon the maintenance of all of the structural and stereochemical features of the expression **6**, wherein the groups R_1–R_4 are the only functions which may be varied without effecting a substantial decrease in antibiotic activity. The simplest structure which embodies all of the elements necessary for activity is 6-demethyl-6-deoxytetracycline (**7**), and this paper describes in detail the first total synthesis of this fully biologically active prototype of the tetracycline antibiotic series.[11]

This work was undertaken partly in response to the synthetic challenge presented by the diabolical concatenation[12] of atoms present in the tetracycline system and partly to fill a practical need for a versatile method of synthesis which might be employed in exploring structure–activity relationships more deeply. In the latter sense, the synthesis of 6-demethyl-6-deoxytetracycline was regarded as a testing ground for methods having general applicability in the preparation of tetracyclines which could not be obtained by partial synthesis or directly by fermentation.

The most formidable synthetic problems posed by the structure of 6-demethyl-6-deoxytetracycline (**7**) are concentrated in ring A: every carbon atom of the skeleton of that ring bears at least one substituent, and three of the four asymmetric centers of the molecule fall in the consecutive chain C_4, C_{4a}, C_{12a}. The sole remaining stereochemical problem lies in the relative orientations at C_{4a} and C_{5a}. We determined upon the principle of elaborating ring A upon the framework of an intermediate within which the last of these relationships could be readily established in the desired sense. The tricyclic intermediate **8** appeared to us to provide a favorable and flexible vehicle for realization of this principle.



We anticipated that the tricyclic triketone **8**[13] would exhibit special reactivity in two directions. Thus, it seemed likely that two of its three carbonyl groups should constitute a stabilized vinylogous carboxylic acid system, while the third, like that in simple α-keto acids, should be both highly susceptible to addition reactions and readily enolizable. The latter property should confer high nucleophilic reactivity upon the adjacent methylene group, and thus make possible the attachment of a suitable substituent R, so constituted as

Nat. Prod., **21**, 80 (1963); R. M. Evans, "The Chemistry of the Antibiotics Used in Medicine," Pergamon Press, Oxford, 1965, pp 102–120. (b, pharmacology) C. M. Kunin and M. Finland, *Clin. Pharmacol. Therap.*, **2**, 51 (1961); L. N. Owen, *Vet. Bull.* (Commonwealth Bur. Animal Health), **35**, 187 (1965). (c, general) R. H. Johnson, *J. Oral Therap. Pharmacol.*, 1, 190 (1964); M. Barber in "Experimental Chemotherapy," Vol. 3, R. J. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1964, pp 71–101; K. H. Spitzy, *Antibiot. Chemotherapia*, 10, 193 (1962). (d, mode of action) I. H. Goldberg, *Am. J. Med.*, **39**, 722 (1965); F. L. Jackson in "Experimental Chemotherapy," Vol. 3, R. J. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1964, pp 103–117. (e, clinical application) E. M. Ory and E. M. Yow, *J. Am. Med. Assoc.*, **185**, 273 (1963); C. A. Olson and H. D. Riley, *J. Pediat.*, **68**, 783 (1966). (f, biosynthesis) J. R. D. McCormick, in "Biogenesis of Antibiotic Substances," Z. Vanek and Z. Hostalek, Ed., Academic Press Inc., New York, N. Y., 1965, pp 74–91.

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

(9) R. K. Blackwood, J. J. Beereboom, H. H. Rennhard, M. Schach von Wittenau, and C. R. Stephens, *ibid.*, **83**, 2773 (1961).

(10) For a summary of structure–activity relationships in the tetracycline antibiotic series, *cf.* J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *ibid.*, **82**, 3381 (1960).

(11) Since the preliminary report of this work appeared (see ref 1), an independent synthesis of the same compound has been reported by H. Muxfeldt and W. Rogalski, *ibid.*, 87, 933 (1965). More recently the total synthesis of 12a-deoxy-5a,6-anhydrotetracycline has been published by A. I. Gurevich, M. G. Karapetyan, M. N. Kolosov, V. G. Korobko, V. V. Onoprienko, S. A. Popravko, and M. M. Shemyakin, *Tetrahedron Letters*, 131 (1967).

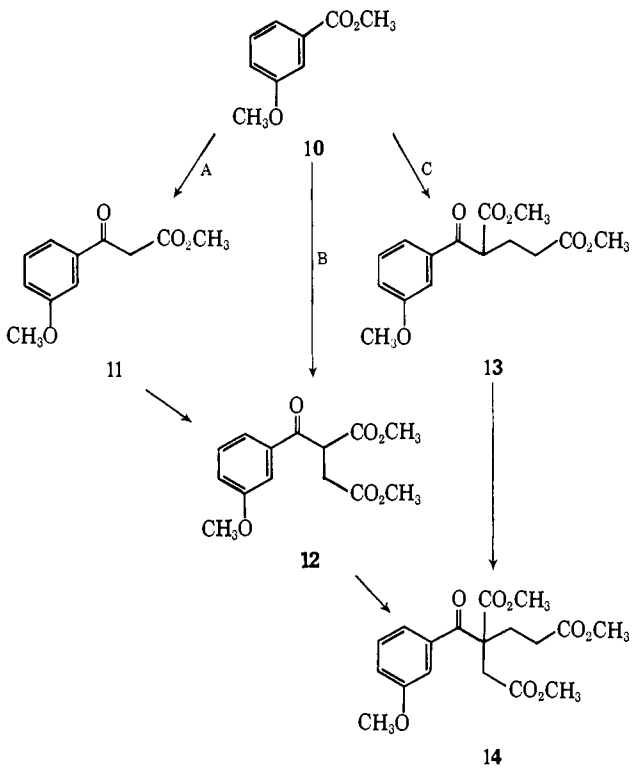
(12) R. B. Woodward in "Perspectives in Organic Chemistry," A. R. Todd, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p 160.

(13) In this and subsequent formulas in which an enolized β-diketo system is represented, alternative tautomeric structures of course are possible.

to permit elaboration to the complete ring A. Enolization of this carbonyl group also should establish in such an appropriately substituted intermediate the desired stereochemical relationship between the hydrogen atoms destined to occupy the tetracycline C_{4a} and C_{5a} positions, since the thermodynamically more stable **9** should have the substituent R oriented in the equatorial sense.

We felt further that our plan should be sufficiently flexible to provide alternative routes for achieving each of our major synthetic objectives, and to permit variation in the direction of preparing a variety of tetracyclines bearing novel substituents.

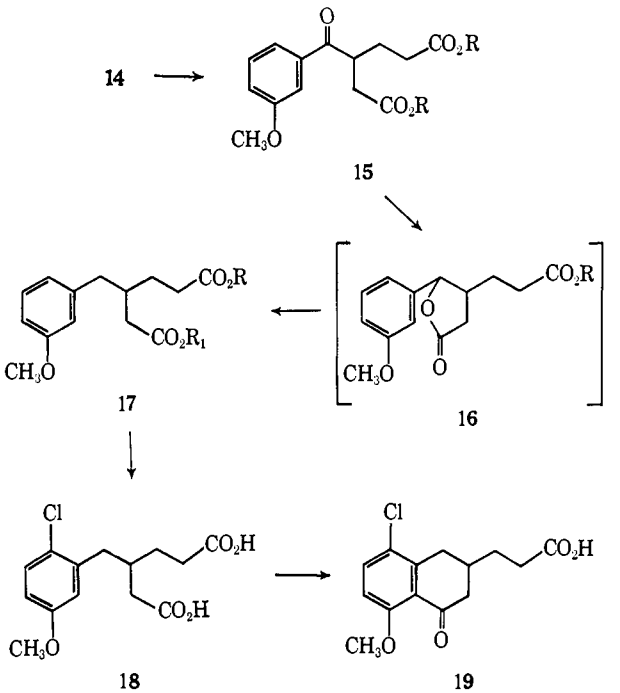
As starting material for the construction of **8**, we chose methyl *m*-methoxybenzoate (**10**) which was elaborated to trimethyl β-carboxy-β-(*m*-methoxybenzoyl)adipate (**14**) by the three different routes shown.



In the first of these methods (A), which was found in practice to be the best, the ester **10** was condensed in dimethylformamide solution in the presence of sodium hydride with methyl acetate; the resulting methyl *m*-methoxybenzoylacetate (**11**) was alkylated without isolation to give dimethyl *m*-methoxybenzoylsuccinate (**12**) in 55% over-all yield. The same product was obtained in 29% yield by direct condensation of **10** with dimethyl succinate (route B). In either event, Michael condensation of the keto diester **12** and methyl acrylate in dioxane solution, with methanolic Triton B as catalyst, gave the desired keto triester **14**. In the third but rather less satisfactory method (C) the same intermediate was prepared from **13**, the product of an initial dimethyl glutarate–methyl *m*-methoxybenzoate condensation, by alkylation with methyl bromoacetate. A mixture of hot aqueous acetic and sulfuric acids was used to hydrolyze the triester **14**; concomitant decarboxylation occurred in the normal fashion to yield β-(*m*-methoxybenzoyl)adipic acid (**15**, R = H) which was esterified for purposes of purification.

The utilization of the keto diester **15** (R = CH_3) for the preparation of the tricyclic triketone **8** was based upon two considerations. First, the ketonic carbonyl group of this ester is so sited as to correspond to the 6 position (see structure **7**) of an eventual tetracycline, and thus provides in principle the means for introducing a variety of substituents at this position. Second, resolution at this stage, could, with racemization and recycling of the unwanted isomer, permit preparation of the desired optical antipode without serious loss of material.

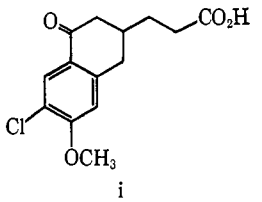
The carbonyl group of the diester **15** (R = CH_3) was hydrogenolyzed in acetic acid under 200 psi using 10% palladium on charcoal as catalyst. The reduction undoubtedly proceeds through the intermediary γ-lactone **16** (R = Me) to the half-ester **17** (R = Me; R_1 = H), which was converted *via* the diester to the diacid **17** (R = R_1 = H).



Chlorination of the diacid **17** (R = R_1 = H) in glacial acetic acid in the absence of light gave β-(2-chloro-5-methoxybenzyl)adipic acid (**18**); with the active position *para* to the methoxyl function now blocked, cyclodehydration of the chloro acid in liquid hydrogen fluoride proceeded smoothly to afford the desired tetralone **19**. The over-all yield from the diester **17** (R = R_1 = CH_3) was 63%. The intermediate **19** was identified as an 8-methoxytetralone by virtue of its ultraviolet absorption spectrum, $\lambda\lambda_{max}$ mμ (ε) 254 (7400), 326 (4200), and carbonyl absorption at 5.99 μ.[14,15]

(14) *Cf.* L. H. Conover, "Progress in the Chemistry of Oxytetracycline and Related Compounds," Special Publication No. 5, The Chemical Society, London, 1956, pp 52–62, who reported spectral data for 8-hydroxytetralone and the corresponding benzyl ether.

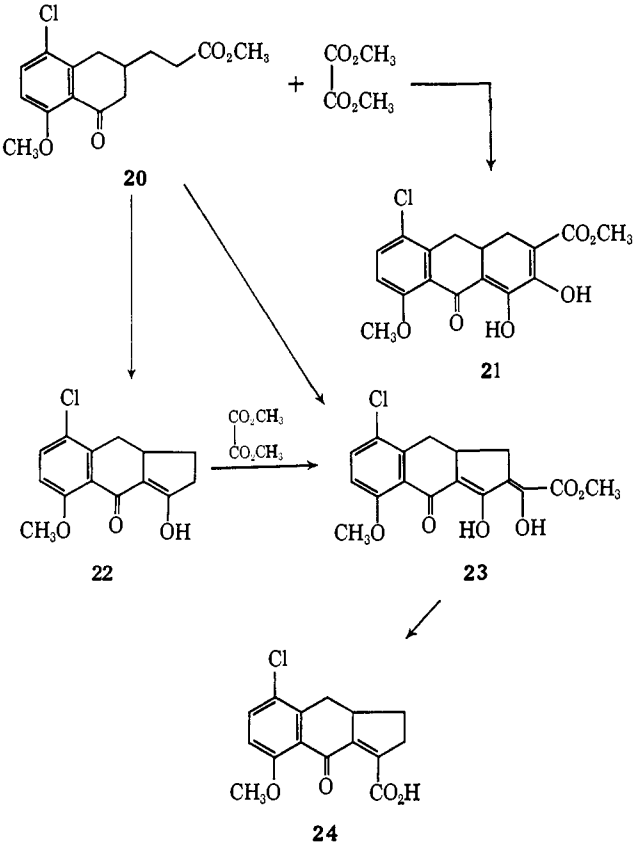
(15) An isomeric ketone, $\lambda\lambda_{max}$ mμ (ε) 270 (14,700), 290–304 sh (6800), was isolated in low yield from the hydrogen fluoride cyclization.



i

Esterification of the acid **19** set the stage for elaboration of the third ring, the critical stage in the synthesis of the tricyclic triketone **8**.

The required transformation (**20** to **21**) was satisfactorily achieved after extensive experimentation. The ester **20** is so constituted as to be susceptible to internal condensation; at room temperature it is transformed in good yield into the tetrahydrobenzindandione **22** when it is treated with sodium hydride in dimethylformamide solution. It is to be expected that under certain conditions this same internal condensation should precede intermolecular acylation by methyl oxalate. Indeed, when equimolar amounts of the latter and the tetralone ester **20** were stirred in dimethyl-



formamide at room temperature in the presence of 2 molar equiv of sodium hydride, and in the absence of methanol, the tricyclic substance **23** was formed in about 60% yield. This same material was obtained in 72% yield from the simple diketone **22** by reaction, under similar conditions, with methyl oxalate.

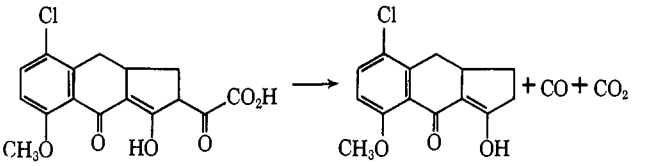
The structures **21** and **23** are of course merely illustrative of the various conjugated, enolized tautomeric forms in which these isomeric esters may exist. These structures emphasize the close similarity of the two chromophoric systems which differ formally only in orientation and in the position of attachment of one hydroxyl group to an otherwise identical conjugated system. Because the ultraviolet absorption spectra of these two compounds are in fact remarkably similar (*cf.* Figure 1), these data did not contribute to the elucidation of the structure **23** when the substance was first obtained. The structure proof rests upon the conversion of **22** to **23** and upon experiments which proved the presence of an α-keto ester function in **23**.[16] Consistent with the assigned structure is the interesting conversion of **23** under acidic conditions to the unsaturated carboxylic acid **24**; clearly this transformation involves ester hydrolysis, ring cleavage, decarboxylation, aldol condensation, and dehydration.

Perfection of the intermolecular cyclization reaction leading to **21** constituted one of the major practical obstacles which we surmounted in the course of this work. Eventually this conversion was accomplished routinely on a molar scale with an average yield of 45%.[17] Intramolecular cyclization was suppressed and the yield of **21** reached a maximum when the tetralone ester **20** was treated in dimethylformamide with a mixture of 4 equiv of sodium hydride, 2 equiv of dimethyl oxalate, and 1 of methanol in a reaction initiated at 20° and concluded at 80°.

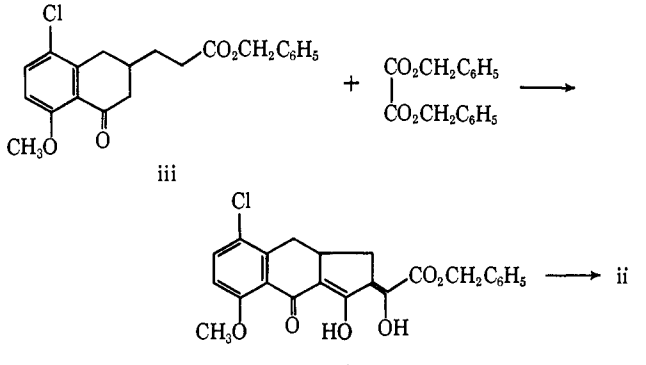
The tricyclic ester **21** was smoothly transformed to the hydroanthracene triketone **8** by hot aqueous hydrochloric and acetic acids. The infrared spectrum of **8** (in chloroform) exhibited peaks at 5.84 and 6.10 μ which we assigned to the terminal carbonyl and conjugate-chelate systems, respectively. The ultraviolet absorption characteristics (long-wavelength peaks at 343 and 399 mμ in acid and base, respectively) were in qualitative agreement with our expectations. These physical data taken together with the route of synthesis provided strong support for the assigned structure, but in the absence of exact models, they could not be regarded as conclusive. Particular pains were taken to establish this structure beyond all doubt and to confirm our postulates concerning the influence and reactivity of the terminal carbonyl group, since our principle of synthesis rested upon these predicted properties.

The carbon skeleton and positioning of carbonyl groups were established as follows. Zinc dust distilla-

(16) We are indebted to our colleague M. Schach von Wittenau who demonstrated the products from thermal degradation of the α-keto acid ii to be carbon monoxide, carbon dioxide, and the diketone **22**.



The α-keto acid ii was obtained (along with the unsaturated acid **24**) by acid hydrolysis of the corresponding ester **23**. In addition, the benzyl ester iv, prepared from the benzyl tetralone ester iii and dibenzyl oxalate under reaction conditions effective for the conversion of **20** to **23**, afforded the α-keto acid ii in high yield upon hydrogenolysis.



We believe that it is the 6-methoxytetralone i which arose from a minor contaminant in the product from the chlorination reaction.

(17) These large-scale preparations which were vital to the success of our work were carried out by Drs. C. E. Larrabee and C. Buck.

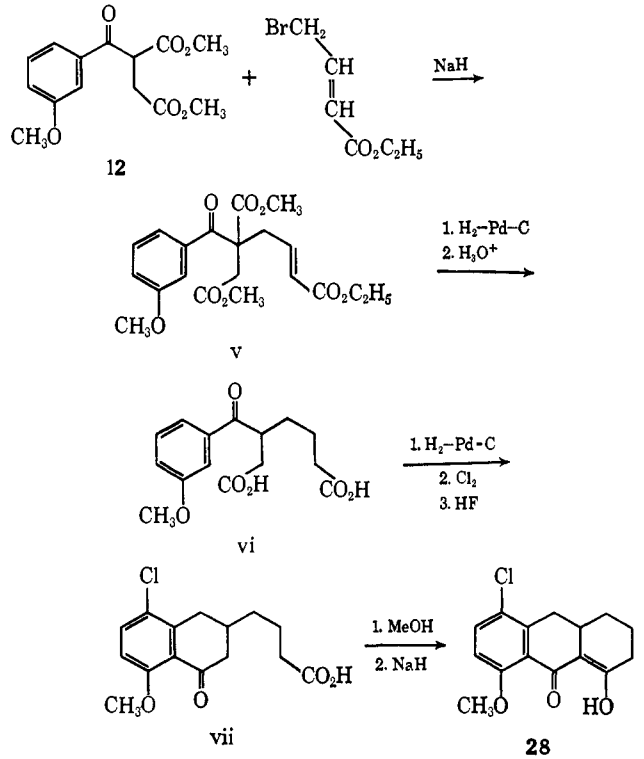
tion of the triketone **8** gave anthracene, while reaction with *o*-phenylenediamine led to a quinoxaline **25**. Aqueous ethanolic sodium hydroxide treatment brought about scission of the β-dicarbonyl system followed by aldolization and dehydration to give the previously described unsaturated keto acid **24**.

Diagnostic probes of the reactivity of the terminal carbonyl group fulfilled all expectations. The ketone was readily converted to a dithioketal **26** and was readily reduced either by catalytic or chemical methods to the alcohol **27**. The dithioketal **26** was converted to the enolized octahydroanthracenedione **28** by Raney nickel desulfurization. The compound thus prepared was compared and found to be identical with material of the same structure synthesized by an independent route.[18]

Now satisfied that the substance **8** in hand possessed the requisite structure and properties, we turned our attention to the crucial phase of the synthesis—the construction of the functionally and stereochemically complicated ring A.

The hydroanthracenetrione **8** combined with *n*-butyl glyoxylate in refluxing toluene with magnesium methoxide as catalyst to give the glyoxylidene derivative **29** in 52% yield. Only one geometrical isomer, presumably **29**, was isolated. The catalyst, which was selected after considerable experimentation, had the special virtue of protecting the β-dicarbonyl system against base cleavage. Conjugate addition of dimethylamine to the unsaturated ketone **29** took place at −10°; although other solvents were employed, liquid dimethylamine proved to be the best medium for the reaction. In this case, the Mannich base **30** crystallized from the reaction mixture, and was sufficiently stable to permit isolation and spectroscopic examination.

(18) The synthesis of this compound was accomplished by modifying appropriate early steps in the main-line synthesis.



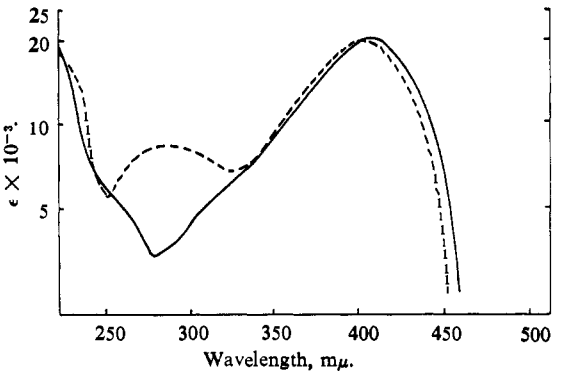
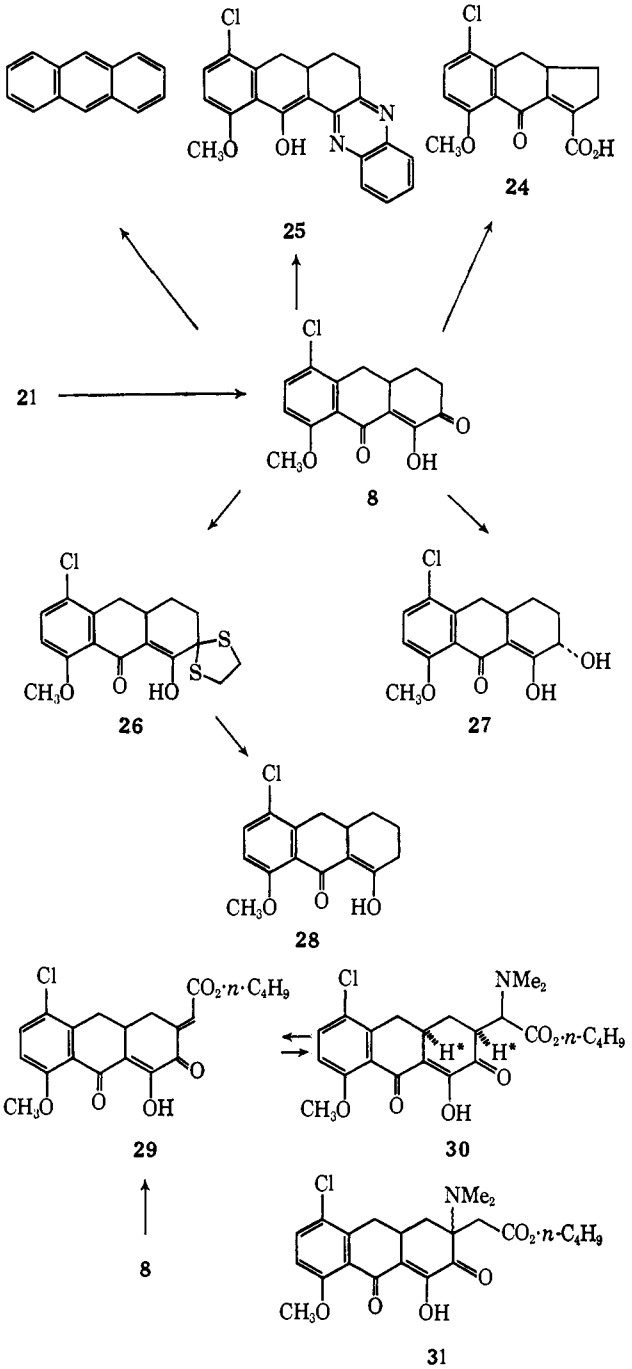


Figure 1. Ultraviolet spectra in methanol–0.01 *N* HCl of methyl 8-chloro-1,9,9a,10-tetrahydro-3,4-dihydroxy-5-methoxy-10-oxoanthracene-2-carboxylate (**21**), ----; and methyl 5-chloro-3,3a,4,9-tetrahydro-1,α-dihydroxy-8-methoxy-9-oxo-2*H*-benz[*f*]indene-Δ²,α-acetate (**23**), ——.



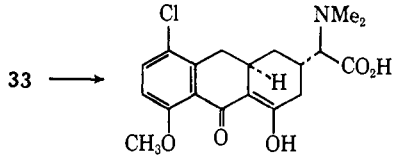
The structure of the base **30** deserves special comment in three directions. *A priori*, a path is conceivable by which an isomeric base **31** might be produced by the addition of dimethylamine to the double bond of **29**. In fact, both steric and electronic considerations led us to suppose that the reaction would occur in the desired sense, with the formation of **30**, and subsequent developments fully justified this view. Of equal importance was our expectation that the very bulky α-dimethylamino ester grouping would occupy by preference the equatorial orientation in its attachment to the tricyclic nucleus, and thus establish the crucial desired *cis* relationship of the starred hydrogen atoms in **30**. This presumption too turned out to be gratifying in accord with our adumbration. Finally, the orientation at the newly created center at the point of attachment of the dimethylamino group in **30** was in no sense crucial, since we know that the stereochemical relationships at this center would be susceptible to manipulation by known methods at a later stage in our work.

Having performed its key synthetic role, the terminal carbonyl group in **30** was next reduced. Our previous experience had provided solid ground for the supposition that there would be no difficulty in bringing about reduction specifically at this center, nor was any encountered. But a special point does require comment. The Mannich base **30** loses dimethylamine with such extraordinary readiness that it was found to be desirable to subject the intermediate to as little manipulation as possible. To this end, the freshly prepared Mannich base, directly after removal of the dimethylamine solvent in which it was prepared, was reduced at $-70°$ in 1,2-dimethoxyethane, using a fourfold excess of sodium borohydride.

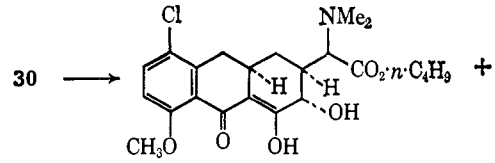
From this reaction the pure crystalline hydrochloride of the amino alcohol **32** was isolated. The yield over the two steps, amine addition and reduction, was 53%. Although three asymmetric centers were generated in this sequence the only other product isolated was a lactone, for which we suggest tentatively the structure **33**.[19] The yield of the by-product lactone was variable and depended in great measure on the temperature during the borohydride reduction. At $-70°$, 5% (or less) was obtained, whereas at somewhat higher temperatures (*ca.* $-30°$), up to 20% yields were generally obtained.

The equatorial orientation assigned to the hydroxyl group in **32** is consistent with the relative stability of the hydroxy ester toward lactonization. Such a lactonization was brought about, however, under vigorous conditions: **32** when refluxed in toluene in the presence of half its weight of *p*-toluenesulfonic acid gave the lactone **34** in 90–95% yield. This compound was reduced in 81% yield by zinc dust and formic acid, in a reaction of 1-min duration, to the dimethylamino acid

(19) Reduction of the lactone **33** with zinc in formic acid afforded an amino acid viii, isomeric with the acid **35**, which, when subjected to a sequence analogous to **36** → **39**, failed to yield any tetracyclic material.



viii



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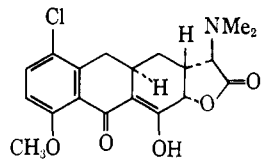
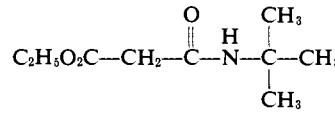


33

35; catalytic hydrogenolysis over palladized charcoal gave the dechloro acid **36** (X = H) in 91% yield.

The stage was now set for the incorporation into the molecule of the remaining elements of the final ring of the hydronaphthacene skeleton. An important key to our success in this phase of the synthesis was the use of a new derivative of malonic acid, *viz.*, ethyl N-*t*-butylmalonamate (**37**);[20] this substance provided a highly

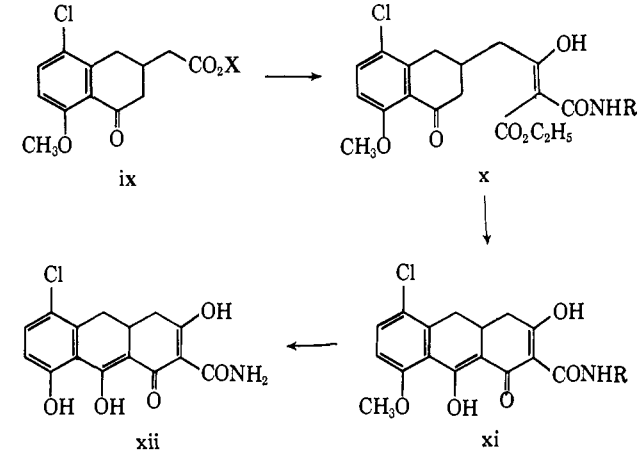


37

convenient means of introducing the carboxamide function characteristic of the tetracyclines in a protected form from which it could readily be released.

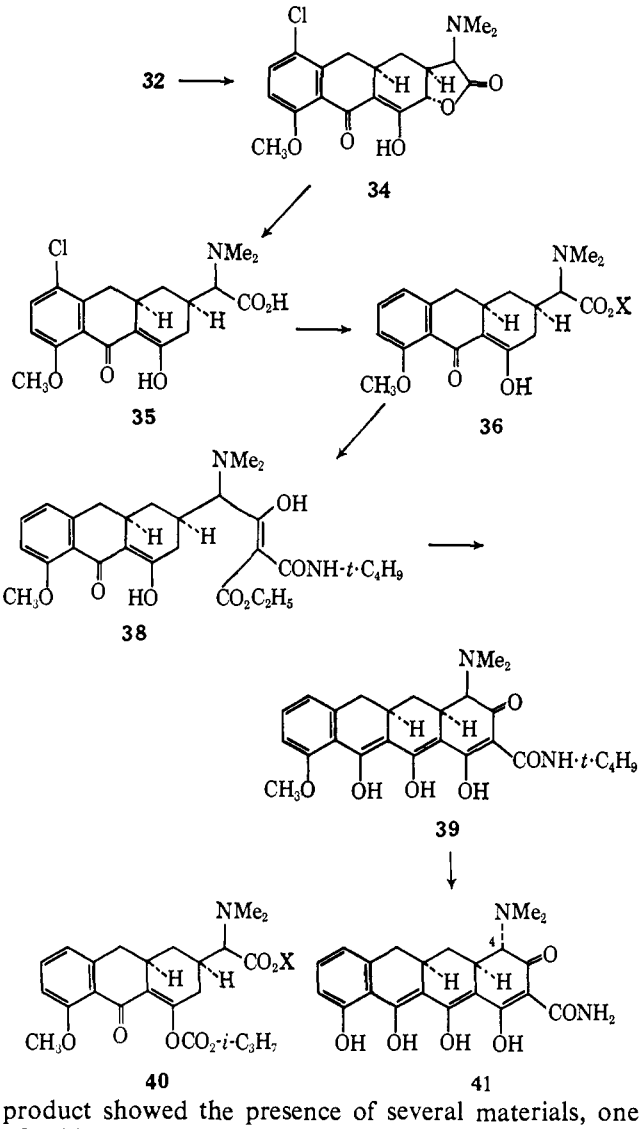
It was found the acid **36** (X = H) afforded mixed anhydrides in high yields when treated with various esters of chloroformic acid in the presence of triethylamine. For example, the crystalline isopropyl mixed anhydride **36** (X = CO_2-*i*-C_3H_7) was prepared in 72% yield in this manner. There proved to be no advantage in isolating the anhydride, however, and it was

(20) We are indebted to our colleague Dr. J. W. McFarland who first synthesized this compound and studied its reactivity and that of the simple amide, ethyl malonamate, in a model system.



The anhydride ix (X = CO_2-*i*-C_3H_7), prepared in high yield from the acid ix (X = H) (see reference below) and isopropyl chloroformate, when treated with the ethoxymagnesio derivatives of both ethyl N-*t*-butylmalonamate and ethyl malonamate, afforded the acyl malonamate derivatives x (R = *t*-C_4H_9) and x (R = H), respectively. In the latter case, the substance was crystalline and was obtained in 68% yield from the starting acid ix (X = H). The acyl malonamates x were cylized readily in dimethylformamide solution in the presence of sodium hydride to give the tricyclic substances xi (R = *t*-C_4H_9; R = H). The substituted amide xi (R = *t*-C_4H_9) was converted smoothly by hot hydrogen bromide in acetic acid into the phenol amide xii. This hydrolysis procedure had previously been utilized for the conversion of xi (R = H) to xii [R. G. Wilkinson, T. L. Fields, and J. H. Boothe, *J. Org. Chem.*, **26**, 637 (1961)].

brought, in the crude state, directly into reaction with the ethoxymagnesio derivative of ethyl N-*t*-butylmalonamate (**37**). The acylation reaction, carried out in acetonitrile as solvent, was followed by the appearance of increased absorption in the ultraviolet at 265 mμ, associated with an enolized acyl malonate system. Paper chromatography of the crude acylation



product showed the presence of several materials, one of which was demonstrated to be the ethyl ester **36** (X = C_2H_5)[21] of the starting amino acid, a by-product probably arising by attack of ethoxyl anion from the magnesioethoxymalonamate on the anhydride. Since efforts to isolate the acyl malonamate **38** in a pure state were not successful, the crude reaction mixture was treated briefly with sodium hydride in dimethylformamide in the presence of a small amount of methanol at 120°. The formation of a 12a-deoxytetracycline derivative was followed by the appearance in the visible spectrum of absorption at 430 mμ. The desired crystalline cyclization product **39** was obtained from such a reaction sequence in 15% yield from the acid **36** (X = H), allowance being made for recovery of up to 30% of the latter.

Several aspects of the reaction sequence just described are worthy of detailed discussion. It is obvious that formation of an enol ester of the β-diketone system (*cf.* **40**) is a possible side reaction which might accompany anhydride preparation. Indeed when 2 equiv of triethylamine and isopropyl chloroformate was used in the reaction, enol ester formation did occur, as shown by infrared and ultraviolet spectra, but *not* during the course of the anhydride formation. In fact, enol ester was obtained only after anhydride formation was complete and the chloroform solvent had been removed; the resulting reaction mixture, shown by spectroscopic observation to be free of enol ester, was slowly converted into the enol ester anhydride **40** (X = CO_2-*i*-C_3H_7).[22] Highest yields of the tetracyclic compound **39** were obtained when the substrate used in the acylation was anhydride which contained no enol ester. Consequently, in practice the anhydride was used immediately after preparation. Finally, the solvent of choice for the acylation reaction, acetonitrile, was found to be vastly superior to the solvents commonly used in similar reactions. Indeed, the yield of acyl malonamate **38** was negligible when either chloroform or toluene was used! The cyclization reaction itself is most remarkable for it appears to require acylation of a dianionic β-dicarbonyl system by the ester function of a mono- or possibly dianionic acyl malonamate system.

Treatment of the tetracyclic product **39** at 100° for a short time with 48% hydrobromic acid resulted in the smooth cleavage of both the N-*t*-butyl and the O-methyl groups. When pure crystalline **39** was subjected to these acidic conditions, the dealkylated substance **41** crystallized directly from the reaction mixture in high yield. It proved to be expeditious, however, to subject the entire cyclization mixture containing **39** to the hydrobromic acid treatment. The resulting desired *dl*-6-demethyl-6,12a-dideoxytetracycline (**41**) was readily isolated by partition chromatography of the reaction mixture. Since optically active **41** is available by deoxygenation of 6-demethyl-6-deoxytetracycline,[23] comparative spectroscopic and paper chromatographic studies of samples of **41**, prepared respectively by synthesis and by degradation of 6-demethyl-6-deoxytetracycline, established that our synthetic sequence had followed the course here set forth. Particularly striking was the identity of the highly characteristic and time-variable visible and ultraviolet absorption spectra of the two samples (*cf.* Figures 2 and 3).

It should be noted that in 6-demethyl-6,12a-dideoxytetracycline as depicted in **41**, the C_4-dimethylamino function has been represented as corresponding to the normal C_4-tetracyclines. Though not rigorously demonstrated to be the case, this assignment is based on the fact that in the subsequent 12a-hydroxylation reaction, the initial oxidation product contained only the normal (α) C_4 epimer.[24]

(21) The ethyl ester **36** (X = C_2H_5) was prepared from the anhydride **36** (X = CO_2-*i*-C_3H_7) and absolute ethanol [48% yield from starting acid **36** (X = H)].

(22) Though the enol ester anhydride **40** (X = CO_2-*i*-C_3H_7) was not obtained crystalline, the structure was well defined by its spectral characteristics. A crystalline, well-characterized enol ester methyl ester **40** (X = CH_3) was obtained however in 63% yield [from acid **36** (X = H)] by treatment of crude **40** (X = CO_2-*i*-C_3H_7) with methanol.

(23) R. K. Blackwood, H. H. Rennhard, and C. R. Stephens, *J. Am. Chem. Soc.*, **82**, 5194 (1960).

(24) In ref 1b, the dimethylamino group of **41** was presented as being in the C_4-*epi* configuration. This conclusion was based in part on model arguments and also on the results of the 12a-hydroxylation reaction. With respect to the latter, it was believed that hydroxylation afforded a mixture of C_4-*epi* (β) and C_4-normal (α) compounds. It was subsequently determined, however, that the hydroxylation reaction initially yielded only the C_4-normal tetracycline, and that epimerization at that position occurred during the isolation procedure. If, in fact,

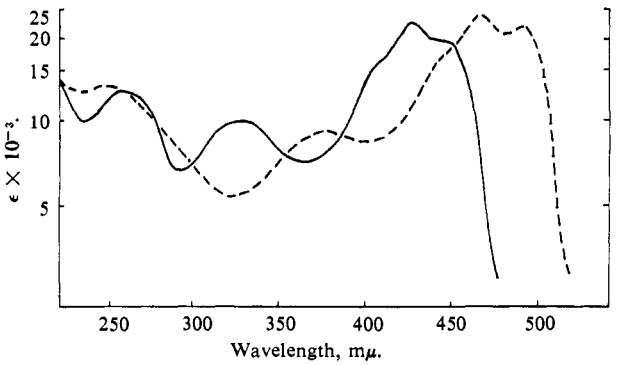


Figure 2. Visible and ultraviolet spectra of both *dl*- and optically active 6-demethyl-6,12a-dideoxytetracycline (**41**): in methanol–0.01 *N* HCl, ——; methanol–0.01 *N* NaOH, -----. The spectra were taken immediately after the samples were dissolved.

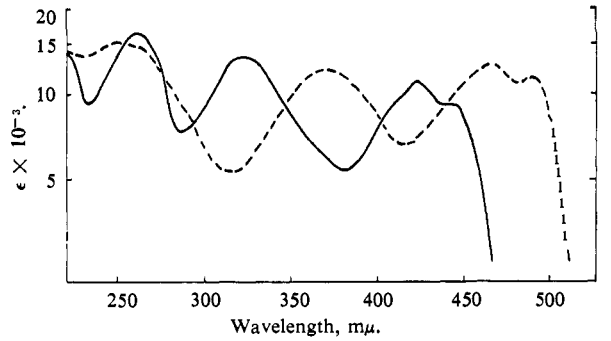


Figure 3. As in Figure 2, the spectra being taken 1 hr after the samples were dissolved.

It now remained to introduce an hydroxyl group at C_{12a} to produce the *cis*-locked A/B ring system and to ensure the correct orientation of the dimethylamino function at C_4. We had discovered previously that, in general, 12a-deoxytetracyclines can be hydroxylated in the desired manner by the action of molecular oxygen on a variety of metal chelates, in yields which vary considerably from substrate to substrate. The case in hand turned out to be by no means the smoothest that we had encountered. In addition to the desired tetracycline **7**, several products were produced when optically active 6-demethyl-6,12a-dideoxytetracycline (**41**) was oxygenated in the presence of cerous chloride. The major by-product was shown to be 6,N-didemethyl-6-deoxytetracycline;[25] further, an 11a-hydroxylated substance was believed to have been formed.

Carefully controlled oxygenation of racemic **41** in the presence of cerous chloride in buffered methanol–dimethylformamide solution afforded racemic products corresponding to those obtained in the experiments with optically active material. Pure crystalline totally synthetic racemic 6-demethyl-6-deoxytetracycline hydrochloride (**7**) was isolated in 6.5% over-all yield as the end product of an elaborate separation and purification procedure. Since partial epimerization at C_4 occurred in the purification sequence, a later step of this process was the conversion of the mixture of C_4 epimers to **7** by the method of Noseworthy.[26]

the 12a-deoxy derivative **41** is the C_4-normal epimer, it is reasonable to assume that its immediate precursor **39** has corresponding geometry at C_4, rather than that depicted in **39**.

(25) J. J. Korst and K. Butler, to be published.

(26) M. M. Noseworthy, U. S. Patent 3,009,956; *Chem. Abstr.*, **56**, 6101 (1962).

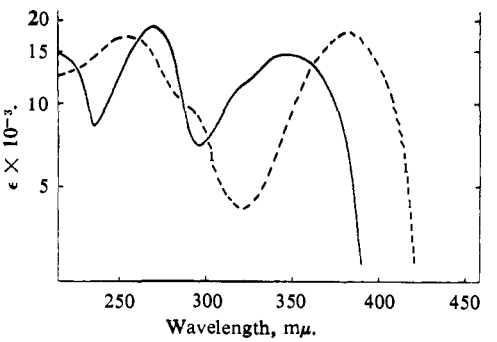


Figure 4. Ultraviolet spectra of both *dl*- and optically active 6-demethyl-6-deoxytetracycline (**7**): in methanol–0.01 *N* HCl, ——; methanol–0.01 *N* NaOH, -----.

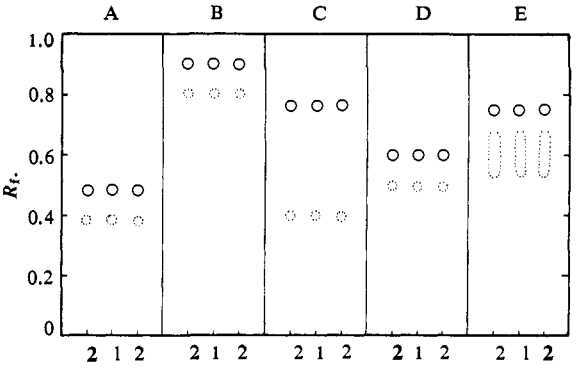


Figure 5. Paper chromatographic behavior of 6-demethyl-6-deoxytetracycline (**7**): *dl*, 1; optically active, 2; system A, pyridine–toluene (3:20), saturated with water, pH 4.2 paper; system B, toluene–1-butanol–nitromethane–pyridine (10:5:20:3), pH 3.5 paper; system C, ethyl acetate–nitromethane–chloroform (40:25:7), pH 4.2 paper; system D, ethyl acetate–chloroform–pyridine (40:15:5), pH 4.2 paper; system E, ethyl acetate saturated with water, pH 4.2 paper. The dotted areas show the presence of trace amounts of the corresponding C_4 epimers.

The care with which it was necessary to examine the reaction mixture in the last two steps of our synthesis justifies the conclusion that the oxygenation reaction does not give rise to any compounds with the unnatural C_{12a}-*epi* (rings A/B *trans*) configuration.

The identity of our synthetic *dl*-6-demethyl-6-deoxytetracycline (**7**) was established beyond question by spectroscopic and paper chromatographic studies, which are summarized in Figures 4 and 5. It is of particular interest that the synthetic racemic compound is just half as active against pathogenic organisms as its optically active counterpart; the not surprising, but none-the-less interesting, conclusion may be drawn that the unnatural isomer is completely devoid of biological activity.

Experimental Section[27]

Dimethyl α-(3-Methoxybenzoyl)succinate (12). Route A, *via* the Intermediate Methyl 3-Methoxybenzoylacetate (11). The Preferred Route. In a flask fitted with a thermometer, condenser,

(27) Boiling points and melting points are uncorrected. The latter were taken on a Thomas-Hoover "Uni-Melt" capillary apparatus. Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer unless otherwise noted. Ultraviolet and visible spectra were taken with a Cary recording spectrophotometer Model 13. Gas–liquid chromatographic results were obtained with a Burrell-K2 Kromo-Tog apparatus, utilizing a 20% silicone fluid [General Electric SF 81 (50)] on Kromat-FB (30–60 mesh) column. Dimethylformamide was stored a minimum of 18 hr over anhydrous magnesium sulfate, then

mechanical stirrer, dropping funnel, and nitrogen inlet was placed 500 g (10.4 moles) of a 50% dispersion of sodium hydride in mineral oil, 831 g (5.0 moles) of methyl *m*-methoxybenzoate (**10**), bp 80–81° (0.3 mm), n^{24}D 1.5250 [lit.[28] bp 121–124° (10 mm), nD 1.5224], and 1500 ml of dimethylformamide. A solution of 400 g (5.40 moles) of methyl acetate in 750 ml of dimethylformamide was then added through the dropping funnel during a 90-min period, the temperature being maintained at 60°. After the addition, the mixture was heated at 60° for 1 hr, then cooled, and 1 l. of acetic acid was slowly added. During the addition of the acid, a solid precipitated from the mixture. It became necessary to add some chloroform to keep the mixture mobile enough to be stirred. The mixture was transferred to a separatory funnel and more chloroform and 10 l. of water was added. The mixture was shaken; the layers were separated, and the aqueous solution was extracted twice with chloroform. The organic solutions were combined, washed with water several times, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residual oil was washed with hexane several times to remove the mineral oil, then dried under reduced pressure. There was obtained 1171 g of a dark oil which was distilled through a 30-cm Vigreux column. After a forerun, there was obtained 878 g (84% yield) of a colorless oil, bp 140–148° (0.8–1.4 mm), n^{25} D 1.5442. A sample, redistilled through an 8-cm, glass-helices column, afforded the benzoyl acetate **11** as a colorless oil, bp 136–137° (0.6 mm), n^{25}D 1.5446, $\lambda\lambda_{max}^{film}$ 5.70 and 5.90 μ, which gave a violet color with methanolic ferric chloride solution.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.57; H, 5.91.

Isolation of the benzoyl acetate **11** was unnecessary in practice, and the crude substance was alkylated directly with methyl bromoacetate to give the desired succinate **12**.

To a vigorously stirred mixture of 1.66 kg (10.0 moles) of methyl *m*-methoxybenzoate (**10**), bp 80–81° (0.3 mm), n^{24}D 1.5250 [lit.[28] bp 121–124° (10 mm), nD 1.5224], 1.01 kg (21.0 moles) of a 50% dispersion of sodium hydride in mineral oil, and 3.0 l. of dimethylformamide in a nitrogen atmosphere was added slowly a solution of 860 ml (800 g, 10.8 moles) of methyl acetate in 1.5 l. of dimethylformamide, a temperature of 50–60° being maintained. After the addition, which required about 3 hr and was accompanied by considerable hydrogen gas evolution, the mixture was stirred for 1 hr at 60°, then cooled to 25°. A solution of 2.28 kg (21.0 moles) of methyl chloroacetate in 3.0 l. of dimethylformamide was then added at such a rate that a temperature of 50–60° was again maintained. After the 20-min addition, the resulting mixture was stirred at 50° for 1 hr, cooled to 30°, and poured into a solution of 1.5 l. of acetic acid in 8 l. of chloroform with stirring. To the mixture was added 12 l. of water and the layers were separated. The aqueous phase was extracted with 4 l. of chloroform and the organic solutions were combined, washed three times with 6-l. portions of water, and dried over anhydrous magnesium sulfate. The solution was treated with 200 g of Darco KB and evaporated under reduced pressure to a brown oil. The separate mineral oil layer was removed and the brown product layer extracted three times with hexane to remove the remainder of the mineral oil. Residual hexane was removed under reduced pressure, and the product was rapidly distilled with a high-capacity pump. After a forerun, there was obtained 2.36 kg of a yellow oil, bp 170–225° (0.5–2.5 mm), n^{25}D >1.5000. Fractional distillation through a 34-cm porcelain saddle column afforded 1.54 kg (55% yield) of the keto diester **12** as a yellow oil, bp 175–200° (1.5 mm), n^{25}D 1.5220.

A sample was redistilled through a porcelain saddle column to give **12** as a pale yellow oil, bp 161–162° (0.35 mm), n^{25}D 1.5232, $\lambda\lambda_{max}^{film}$ 5.74 (very strong) and 5.90 μ.

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.10; H, 5.79.

Route B, Direct Dimethyl Succinate Condensation. To a mechanically stirred solution of 29.0 g (0.175 mole) of methyl *m*-methoxybenzoate (**10**), bp 80–81° (0.3 mm), n^{24}D 1.5250 [lit.[28] bp 121–124° (10 mm), nD 1.5224], in 75 ml of dimethylformamide under nitrogen was added 15.0 g (0.29 mole) of a 46% dispersion of sodium hydride in mineral oil. Then a solution of 19.0 g (0.130 mole) of dimethyl succinate in 175 ml of dimethylformamide was added over a period of 12 hr. After this time, 25 ml of glacial acetic acid was added slowly and the mixture was stirred at room temperature for 2 hr, then filtered. The cake was washed well with ether and the filtrate and washings were combined and concentrated under reduced pressure to an oil. Ether was added, the mixture filtered, and the filtrate again concentrated under reduced pressure to an oil. This residue was washed in a separatory funnel three times with hexane to remove the mineral oil, then distilled under reduced pressure. After a forerun to 195° (0.5 mm), there was obtained 14.2 g (29.0% yield) of benzoylsuccinic ester **12** as a yellow oil, bp 195–198° (1.5 mm), having an infrared spectrum identical with the above described analytical sample.

Trimethyl β-Carboxy-β-(3-methoxybenzoyl)adipate (14). 1. Routes A and B. A solution of 3.08 kg (11.0 moles) of benzoylsuccinate **12**, n^{25}D 1.5220, prepared as described above in the preferred procedure, in 10 l. of dioxane was heated to 60° with mechanical stirring under nitrogen and 219 ml of a 40% methanolic solution of benzyltrimethylammonium hydroxide (Triton B) was added. The mixture became dark immediately and 4.77 kg (55.4 moles) of methyl acrylate was added as rapidly as possible. The mixture was stirred 1 hr at 50–70° and then 328 ml of acetic acid was added. The excess methyl acrylate and dioxane were removed by distillation under reduced pressure, and the residue was dissolved in 9 l. of chloroform. The solution was washed four times with 6-l. portions of water, dried over anhydrous sodium sulfate, treated with Darco KB, and concentrated under reduced pressure to a dark viscous oil. Simple distillation of this oil afforded 3.55 kg (88% yield) of crude benzoyl triester **14**, bp 185–235° (0.8 mm), n^{25}D 1.5170, $\lambda\lambda_{max}^{film}$ 5.74 (very strong) and 5.90 μ. This material was subsequently hydrolyzed without further purification.

2. Route C. a. Dimethyl α-(3-Methoxybenzoyl)glutarate (13). To a mechanically stirred solution of 27.7 g (0.167 mole) of methyl *m*-methoxybenzoate (**10**), bp 80–81° (0.3 mm), n^{24}D 1.5250 [lit.[28] bp 121–124° (10 mm), nD 1.5224], in 100 ml of dimethylformamide under nitrogen was added 8.0 g (0.18 mole) of a 53% dispersion of sodium hydride in mineral oil. Then a solution of 27.0 g (0.169 mole) of dimethyl glutarate in 100 ml of dimethylformamide was added dropwise during 1 hr. The mixture was stirred overnight and 25 ml of glacial acetic acid was added. Chloroform and water were added, the mixture shaken, and the layers separated. The aqueous solution was extracted twice with chloroform; the organic solutions were combined, washed twice with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to an oil. The oil was washed three times with hexane by decantation to remove mineral oil, and then distilled. After a considerable forerun, there was obtained 33.0 g of a pale yellow oil, bp 146–198° (0.3–0.5 mm), n^{24}D 1.5118.

Redistillation afforded 16.0 g of a yellow oil, bp 188–190° (0.2 mm), n^{23}D 1.5137. A second redistillation gave 11.8 g (24% yield) of the glutarate **13** as a pale yellow oil, bp 188–200° (0.1–0.3 mm), n^{24}D 1.5190.

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 60.94; H, 6.26.

b. Alkylation of the Benzoyl Glutarate 13. To a mechanically stirred solution of 41.6 g (0.141 mole) of benzoyl glutarate **13** (triply distilled—prepared as in a above) in 350 ml of dimethylformamide under nitrogen was added, in portions, 14.0 g (0.31 mole) of a 53% dispersion of sodium hydride in mineral oil. After the bubbling had subsided, a solution of 53.5 g (0.35 mole) of methyl bromoacetate in 350 ml of dimethylformamide was slowly added over 0.5 hr. The mixture was stirred overnight at room temperature, then acidified with acetic acid. The dimethylformamide was removed under reduced pressure (vacuum pump) and chloroform (600 ml) and water (500 ml) were added to the residual oil. The mixture was shaken; the layers were separated, and the chloroform solution was washed four times with water, dried over anhydrous sodium sulfate, and filtered. The solution was concentrated under reduced pressure to a thick oil which contained mineral oil as a separate phase. The material was washed with hexane by decantation several times to remove the mineral oil, and residual hexane was removed by evaporation under reduced pressure. There was obtained 57.0 g of crude benzoyl triester **14** as a thick brown oil which was distilled at low pressure to give 34.2 g (66.2% yield) of product, bp 200–236° (0.3 mm), n^{24}D 1.5145.

This substance had an infrared spectrum indistinguishable from that of the keto triester **14** prepared in 1 above. Its identity was proven by hydrolysis and subsequent esterification to the benzoyl adipate **15** (R = CH_3) (see below).

Dimethyl β-(3-Methoxybenzoyl)adipate (15, R = CH_3). 1. Hydrolysis and Decarboxylation of the Keto Triester 14 Obtained

filtered and distilled before use. Super-Cel was washed with concentrated hydrochloric acid, then water until acid free, followed by acetone, and dried. All synthetic compounds herein described containing an asymmetric carbon atom are racemic substances. The prefix "*dl*" has been omitted in the naming of such compounds.

(28) F. W. Semmler, *Ber.*, 41, 1768 (1908).

via **Route A.** **β-(3-Methoxybenzoyl)adipic Acid (15, R = H).** In a flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser with a Dean–Stark trap was placed 10.8 kg (29.5 moles) of benzoyl triester **14** (crude, once distilled as described above), 8.7 l. of acetic acid, 5.2 l. of water, and 5.2 l. of concentrated sulfuric acid. The mixture was refluxed for 24 hr, during which time 1.8 l. of distillate was slowly removed through the Dean–Stark trap and replaced by 1.8 l. of water added through the dropping funnel. Evolution of carbon dioxide was quite rapid at the beginning of the reflux period. The mixture was then cooled and added to 18 l. of chloroform. After being stirred, the layers were separated and the aqueous solution was extracted twice with 6-l. portions of chloroform. The chloroform extracts were combined, washed four times with 18-l. portions of water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 8.1 kg (98% yield) of crude diacid **15** (R = H) as a viscous oil. A sample of this acid, triturated in the cold with ether, afforded colorless prisms, mp 105–109°. Recrystallization of a sample of this substance from methanol–water followed by recrystallization from ethyl acetate–hexane gave β-(3-methoxybenzoyl)adipic acid (**15** R = H) as colorless needles, mp 107.5–109°, $\lambda\lambda_{max}^{KBr}$ 5.74, 5.82, and 6.10 μ.

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75; neut equiv, 140. Found: C, 60.12; H, 5.74; neut equiv, 141.

It proved to be disadvantageous to purify large samples of diacid **15** (R = H) by crystallization. Hence, the crude material was esterified directly and the ester **15** (R = CH_3) purified by distillation.

2. Esterification of the Keto Diacid 15 (R = H). A mixture of 8.1 kg (28.9 moles) of crude diacid **15** (R = H) obtained in the previous experiment, 6.2 l. (4.9 kg, 153 moles) of methanol, 40 l. of chloroform, and 177 ml of concentrated sulfuric acid was refluxed for 18 hr. During this time a water layer had separated from the chloroform solution. The mixture was cooled and the chloroform layer washed once with 4 l. of water, once with 3 l. of 2% sodium hydroxide solution, and once again with 4 l. of water. After being dried over anhydrous sodium sulfate and treated with Darco KB, the chloroform solution was evaporated under reduced pressure to give 6.6 kg of a dark oil. Fractional distillation through a 50-cm porcelain saddle column afforded 4.0 kg (44% yield from benzoyl triester **14**) of benzoyladipic ester **15** (R = CH_3) as an orange oil, bp 180–190° (0.6 mm), $n^{25}D$ 1.5202. This material was shown to be 85–90% pure by gas–liquid partition chromatography. A pure sample of the ester **15** (R = CH_3) was prepared by esterification of the corresponding crystalline diacid **15** (R = H), followed by distillation through a 10-cm, glass-helices column, bp 163–164° (0.15 mm), $n^{23}D$ 1.5184, $\lambda\lambda_{max}^{film}$ 5.74 (very strong) and 5.91 μ.

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.42; H, 6.51.

3. From the Benzoyl Triester 14 Obtained *via* Route C. The crude triester **14**, 34.2 g, $n^{24}D$ 1.5145, obtained from route C above, was subjected to hydrolysis and esterification procedures analogous to those just described in 1 and 2. There was obtained 22.7 g of crude benzoyladipic ester which, on distillation, afforded 16.1 g (37% yield from benzoylglutarate **13**) of product **15** (R = CH_3) as a yellow oil, bp 150–180° (0.2–0.4 mm), $n^{24}D$ 1.5191. The substance had an infrared spectrum indistinguishable from that of the analytical sample described above.

Dimethyl β-(3-Methoxybenzyl)adipate (17, R = R_1 = CH_3).

1. Hydrogenation of the Benzoyladipate 15 (R = CH_3). A mixture of 5.00 kg (16.2 moles) of benzoyladipic ester **15** (R = CH_3) (85–90% pure by glpc), 2.80 g of 10% palladized charcoal, and 32 l. of acetic acid was hydrogenated at 30° and 200 psi. Samples were removed periodically from the hydrogenation mixture for infrared spectra. During the first 30–45 min of the reaction, a 5.60-μ band (five-membered ring lactone, **16**) developed in the infrared along with a concomitant loss in intensity of the 5.90-μ ketone band. As the reaction progressed, the intensity of the lactone band decreased and the appearance of an acid carbonyl was noted at 5.85 μ. Two hours from the start of the hydrogenation, absence of the 5.60-μ band was noted and the reaction was stopped. Care was taken not to over-hydrogenate as it was found possible under these conditions to reduce the aromatic ring. The mixture was filtered and the colorless filtrate evaporated under reduced pressure to give 4.2 kg (93% yield) of crude acid ester **17** (R = CH_3; R_1 = H) as a colorless oil. This material was esterified and distilled in the next step as a means of purification.

2. Esterification. A procedure similar to that used for the preparation of the benzoyladipic ester **15** (R = CH_3) was employed. From a mixture of 4.2 kg (15 moles) of crude monoester **17** (R = CH_3; R_1 = H) obtained above, 1.5 kg (47 moles) of methanol, 53 ml of concentrated sulfuric acid, and 5.5 l. of chloroform, an oil was obtained which was fractionally distilled through a 30-cm column packed with stainless steel helices. After a small forerun, there was obtained 3.3 kg [69% yield from keto diester **15** (R = CH_3)] of benzyladipic ester **17** (R = R_1 = CH_3) as a colorless oil, bp 165–168° (0.5 mm), $n^{25}D$ 1.5045. The material was shown to be 95–98% pure by gas–liquid partition chromatography. Redistillation of a sample through a 10-cm, glass-helices column afforded **17** (R = R_1 = CH_3) as a colorless oil, bp 152–154° (0.2 mm), $n^{25}D$ 1.5023.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.22; H, 7.62.

5-Chloro-8-methoxy-1-tetralone-3-propionic Acid (19).

1. Saponification of the Diester 17 (R = R_1 = CH_3). A mixture of 3.3 kg (11.2 moles) of benzyladipic ester **17** (R = R_1 = CH_3), bp 165–168° (0.5 mm), 1.2 kg (30 moles) of sodium hydroxide, and 6.9 l. of water was stirred and heated on a steam bath for 18 hr. The solution was cooled and acidified to pH 2 with 3.0 l. of concentrated hydrochloric acid. The acid was added quite rapidly to preclude crystallization of the monosodium salt of the benzyladipic acid **17** (R = R_1 = H). The mixture was extracted once with 6 l. of chloroform and twice with 3-l. portions of chloroform. The extracts were combined and washed three times with 6-l. portions of water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 2.9 kg (97% yield) of a viscous oil. This crude diacid **17** (R = R_1 = H) was used directly in the next step without further purification.

2. Chlorination. In a flask covered with aluminum foil was placed 2.9 kg (11.0 moles) of crude benzyladipic acid **17** (R = R_1 = H) obtained above, 15.6 l. of acetic acid, and 0.15 g of iodine. The mixture was cooled to 12° with stirring and a solution of 778 g (10.9 moles) of chlorine in 13.6 l. of acetic acid was added over 7 hr, the temperature being maintained at 12–17°. After being stirred an additional 30 min, the mixture was concentrated under reduced pressure to give 3.2 kg (97% yield) of a viscous oil. This crude product **18** was used directly in the cyclization reaction without purification.

3. Cyclization. The chloro diacid **18** obtained in 2 above (3.2 kg, 10.6 moles), was placed in a polyethylene container equipped with a mechanical stirrer, and 12.3 kg of liquid hydrogen fluoride was added with ice-bath cooling. After being stirred at 15° for 18 hr, the mixture was poured into 20 l. of water with vigorous stirring, pale brown crystals being formed. The slurry was stirred for 1 hr at room temperature and filtered, and the crystals were washed well with water. After being air dried, there was obtained 2.9 kg of crude tetralonepropionic acid **19**, which was leeched three times with 8-l. portions of hot chloroform. The chloroform solutions were combined, treated with Darco KB, and concentrated under reduced pressure to a volume of 12 l. The chloroform concentrate was then stirred at room temperature and 9 l. of hexane was slowly added, causing the product to crystallize. The mixture was cooled to 5° with stirring, then filtered. The crystals were washed with hexane and air dried to give 2.0 kg [63% yield from dimethyl β-(3-methoxybenzyl)adipate (**17**, R = R_1 = CH_3)] of the desired tetralonepropionic acid **19**, mp 170–178°. A sample prepared in a similar experiment was recrystallized several times from chloroform–ethyl acetate and once from acetone. The tetralonepropionic acid **19** was obtained as colorless prisms, mp 179–181°; $\lambda\lambda_{max}$ mμ (ε) 254 (7400), 326 (4200) in methanol–0.01 *N* HCl; 254 (7600) and 325 (4400) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 5.77, 5.99, and 6.31 μ.

Anal. Calcd for $C_{14}H_{13}O_4Cl$: C, 59.48; H, 5.35; Cl, 12.54. Found: C, 59.54; H, 5.32; Cl, 12.66.

There was obtained as residue from the above-described chloroform leeches 170 g of colorless prisms, mp 236–239°. Recrystallization of this substance from tetrahydrofuran followed by two methanol leeches, and an additional recrystallization from tetrahydrofuran, yielded an isomeric tetralone acid, presumably i, as colorless crystals, mp 242.5–245°; $\lambda\lambda_{max}^{KBr}$ 5.86, 5.95, and 6.31 μ; $\lambda\lambda_{max}$ mμ (ε) 270 (14,700), 290–304 sh (6800) in methanol–0.01 *N* NaOH. In methanol–0.01 *N* HCl, an essentially identical ultraviolet spectrum was obtained.

Anal. Calcd for $C_{14}H_{13}O_4Cl$: C, 59.48; H, 5.35; Cl, 12.54; neut equiv, 283. Found: C, 59.17; H, 5.36; Cl, 12.41; neut equiv, 287.

Methyl 5-Chloro-8-methoxy-1-tetralone-3-propionate (20). A mixture of 2.0 kg (7.1 moles) of 5-chloro-8-methoxy-1-tetralone-3-propionic acid (**19**), mp 170–178°, 3.0 l. of chloroform, 860 ml (682 g, 21.3 moles) of methanol, and 21.2 ml of concentrated sulfuric

acid was refluxed for 20 hr with stirring. The mixture was cooled and washed once with 3 l. of water, once with 1 l. of 2% sodium hydroxide solution, and twice with 2-l. portions of water. The chloroform solution was dried over anhydrous sodium sulfate, treated with Darco KB, and evaporated under reduced pressure. The residual dark oil was dissolved in 6 l. of hot ethyl acetate, and the resulting solution was diluted with 11 l. of warm hexane. Upon cooling, a fluffy crystalline precipitate began to form. After being chilled to −5°, the mixture was filtered and the cake washed with hexane. There was obtained 1.4 kg (66% yield) of ester **20** as colorless rods, mp 102–103°. A sample, recrystallized once from ethyl acetate–hexane, afforded colorless elongated rods, mp 102–103.5°; $\lambda\lambda_{max}^{CHCl_3}$ 5.75, 5.94, and 6.31 μ.

Anal. Calcd for $C_{15}H_{17}O_4Cl$: C, 60.70; H, 5.77; Cl, 11.95. Found: C, 60.87; H, 5.80; Cl, 12.0.

Methyl 8-Chloro-1,9,9a,10-tetrahydro-3,4-dihydroxy-5-methoxy-10-oxoanthracene-2-carboxylate (21). To a mechanically stirred mixture of 297 g (1.00 mole) of tetralonepropionic ester **20**, mp 102–103°, 236 g (2.00 moles) of dimethyl oxalate, and 2 l. of dimethylformamide under nitrogen was added all at once, at 20°, 190 g (3.80 moles) of a 50% dispersion of sodium hydride in mineral oil. Methanol (40 ml) was then added and the temperature spontaneously increased slowly to 35°. At this stage, a vigorous reaction began with the evolution of hydrogen gas. At the start of the vigorous reaction, the flask was immersed immediately in an ice–methanol bath. The temperature of the mixture increased rapidly to 80°, then decreased. When the temperature had dropped to 50°, the ice bath was removed and the mixture heated on the steam bath to 80°. The mixture was then cooled to 20° and 1.24 l. of acetic acid was slowly added, a temperature of 25–30° being maintained. To the resulting slurry, 8 l. of water and 3 l. of methylene chloride were added. The mixture was shaken, the layers separated, and the aqueous solution was extracted twice with 3-l. portions of methylene chloride. The combined organic extracts were washed three times with 6-l. portions of water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to a volume of 1.5 l. To this solution was added 10 l. of isopropyl alcohol, and the mixture was evaporated under reduced pressure to a volume of 8 l. at which time crystallization began. The slurry was cooled to 20° with stirring and was filtered after crystallization was complete. The crystals were washed with isopropyl alcohol, then hexane, and air dried to give 166 g of crude tricyclic ester **21** as yellow-orange needles, mp 198–201° dec.

The crude product was dissolved in 1.3 l. of hot chloroform and treated with Darco KB, and the solution was concentrated to a volume of 650 ml under reduced pressure. This solution was diluted with 2.2 l. of isopropyl alcohol, concentrated to a volume of 1.5 l. under reduced pressure, and cooled. After crystallization was complete, the mixture was filtered, and the crystals were washed with cold isopropyl alcohol. After air drying, there was obtained 154 g (44% yield) of tricyclic ester **21** as yellow needles, mp 201–203° dec. One recrystallization from methanol afforded yellow needles, mp 201–203.5° dec; $\lambda\lambda_{max}$ mμ (ε) 279 (6300), 408 (18,000) in methanol–0.01 *N* HCl (see Figure 1); 274 (5600), 325 (7900), 413 (15,600) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{CHCl_3}$ 6.0, 6.11, and 6.30 (very strong) μ.

Anal. Calcd for $C_{17}H_{15}O_6Cl$: C, 58.20; H, 4.31; Cl, 10.12. Found: C, 58.39; H, 4.32; Cl, 10.34.

5-Chloro-3,3a,4,9-tetrahydro-1-hydroxy-8-methoxy-2*H*-benz[*f*]inden-9-one (22). 1. Cyclization of the Tetralonepropionic Ester 20. To a mechanically stirred slurry of sodium hydride (4.25 g of a 57% suspension in mineral oil, 0.10 mole) in 100 ml of dimethylformamide under nitrogen was added dropwise over 0.5 hr a solution of 14.8 g (0.05 mole) of tetralone ester **20** in 200 ml of dimethylformamide. After being stirred for an additional 0.5 hr at room temperature, the mixture was slowly heated to 65°, at which temperature hydrogen evolution became vigorous. The heat was removed and the mixture was allowed to cool to room temperature (0.5 hr). Acetic acid (20 ml) was added dropwise to the dark red solution, the color changing to a deep yellow. Chloroform (500 ml) was added and the entire mixture was poured into 1.5 l. of water. The mixture was shaken and the chloroform layer separated. The aqueous layer was extracted once with chloroform and the organic solutions were combined, washed with water several times, dried over anhydrous sodium sulfate, and filtered. The chloroform was removed by evaporation under reduced pressure, affording a liquid residue which contained dimethylformamide. Water was added to the hot residue until crystallization began. The mixture was refrigerated overnight, then filtered, and the yellow crystals were washed with a small amount of methanol. Recrystallization from methanol afforded 9.1 g (69% yield) of yellow crystals, mp 133–140°. A second crop, mp 129–133° (1.25 g, 78% total yield), was obtained. The main-crop material was recrystallized three times from methanol to give **22** as yellow platelets, mp 149–151°. Sublimation of the recrystallized sample afforded **22** as yellow crystals, mp 148–149°; $\lambda\lambda_{max}$ mμ (ε) 349 (13,700) in methanol–0.01 *N* HCl; 265 (6900), 365 (15,300) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 6.0, 6.21, 6.30 sh, and 6.36 (sh) μ.

Anal. Calcd for $C_{14}H_{13}O_3Cl$: C, 63.52; H, 4.96. Found: C, 63.65; H, 5.23.

2. Degradation of the α-Keto Acid ii.[16] A 0.50-g sample of α-keto acid ii, mp 214–215° dec, was decomposed by heating in a small tube. The evolved gases were passed initially through a 0.005 *N* palladium chloride solution, a fine dark precipitate of metallic palladium being quickly obtained. A barium carbonate precipitate was then obtained when the decomposition gases were passed through a barium hydroxide solution. When the bubbling had ceased, the dark gummy residue was dissolved in benzene and chromatographed on 10 g of Florisil. The column was eluted with benzene and the eluates were evaporated under reduced pressure. There was obtained 20 mg of a yellow crystalline substance which had ultraviolet and infrared spectra identical with those of the above described diketone **22**.

Methyl 5-Chloro-3,3a,4,9-tetrahydro-1,α-dihydroxy-8-methoxy-9-oxo-2*H*-benz[*f*]indene-Δ$^{2,\alpha}$-acetate (23). 1. From the Tetralonepropionic Ester 20. A solution of 29.7 g (0.10 mole) of methyl 5-chloro-8-methoxy-1-tetralone-3-propionate (**20**), mp 103–105°, in 100 ml of dimethylformamide was added at room temperature to a mechanically stirred slurry of 8.58 g (0.20 mole, 56% in mineral oil) of sodium hydride in 200 ml of dimethylformamide under nitrogen. During the addition, the mixture became red and the temperature rose to 38°. After 0.5 hr, a solution of 11.8 g (0.10 mole) of dimethyl oxalate in 100 ml of dimethylformamide was added during a 1-hr period. The mixture became dark red and was stirred overnight at room temperature. To the mixture, which contained a precipitated solid, was slowly added 75 ml of glacial acetic acid, followed by 500 ml of chloroform. The solution was washed three times with 500-ml portions of water, dried over anhydrous magnesium sulfate, treated with Darco, filtered, and evaporated under reduced pressure to a thick, partially solid gum. The gum was dissolved in chloroform and hexane was added until crystallization began. After crystallization was complete the mixture was filtered and the crystals were washed with chloroform–hexane, then hexane, and air dried. There was obtained 2.15 g (61% yield) of product as brown crystals, mp 188–192° dec. Recrystallization from ethyl acetate afforded red-brown crystals, mp 198–201° dec. Sublimation of a sample gave the α-keto ester **23** as yellow-orange crystals, mp 198–201° dec; $\lambda\lambda_{max}$ mμ (ε) 411 (21,000) in methanol–0.01 *N* HCl (see Figure 1); 260 (6100), 307 (10,100), 418 (12,800) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{CH_2Cl_2}$ 5.78, 6.04, 6.23, and 6.30 (sh) μ.[29]

Anal. Calcd for $C_{17}H_{15}O_6Cl$: C, 58.21; H, 4.31; Cl, 10.11. Found: C, 58.19; H, 4.37; Cl, 10.05.

2. From the Diketone 22. A mixture of 2.65 g (0.01 mole) of diketone **22**, mp 146–148°, 4.20 g (0.036 mole) of dimethyl oxalate, and 1.35 g (0.032 mole, 56% dispersion in mineral oil) of sodium hydride in 75 ml of dimethylformamide under nitrogen was stirred at room temperature for 15 min, then heated. At 80–85° a vigorous reaction occurred with the evolution of hydrogen gas, the color of the mixture changing from yellow to orange. After the reaction had subsided, the mixture was cooled to room temperature, stirred for 1 hr, then acidified with 25 ml of glacial acetic acid. Chloroform was added, and the mixture was washed four times with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to a small volume. Hexane was added to incipient turbidity and crystallization began. The mixture, after crystallization was complete, was filtered and the crystals were washed with chloroform–hexane, then hexane, and air dried. There was obtained 2.51 g (72% yield) of product **23** as orange crystals, mp 195–198° dec, the infrared and ultraviolet spectra of which were indistinguishable from those of the analytical sample described above.

5-Chloro-3,3a,4,9-tetrahydro-8-methoxy-9-oxo-2*H*-benz[*f*]indene-1-carboxylic Acid (24). 1. From the α-Keto Ester 23. A mixture of 5.00 g (1.42 mmoles) of ester **23**, mp 198–201°, in 120 ml of glacial acetic acid and 20 ml of concentrated hydrochloric

(29) The infrared spectrum was taken on a Perkin-Elmer Infracord, Model 137.

acid was heated under nitrogen on the steam bath for 12 hr. The dark solution was cooled and poured into chloroform. The mixture was washed several times with water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to a gummy, partially crystalline solid. The crude product was recrystallized from aqueous methanol to give 2.0 g of brown crystals, mp 187–190° dec. The mother liquor was evaporated and 1.52 g of additional crystalline material, mp 208° dec, was obtained by trituration with methanol.

A 0.54-g sample of the first-crop material was passed through a 10-g silicic acid column with chloroform. Evaporation of the eluate afforded yellow crystals which were recrystallized twice from chloroform–hexane to give 0.20 g of pale yellow crystals, mp 201–203° dec. Two recrystallizations from chloroform–ethanol afforded the unsaturated acid **24** as small yellow crystals, mp 212–214° dec; $\lambda\lambda_{max}$ mμ (ε) 296 (10,300), 360 (3200) in methanol–0.01 *N* HCl; 278 sh (7000), 299 (9400), 335 sh (5700) in 0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 4.4 (broad), 5.83, 6.20, 6.30, and 6.44 μ.

Anal. Calcd for $C_{15}H_{13}O_4Cl$: C, 61.55; H, 4.48; Cl, 12.11; neut equiv, 293. Found: C, 61.44; H, 4.72; Cl, 12.40; neut equiv, 290.

The second-crop material (1.52 g) from the reaction was also chromatographed on silicic acid. Elution with chloroform and evaporation of the eluates gave golden crystals. This substance was recrystallized twice from chloroform–hexane to give 0.90 g of golden needles, mp 214–215° dec. The infrared and ultraviolet spectra of this material were identical with those of the α-keto acid ii described below.

2. From the Triketone 8. A mixture of 0.20 g (0.68 mmole) of triketone **8**, mp 175–177° dec, in a solution of 0.35 g of sodium hydroxide in 30 ml of water was refluxed 10 min, the organic substance not completely dissolving in this time. Sodium hydroxide (0.35 g) was added followed by 5 ml of ethanol and the now clear red solution was refluxed an additional 20 min, treated with Darco, filtered through Super-Cel, cooled, and acidified with hydrochloric acid. After a suitable time for crystallization, the mixture was filtered and the solid washed well with water and air dried. There was obtained 0.080 g (40% yield) of yellow crystals, mp 201–205° dec. One recrystallization from chloroform–ethanol afforded 0.055 g of unsaturated acid **24** as yellow crystals, mp 210–212° dec, having infrared and ultraviolet spectra identical with those of the analytical sample described above.

Benzyl 5-Chloro-8-methoxy-1-tetralone-3-propionate (iii). A mixture of 28.3 g (0.10 mole) of tetralone acid **19**, mp 182–184°, 32.4 g (0.30 mole) of benzyl alcohol, and 0.6 ml of concentrated sulfuric acid in 60 ml of ethylene dichloride was refluxed for 4 hr. After being cooled, the solution was washed several times with water, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residual thick oil, 48.0 g, was crystallized from ethyl acetate–hexane to give 25.7 g (69% yield) of ester, mp 81–85°. A sample was recrystallized once from ethyl acetate–hexane to give iii as colorless crystals, mp 84–85°; $\lambda\lambda_{max}^{CH_2Cl_2}$ 5.75 and 5.91 μ.[29]

Anal. Calcd for $C_{21}H_{21}O_4Cl$: C, 67.65; H, 5.68; Cl, 9.51. Found: C, 67.63; H, 5.81; Cl, 9.40.

Benzyl 5-Chloro-3,3a,4,9-tetrahydro-1,α-dihydroxy-8-methoxy-9-oxo-2*H*-benz[*f*]indene-Δ$^{2,\alpha}$-acetate (iv). To a mechanically stirred slurry of 8.58 g (0.02 mole, 56% in mineral oil) of sodium hydride in 200 ml of dimethylformamide under nitrogen was added 37.2 g (0.10 mole) of tetralone benzyl ester iii, mp 78–80°, in 100 ml of dimethylformamide over a 30-min period. A solution of 27.0 g (0.10 mole) of dibenzyl oxalate, mp 73–75°, in 100 ml of dimethylformamide was then added and the mixture was stirred at 45–50° for 5 hr. The mixture was cooled and 300 ml of glacial acetic acid was added, followed by 1 l. of chloroform. After being washed four times with 2-l. portions of water, the chloroform solution was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to a dark gum. The product crystallized upon the addition of ether and was filtered, washed with ether, and air dried. There was obtained 21.5 g (50.3% yield) of α-keto benzyl ester iv as orange crystals, mp 136–137°. A sample prepared in a similar manner was recrystallized twice from chloroform–hexane to give iv as small clusters of orange rods and prisms, mp 138–139° dec; $\lambda\lambda_{max}$ mμ (ε) 411 (19,000) in 0.01 *N* HCl; 259 (6400), 307 (9200), 423 (14,700) in 0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 5.75, 6.01, 6.18, and 6.30 μ.

Anal. Calcd for $C_{23}H_{19}O_6Cl$: C, 64.73; H, 4.49; Cl, 8.31. Found: C, 64.82; H, 4.46; Cl, 8.22.

5-Chloro-3,3a,4,9-tetrahydro-1,α-dihydroxy-8-methoxy-9-oxo-2*H*-benz[*f*]indene-Δ$^{2,\alpha}$-acetic Acid (ii). A mixture of 21.3 g (0.05 mole) of benzyl ester iv and 1.0 g of 5% palladium on charcoal in 150 ml of dimethylformamide was hydrogenated in a Parr apparatus at room temperature and 40 psi. Within 1 hr, uptake had ceased at 1 molar equiv. Some crystalline product had separated during the reaction. Dimethylformamide (50 ml) was added and the mixture warmed to dissolve the precipitated material. The mixture was filtered, and the filtrate was diluted with an equal volume of water, causing the product to crystallize. The crystals were collected by filtration, washed with dimethylformamide–water, then water, and dried at 65° *in vacuo*. The products from eight such runs were composited, affording 123.0 g (91.5% yield) of the acid ii as orange crystals, mp 208–210° dec. A sample prepared in a similar manner, mp 206–207° dec, was recrystallized once from chloroform–hexane. The product ii was obtained as small golden needles, mp 214° dec; $\lambda\lambda_{max}$ mμ (ε) 415 (20,800), 430 sh (18,700) in methanol–0.01 *N* HCl; 261 (6200), 303 (7700), 400 sh (13,400), 420 (15,700), 440 sh (13,400) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 6.13, 6.30, and 6.40 μ.

Anal. Calcd for $C_{16}H_{13}O_6Cl$: C, 57.07; H, 3.88; Cl, 10.53; neut equiv, 338. Found: C, 57.09; H, 3.94; Cl, 10.74; neut equiv, 338.

8-Chloro-1,2,3,9,9a,10-hexahydro-4-hydroxy-5-methoxy-3,10-dioxoanthracene (8). A mixture of 357 g (1.02 moles) of triketo ester **21**, mp 202–205°, 7.4 l. of acetic acid, 4.9 l. of concentrated hydrochloric acid, and 1.0 l. of water was stirred under nitrogen at 90–94° for 0.75 hr. The mixture was cooled to 25° and 4 l. of ice water followed by 3 l. of chloroform was added with stirring. The layers were separated, and the aqueous solution was extracted three times with 1.5-l. portions of chloroform. The chloroform extracts were combined and washed four times with water, dried over anhydrous sodium sulfate, treated with Darco KB, and evaporated to dryness under reduced pressure. The dark residue was dissolved in 2.0 l. of warm ethyl acetate and the resulting solution concentrated under reduced pressure to 800 ml, then cooled. After crystallization was complete, the mixture was filtered and the product washed with cold ethyl acetate. There was obtained 216 g (73% yield) of triketone **8** as yellow-orange platelets, mp 172–175° dec. A sample prepared in a similar manner was recrystallized once from chloroform–ethyl acetate and again from ethyl acetate, affording orange rods and platelets, mp 174.5–176.5° dec; $\lambda\lambda_{max}$ mμ (ε) 271 (3600), 343 (12,300) in methanol–0.01 *N* HCl; 399 (15,100) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{CHCl_3}$ 5.84, 6.10, and 6.30 μ.

Anal. Calcd for $C_{15}H_{13}O_4Cl$: C, 61.56; H, 4.48; Cl, 12.1. Found: C, 61.89; H, 4.50; Cl, 12.2.

Zinc Dust Distillation of the Triketone 8. A 6.0-cm bore glass tube was fitted with a porous asbestos plug and zinc dust was placed on top of the plug to a depth of 2.5 cm. An intimate mixture of 10 mg of triketone **8**, mp 175–177° dec, and 1.0 g of zinc dust was then placed in the tube followed by a 5-cm column of pure zinc dust and another asbestos plug. A very slow stream of hydrogen was passed through the tube and then, while being slowly rotated, the tube containing the zinc was heated with two burners. After 5 min, a blue fluorescent area appeared in the cold part of the tube at the gas-exit end, then crystals began to form. The tube was cooled and the crystals were collected. There was obtained 0.8 mg, mp 185–190° (anthracene mp 217°), the ultraviolet spectrum of which was in excellent agreement with authentic anthracene.

The Quinoxaline Derivative 25 of the Triketone 8. A mixture of 0.15 g (0.51 mmole) of triketone **8**, mp 175–177° dec, 0.065 g of *o*-phenylenediamine, and 3 mg of *p*-toluenesulfonic acid monohydrate in 50 ml of methanol was allowed to stand at room temperature. After 3 hr the solution became dark red and brown crystals began to form. After standing overnight, the mixture was filtered, and the rust-brown needles were washed with methanol and dried. There was obtained 0.090 g (49% yield), mp 232–240° dec.

Anal. Calcd for $C_{21}H_{17}O_2N_2Cl$: C, 69.13; H, 4.70; N, 7.68; Cl, 9.72. Found: C, 68.77; H, 4.93; N, 7.97; Cl, 9.70.

5-Chloro-2,3,4,4a,9,10-hexahydro-1-hydroxy-8-methoxyspiro-[anthracene-2,2′-dithiolan]-9-one (26). A mixture of 0.55 g (1.9 mmoles) of triketone **8**, mp 175–177° dec, 0.050 g of *p*-toluenesulfonic acid monohydrate, and 1.00 g of ethanedithiol in 250 ml of dry benzene was slowly distilled for 2 hr, 150 ml of benzene being removed during this time. The remaining benzene solution was then evaporated under reduced pressure to a red gum which was crystallized from acetone–hexane. After filtration, the crystals were washed with acetone–hexane, then hexane, and air dried. There was obtained 0.40 g (57% yield) of **26** as yellow crystals, mp 152–154°. Two recrystallizations from acetone–hexane afforded yellow crystals, mp 158–159°.

Anal. Calcd for $C_{17}H_{17}O_3S_2Cl$: C, 55.35; H, 4.65; S, 17.39. Found: C, 55.42; H, 4.83; S, 17.53.

8-Chloro-1,2,3,9,9aα,10-hexahydro-3α,4-dihydroxy-5-methoxy-10-anthracenone (27). 1. Borohydride Reduction of the Triketone 8. A solution of 292 mg (1.00 mmole) of triketone **8** in 25 ml of 1,2-dimethoxyethane was magnetically stirred and cooled in an ice bath. Sodium borohydride (20 mg, 0.53 mmole) was added, and the mixture was stirred for 2 hr, after which time 2 ml of 1 *N* hydrochloric acid was added. After an additional 30-min stirring, chloroform was added, and the mixture was extracted four times with water. The organic solution was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to a yellow solid. The residue was slurried in ether and filtered, and the crystals were washed with ether. There was obtained 180 mg (61% yield) of product as yellow crystals, mp 172–173°. A single recrystallization from benzene–hexane afforded the diketo alcohol **27** as yellow rods, mp 179–181°, having infrared and ultraviolet spectra identical with those of the analytical sample described below.

2. Catalytic Reduction of the Triketone 8. A mixture of 1.00 g (3.42 mmoles) of triketone **8**, mp 175–177° dec, and 0.50 g of 10% palladium on charcoal in 50 ml of chloroform and 80 ml of ethanol was hydrogenated in a Parr shaker at 40 psi until hydrogen uptake ceased. The mixture was filtered and the filtrate was evaporated under reduced pressure to a yellow, partially crystalline gum. The ultraviolet spectrum indicated complete reduction of the terminal carbonyl group. Five recrystallizations afforded 0.21 g (21% yield) of yellow prisms, mp 175–176°. Sublimation of a sample of the recrystallized substance gave the diketo alcohol **27** as yellow prisms, mp 177–178°; $\lambda\lambda_{max}$ mμ (ϵ) 269 (4300), 348 (13,500) in methanol–0.01 *N* HCl; 263 (5900), 360 (13,100) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{CHCl_3}$ 2.80, 6.20 sh, and 6.30 μ.

Anal. Calcd for $C_{15}H_{15}O_4Cl$: C, 61.16; H, 5.13; Cl, 12.0. Found: C, 61.16; H, 5.20; Cl, 11.5.

8-Chloro-1,2,3,9,9a,10-hexahydro-4-hydroxy-5-methoxy-10-anthracenone (28). 1. By Desulfurization of the Dithio Ketal 26. A mixture of 0.30 g (0.81 mmole) of dithio ketal **26**, mp 152–154°, and 3.0 g of Raney nickel in 250 ml of absolute ethanol was stirred at room temperature overnight. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform, and the solution was washed once with 1 *N* hydrochloric acid and several times with water. The organic solution was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was chromatographed on 6.0 g of silicic acid, the substance being put onto the column with chloroform. Elution with chloroform afforded a fluorescent solution which, when evaporated under reduced pressure, afforded yellow crystals. The substance was recrystallized twice from acetone–hexane, then sublimed, to give 0.14 g (62% yield) of **28** as yellow crystals, mp 135–137°, no depression on admixture with the tricyclic diketone described below.

2. *Via* **the Independent Route[18] from the Benzoylsuccinic Ester 12. a. Alkylation of the Succinate to Obtain the Unsaturated Triester v.** A solution of 140 g (0.50 mole) of benzoylsuccinate **12** in 300 ml of dimethylformamide was added dropwise at room temperature to a mechanically stirred suspension of 23.5 g (0.55 mole) of sodium hydride (56% in mineral oil) in 300 ml of dimethylformamide. The mixture was stirred at room temperature for 1 hr and a solution of 212 g (1.1 moles) of ethyl γ-bromocrotonate, bp 60–70° (1–2 mm), $n^{24}D$ 1.4916, in 300 ml of dimethylformamide was added dropwise and stirring continued overnight. The mixture was acidified with acetic acid, poured into chloroform, and washed once with water. The water wash was extracted twice with chloroform; the organic solutions were combined, extracted several times with water, and dried over anhydrous sodium sulfate. After being filtered, the mixture was concentrated under reduced pressure to a heavy oil. The products from two such experiments were combined and washed by decantation with hexane several times to remove the mineral oil. The residual heavy oil crystallized on standing overnight. The mixture was filtered and the crystals were washed with methanol. There was obtained 56.0 g of product as colorless crystals, mp 75–77°, $\lambda\lambda_{max}^{KBr}$ 5.78, 5.90, 6.01, and 6.24 μ. The mother liquor was reworked several times with methanol to give an additional 58.0 g (total yield 114.0 g; 29% yield) of product v, mp 72–77°.

b. Hydrogenation, Hydrolysis, and Decarboxylation of the Unsaturated Triester v to Obtain the Keto Diacid vi. The unsaturated ester v (56.0 g, mp 75–77°) was dissolved in 500 ml of an equivolume mixture of ethanol and chloroform and hydrogenated at room temperature and atmospheric pressure over 1.0 g of 5% palladium on charcoal. A molar equivalent of hydrogen was rapidly absorbed and the uptake ceased. The mixture was filtered, and the solvent was evaporated from the filtrate under reduced pressure to yield 55.3 g of a colorless gum; $\lambda\lambda_{max}^{film}$ 5.75 (very strong), 5.90, 6.24, and 6.30 μ.

The hydrogenated product (55.3 g) was dissolved in 45 ml of acetic acid, 26 ml of concentrated sulfuric acid, and 26 ml of water, and the mixture was refluxed for 24 hr. The brown solution was cooled and poured into chloroform, and the mixture was washed several times with water. After being dried over anhydrous sodium sulfate, the solution was filtered and the filtrate evaporated under reduced pressure to give 37.7 g of vi as a red gum; $\lambda\lambda_{max}^{film}$ 3.0–4.0 (broad), 5.75–5.95 (broad), 6.25, and 6.30 μ.

c. Reduction, Chlorination, and Cyclization of the Keto Diacid vi to Obtain 5-Chloro-8-methoxy-1-tetralone-3-butyric Acid (vii). The total sample (37.7 g) of crude keto diacid vi was dissolved in 150 ml of acetic acid and hydrogenated over 5.0 g of 5% palladium on charcoal at 50° and 40 psi. Uptake of 1 molar equiv of hydrogen was rapid (1 hr), whereas the second equivalent required 72 hr. The mixture was cooled, filtered, and evaporated under reduced pressure to a gum (32.2 g); $\lambda\lambda_{max}^{film}$ 3.0–4.0 (broad), 5.75–5.85 (broad), 6.25, and 6.30 μ. The crude benzylpimelic acid was dissolved in a minimum amount of chloroform and chromatographed on 500 g of silicic acid. The column was eluted with chloroform until the eluates, upon evaporation, afforded no additional material. All chloroform eluates were combined and evaporated under reduced pressure to give 13.1 g of a yellow gum; $\lambda\lambda_{max}^{film}$ 3.0–4.0 (broad), 5.75, 5.84, 6.24, and 6.29 μ (see below). Continued elution of the column with 5% methanol in chloroform, followed by evaporation of the eluate, afforded an additional 18.1 g of a yellow gum which had $\lambda\lambda_{max}^{film}$ 5.85 (very strong), 6.24, and 6.29 μ.

The substance (18.1 g) obtained from the methanol–chloroform eluate of the column was dissolved in 200 ml of acetic acid. The solution was cooled to 10–15° and placed in the dark, and 0.18 g of anhydrous ferric chloride was added. A solution of chlorine in acetic acid (73.0 ml, containing 4.60 g of chlorine) was then added dropwise during 1 hr with stirring. After an additional 15 min, the mixture was concentrated under reduced pressure to a brown gum. The residue was dissolved in chloroform and washed several times with water. The chloroform solution was dried over anhydrous sodium sulfate and filtered and the solvent evaporated under reduced pressure to a brown gum.

The crude chloro diacid was placed in a polyethylene container and 50 ml of hydrogen fluoride was added. The mixture was stirred at room temperature overnight, then poured onto ice. After the ice had melted the water was extracted twice with chloroform. The organic extracts were combined, washed several times with water, dried over anhydrous sodium sulfate, treated with Darco KB, filtered, and concentrated under reduced pressure. The residue, 14.4 g of a brown gum, crystallized when triturated with ether. The mixture was filtered and the crystals were washed with ether and air dried. There was obtained 9.1 g (22% yield from crystalline unsaturated ester v) of tetralonebutyric acid vii as colorless crystals, mp 133–136°. The ultraviolet spectrum showed characteristic tetralone absorption (see the spectral data for the acid **19**). Recrystallization from acetone afforded colorless crystals, mp 144–147°; $\lambda\lambda_{max}^{KBr}$ 5.79, 5.96, and 6.32 μ.

Anal. Calcd for $C_{15}H_{17}O_4Cl$: C, 60.74; H, 5.78. Found: C, 60.98; H, 6.09.

The substance (13.1 g) eluted from the above-described silicic acid column with chloroform, when subjected to a chlorination–cyclization sequence analogous to that just described, failed to yield any material recognizable as a tetralone.

d. Esterification and Cyclization of the Tetralone Acid vii to Obtain the Diketone 28. A 5.0-g sample of tetralonebutyric acid vii, mp 134–147°, was esterified by refluxing overnight in a mixture of methanol (25 ml), chloroform (250 ml), and concentrated sulfuric acid (10 ml). The solution was cooled, extracted several times with water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. There was obtained 5.04 g of ester as a tan gum.

The crude ester, 5.04 g, dissolved in 100 ml of dimethylformamide, was added dropwise with stirring to a suspension of sodium hydride (1.38 g, 56% in mineral oil) in 100 ml of dimethylformamide at room temperature. The mixture was heated to 65° for 15 min, hydrogen evolution becoming fairly vigorous at 45°. The mixture was then cooled, stirred overnight at room temperature, acidified with 25 ml of acetic acid, and poured into chloroform and water. The mixture was shaken, the layers separated, and the aqueous solution was extracted once with chloroform. The chloroform solutions were combined, washed well with water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to

an orange solid. The crude product was put onto a 100-g silicic acid column with chloroform. Elution with chloroform and evaporation of the solvent afforded 3.0 g of a pale yellow crystalline solid which was recrystallized once from aqueous acetone. There was obtained 1.60 g (35% yield from the tetralonebutyric acid vii) of the tricyclic diketone **28** as yellow needles, mp 132–135°. Two recrystallizations from acetone–hexane gave pale yellow prisms and rods, mp 136–137°; $\lambda\lambda_{max}$ mμ (ε) 267 (4400), 346 (14,200) in methanol–0.01 *N* HCl; 262 (6600), 359 (14,500) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{CHCl_3}$ 6.20 sh and 6.30 μ.

Anal. Calcd for $C_{15}H_{15}O_3Cl$: C, 64.68; H, 5.43; Cl, 12.7. Found: C, 64.97; H, 5.49; Cl, 12.9.

***n*-Butyl 8-Chloro-3,3,9a,10-tetrahydro-4-hydroxy-5-methoxy-3,-10-dioxo-$\Delta^{2(1H)}$,α-anthracene-2-acetate (29).** A mechanically stirred mixture of 35.0 g (0.120 mole) of triketone **8** and 30.9 g (0.24 mole) of *n*-butyl glyoxylate[30] in 3 l. of toluene was refluxed under nitrogen 1 hr, any water present being removed by a Dean–Stark trap. To the hot orange solution was added 2.55 g (0.03 mole) of freshly prepared magnesium methoxide, the color immediately becoming much darker. Refluxing was continued for 2.5 hr after the methoxide addition, water being collected in the trap during this period. The mixture was then cooled and 500 ml of 6 *N* hydrochloric acid was added. Stirring was continued for 5 min and the layers were separated. The acid layer was extracted once with 500 ml of chloroform, and the organic solutions were combined. The toluene was then washed four times with water (acid free) and twice with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residual red gum was dissolved in ether containing some ethyl acetate and triturated with a glass rod. Crystallization began slowly and was allowed to continue overnight. The mixture was filtered and the crystals were washed with an ether–ethyl acetate solution, then ether. There was obtained 17.8 g of product **29** as small yellow-orange crystals, mp 127–128°.

The mother liquor from the crystallization was evaporated to a red gum and chromatographed on 300 g of silicic acid. Elution of the column with 3:1 chloroform–carbon tetrachloride followed by evaporation of the eluates under reduced pressure afforded red gums which crystallized when triturated with ether. All fractions which crystallized were combined and crystallized from ether. There was obtained 7.14 g (total yield 24.9 g; 51.5%) of yellow-orange crystals, mp 125.5–127°. Recrystallization of a sample prepared in a similar experiment from ethyl acetate–hexane afforded small orange-yellow crystals, mp 127.5–128° dec; $\lambda\lambda_{max}$ mμ (ε) 285 (6100), 366 (13,700) in methanol–0.01 *N* HCl; 240 (12,200), 318 (5100), 440 (10,100) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{CHCl_3}$ 5.79, 5.93, 6.11, and 6.34 μ.

Anal. Calcd for $C_{21}H_{21}O_6Cl$: C, 62.30; H, 5.23; Cl, 8.76. Found: C, 62.58; H, 5.55; Cl, 8.87.

***n*-Butyl 8-Chloro-1,2α,3β,9,9aα,10-hexahydro-3,4-dihydroxy-5-methoxy-10-oxoanthracene-2-(α-dimethylamino)acetate (32).** To a 1-l., three-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen inlet tube, an outlet tube with a stopcock, and a stopper, was added 300 ml of liquid dimethylamine. The flask was placed in an ice–salt bath and 15.0 g (0.037 mole) of the unsaturated ester **29** was added slowly to preclude formation of a gum. During the addition and the subsequent reaction, a vigorous stream of nitrogen was introduced into the flask through the inlet tube. The red solution was stirred for 2 hr, the flask being maintained in the ice–salt bath. During this period, the crude Mannich base **30** precipitated from the reaction mixture as a yellow-orange solid. The flask was then evacuated (water aspirator) *via* the outlet tube, the vigorous stream of nitrogen continuing to be passed through the flask. After the bulk of the excess dimethylamine had been removed, the residue, a yellow-orange gummy solid, was cooled in a Dry Ice–acetone bath; the stopcock on the outlet tube was closed and the aspirator hose connection removed. A finger was placed on the outlet tube, and the stopcock was opened. When the flask was filled with nitrogen, the pressure caused the finger to part from the outlet tube. This technique was necessary to prevent the admittance of *any* air into the reaction flask. It had been found that the base **30** rapidly darkened in the presence of only small quantities of air, low product yields being the end result. In a similar experiment, ether was added to the cold residue, and the mixture was filtered. After being washed with ether, the crystalline Mannich base **30** was dried *in vacuo* to a yellow-orange solid, $\lambda\lambda_{max}^{CHCl_3}$ 5.80, 5.85, 6.11, and 6.31 μ, which darkened in the presence of air. The ultraviolet spectrum of **30** was qualitatively similar to the triketone **8**.

To the cold solid was added 1.76 g (0.047 mole) of sodium borohydride followed by a mixture of 300 ml of 1,2-dimethoxyethane and 2 ml of water which had been precooled to −70°. The flask was then removed from the Dry Ice–acetone bath, placed in an ice bath, and swirled until the solid had dissolved. The mixture was stirred for an additional 30 min in the bath after which time 30 ml of glacial acetic acid was slowly added. After being stirred 5 min, the mixture was slowly poured into 180 ml of 6 *N* hydrochloric acid, vigorous bubbling resulting from the decomposition of the excess borohydride. Water (500 ml) was added and the solution extracted three times with 700 ml of chloroform. The organic extracts were combined, washed three times with 3-l. portions of water and once with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The mixture was treated with Darco, filtered through Super-Cel, and concentrated under reduced pressure to a volume of 100 ml. The solution was cooled in an ice bath and hydrogen chloride gas was bubbled through for 5 min. Evaporation of the remainder of the solvent afforded a yellow foam which crystallized when triturated with ethyl acetate containing a small amount of chloroform. When crystallization was complete, the mixture was filtered and the yellow crystals were washed well with ethyl acetate, followed by ether. There was obtained 12.5 g (69% yield) of crude amino alcohol **32**, mp 165–169°, contaminated with a small amount of lactone as shown by the infrared spectrum.

This sample of alcohol was combined with that obtained from an identical experiment, 11.0 g, mp 172–175°, and dissolved in methanol at room temperature. The resulting mixture, containing a small amount of the lactone which was not soluble, was treated with Darco and filtered through Super-Cel. Methanol was then boiled out of the solution and replaced with ethyl acetate until crystallization began. The mixture was cooled and allowed to crystallize for several hours, after which time it was filtered and the crystals were washed with ethyl acetate followed by ether. There was obtained 15.0 g of amino alcohol **32** as pale yellow crystals, mp 197–199° dec, the infrared spectrum of which exhibited no lactone carbonyl absorption. Concentration of the mother liquor afforded a second crop, 4.0 g (total yield of recrystallized material 19.0 g; 52.5%), mp 192–194° dec, having an infrared spectrum identical with both the first crop material and the analytical specimen. A sample of amino alcohol prepared in a similar experiment was recrystallized from ethanol–ethyl acetate to give the hydrochloride of **32** as pale yellow crystals, mp 190–192° dec; $\lambda\lambda_{max}$ mμ (ε) 269 (4100), 350 (13,600) in methanol–0.01 *N* HCl; 263 (6400), 360 (14,100) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 3.04, 4.2 (broad), 5.76, and 6.31 (broad) μ.

Anal. Calcd for $C_{23}H_{30}O_6NCl \cdot HCl$: C, 56.56; H, 6.40; N, 2.87; Cl, 14.52. Found: C, 56.88; H, 6.44; N, 2.70; Cl, 14.4.

Reactions in which the borohydride reduction was carried out at slightly higher temperatures had a tendency to have more lactone contaminant **33** in the crude alcohol **32**. The lactonic by-product was separated from the desired alcohol by virtue of its great insolubility in methanol at room temperature. Thus, to isolate the lactone, the crude alcohol was dissolved in methanol at room temperature and the solution filtered. The insoluble substance was virtually pure lactone **33** and the alcohol **32** was then crystallized from the filtrate as described above. A sample of lactone by-product **33**, mp 265–270° dec, as the hydrochloride salt, obtained in this manner was recrystallized from chloroform–methanol–ethyl acetate to give small pale yellow crystals, mp 270° dec; $\lambda\lambda_{max}$ mμ (ε) 275 (4700), 320 sh (10,300), 344 (11,000) in methanol–0.01 *N* HCl; 260 (6700), 356 (15,100) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 4.90 (broad), 5.60, 6.12, 6.23, and 6.31 μ.

Anal. Calcd for $C_{19}H_{20}O_5NCl \cdot HCl$: C, 55.08; H, 5.11; N, 3.38; Cl, 17.12. Found: C, 55.38; H, 5.19; N, 3.38; Cl, 17.0.

6-Chloro-3-dimethylamino-11-hydroxy-3aα,4aα,5,11aβ-tetrahydro-9-methoxyanthra[2,3-*b*]furan-2,10(3*H*,4*H*)dione (34). A mixture of 20.5 g (0.042 mole) of amino alcohol hydrochloride **32**, mp 190–192° dec, and 10.2 g of *p*-tolunesulfonic acid in 2.0 l. of toluene was stirred mechanically and refluxed under nitrogen for 3 hr. During the reflux period, 200 ml of solvent was removed *via* a Dean–Stark trap. The mixture was cooled, causing a small amount of gum to form. Chloroform (250 ml) was added followed by 750 ml of water, whereupon the product began to crystallize. The toluene solution was removed by decantation, washed with water until neutral, then washed once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and

(30) F. J. Wolf and J. Weijlard "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 124.

evaporated under reduced pressure to a yellow foam. The crystalline material remaining after decantation of the toluene was dissolved in a mixture of chloroform and water. The organic solution was separated, washed with water until neutral, then washed once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to a yellow foam. The two samples of foam were combined in chloroform and gaseous hydrogen chloride was bubbled through the solution for 5 min. The hydrochloride salt of the product began to crystallize during the addition of the gas. Some of the chloroform was removed under reduced pressure, an equal volume of ether was added, and the product allowed to crystallize overnight. The mixture was filtered and the crystals were washed well with ether. There was obtained 17.2 g (90.0% yield) of the hydrochloride of the desired lactone **34** (0.33 chloroform solvate) as yellow crystals, mp 211–219° dec, having an infrared spectrum identical with the analytical specimen. A sample prepared in a similar manner was recrystallized once from chloroform–methanol–ethyl acetate and once from chloroform–dimethylformamide–ethyl acetate to give **34** as pale yellow needles, mp 222–225° dec; $\lambda\lambda_{max}$ mμ (ϵ) 275 (3900), 320 sh (9500), 347 (10,800) in methanol–0.01 *N* HCl; 261 (6000), 359 (15,300) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}$ 4.35 (broad), 5.61, 6.16, and 6.30 μ.

Anal. Calcd for $C_{19}H_{20}O_5NCl \cdot HCl \cdot 0.33CHCl_3$: C, 51.13; H, 4.74; N, 3.09; Cl, 23.14. Found: C, 51.33; H, 4.76; N, 3.00; Cl, 24.0.

8-Chloro-1,2a,3,9,9aα,10-hexahydro-4-hydroxy-5-methoxy-10-oxoanthracene-2-(α-dimethylamino)acetic Acid (35). To a solution of 2.00 g (4.41 mmoles) of lactone **34**, mp 204–209°, as the 0.33 chloroform-solvated hydrochloride salt, in 30 ml of 97% formic acid was added 2.0 g of zinc dust. The mixture was vigorously swirled for 60 sec and filtered rapidly through Super-Cel, the pad being washed with formic acid. Filtrates from six such reductions were combined and evaporated under reduced pressure to a yellow foam. To the residue was added some methanol and toluene, and the mixture was again evaporated to dryness under reduced pressure. The methanol–toluene evaporation was repeated a total of three times to ensure complete removal of formic acid. The residual yellow solid was dissolved with heating in 400 ml of a 40% solution of water in methanol; the solution was cooled, and hydrogen sulfide was bubbled through for 3 min. To the mixture, now containing precipitated zinc sulfide, was added some Super-Cel, and the mixture was filtered through a Super-Cel pad. The pad was washed a considerable number of times to ensure complete removal of all organic material. The filtrate and washings were combined and concentrated under reduced pressure, the product beginning to crystallize when most of the methanol had been removed. The concentration was continued until all methanol and much of the water was evaporated, the mixture being exceedingly viscous due to the crystallized acid. The mixture was cooled for several hours and filtered; the product was washed well with water and dried under vacuum over phosphorus pentoxide. There was obtained 8.50 g (81% yield) of amino acid **35** as pale yellow needles (0.5 methanol solvate). Recrystallization from methanol of a sample prepared in a similar manner afforded pale yellow needles which partially melted at 165°, resolidified, and melted again at 215–230°. Elemental analyses indicated solvation with 0.5 molar equiv of methanol. A solvent-free sample of **35** was prepared by slurrying the methanol-recrystallized substance in toluene on the steam bath for 10 min. The toluene was then removed by evaporation under reduced pressure. After drying the pale yellow crystals had mp 235–237° dec; $\lambda\lambda_{max}$ mμ (ϵ) 223 (15,500), 267 (4200), 345 (14,000) in methanol–0.01 *N* HCl; 224 (16,100), 265 (4800), 347 (14,600) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 3.8 (broad) and 6.20 (broad) μ.

Anal. Calcd for $C_{19}H_{22}O_5NCl$: C, 60.08; H, 5.84; N, 3.69; Cl, 9.33. Found: C 60.29; H, 5.87; N, 3.49; Cl, 9.7.

1,2aα,3,9,9aα,10-Hexahydro-4-hydroxy-5-methoxy-10-oxoanthracene-2-(α-dimethylamino)acetic Acid (36, X = H). A mixture of 15.0 g (39.4 mmoles) of chloro amino acid **35**, mp 235–237° dec, 22 ml of triethylamine, and 3.75 g of 10% palladium on charcoal in 1 l. of ethanol was hydrogenated at room temperature at 40 psi. Uptake of hydrogen ceased after 30 min but the hydrogenation was continued for an additional 2.25 hr with no further change in the pressure. The hydrogenation mixture was filtered through Super-Cel and the catalyst washed well with ethanol. The combined filtrate and washings were evaporated under reduced pressure to a yellow solid which was chromatographed on 225 g of silicic acid. Elution of the column with chloroform followed by 5% methanol in chloroform removed triethylamine hydrochloride. When all of the amine salt had been removed, methanol was passed through the column until no additional material was obtained. The methanol eluate was evaporated under reduced pressure to a crystalline solid which was slurried in methanol containing a small amount of ether. After filtration, the yellow crystals were washed with ether and dried, 12.7 g of dechloro acid **36** (X = H) being obtained. From the mother liquor, after evaporation and crystallization from methanol there was obtained an additional 0.17 g (total yield 12.9 g, 91%, assuming a 0.5 methanol solvate) of acid having an infrared spectrum identical with that of the main sample and also with that of the methanol-recrystallized material described below. A specimen of acid obtained in a similar experiment was recrystallized once from methanol to give clusters of yellow rods, mp 168–170°, resolidified by 195°, and remelted 214–216° dec. Analytical data indicated the sample to be methanol solvated. This material was slurried in toluene on the steam bath for 15 min, after which time the toluene was removed by evaporation under reduced pressure and the sample dried. The yellow crystals of the dechloro acid **36** (X = H) had mp 210–211° dec; $\lambda\lambda_{max}$ mμ (ϵ) 265 (4700), 338 (14,700) in methanol–0.01 *N* HCl; 264 (5500), 340 (15,900) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{KBr}$ 6.14 and 6.24 μ.

Anal. Calcd for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71; N, 4.06; Cl, 0.0. Found: C, 65.83; H, 6.65; N, 4.12; Cl, 0.03.

The Isomeric Amino Acid viii. From a mixture of 2.57 g (6.20 mmoles) of the hydrochloride salt of the by-product lactone **33**, mp 260° dec, and 2.57 g of zinc dust in 30 ml of 97% formic acid for 1.25 min, in an experiment analogous to that used for the reduction of the lactone **34**, there was obtained 1.76 g (74.5% yield) of acid viii as yellow needles. The sample was dissolved in 50% aqueous methanol using triethylamine. The solution was adjusted to pH 6 with dilute hydrochloric acid, whereupon crystallization began. The mixture was filtered and the crystals were washed with water, followed by acetone, then ether, and air dried. There was obtained 1.32 g of the isomeric acid viii as pale yellow rods, mp 260–261° dec; $\lambda\lambda_{max}$ mμ (ϵ) 267 (4400), 344 (13,000) in methanol–0.01 *N* HCl; $\lambda\lambda_{max}^{KBr}$ 4.3 (broad), 6.15, and 6.30 μ.

Anal. Calcd for $C_{19}H_{22}O_5NCl$: C, 60.08; H, 5.84; N, 3.69; Cl, 9.33. Found: C, 59.54; H, 6.09; N, 3.62; Cl, 8.92.

Ethyl N-*t*-Butylmalonamate (37). A mixture of 240 g (2.12 moles) of ethyl cyanoacetate, 112 ml of concentrated sulfuric acid, and 800 ml of acetic acid was cooled to 0° in an ice bath. Isobutylene was passed into the solution for 3 hr, the temperature being maintained at 10°. The mixture was then washed three times with 300-ml portions of hexane, the washings being discarded. The acid solution was poured onto 2 kg of ice and the mixture was extracted three times with 800-ml portions of chloroform. The organic extracts were combined and washed with water, then with saturated sodium bicarbonate solution until acid free, then again with water. After being dried over anhydrous sodium sulfate, the chloroform solution was concentrated under reduced pressure, and the residual oil was distilled through a 35-cm Vigreux column. After a forerun, there was obtained 235 g (59% yield) of amide **37** as a colorless oil, bp 83–86° (0.1–0.5 mm), $n^{25}D$ 1.4455, $\lambda\lambda_{max}^{film}$ 3.05, 5.75, 6.10, and 6.47 μ.

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.87; H, 9.20; N, 7.93.

5-Chloro-1,4,4a,10-tetrahydro-3,8,9-trihydroxy-1-oxo-2-anthramide (xii). 1. The Tricyclic Amide xi (R = *t*-C_4H_9). To a solution of 6.00 g (22.3 mmoles) of tetraloneacetic acid ix (X = H), mp 190–195°,[20] and 3.41 ml (24.6 mmoles) of triethylamine, magnetically stirred and cooled in an ice bath, was added 3.03 g (24.5 mmoles) of isopropyl chloroformate, bp 101–102°. The solution was stirred in the cold for 1 hr, diluted with additional chloroform, washed twice with water and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to a gum. An infrared spectrum[29] of the residue ix (X = CO_2-*i*-C_3H_7) demonstrated the presence of an anhydride, $\lambda\lambda_{max}^{CHCl_3}$ 5.52 and 5.70 μ.

To the crude anhydride was added 6.30 g of the magnesium derivative of ethyl N-*t*-butylmalonamate (**37**) (see below) followed by 30 ml of acetonitrile. With swirling, the mixture became homogeneous and spontaneously warmed to 55°. After 1 hr, the mixture was concentrated under reduced pressure to a gum which was then dissolved in chloroform. The solution was extracted three times with 1.5 *N* hydrochloric acid, three times with water, and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residual gum gave a red color with methanolic ferric chloride solution, consistent with the acyl malonamate structure x (R = *t*-C_4H_9).

To the total sample of crude acyl malonamate x (R = *t*-C_4H_9) dissolved in 150 ml of dimethylformamide under nitrogen, was

added 4.5 g (0.097 mole) of 52% sodium hydride in mineral oil. Vigorous bubbling ensued, the temperature increased to 43°, and the mixture became red-brown in color. After the reaction subsided, the flask was plunged into a 125° oil bath. At 90°, bubbling increased somewhat. The reaction became vigorous at 106°, the color changing to green. At 110°, the reaction subsided and 1.5 g of the 52% sodium hydride in mineral oil was added, resulting in a further vigorous reaction. After the bubbling had slowed, the red-brown mixture was cooled in an ice bath and acidified by the slow addition of acetic acid. Chloroform and water were added, the mixture shaken, and the layers separated. The aqueous solution was extracted four times with chloroform; the organic solutions were combined and washed three times with large volumes of water and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue, a yellow, somewhat gummy crystalline solid was washed by decantation four times with pentane to remove the mineral oil. Methanol was added to the residue and the mixture was cooled in an ice bath, then filtered. The yellow crystals were washed with cold methanol and air dried. There was obtained 4.22 g [53% yield from tetralone acid ix (X = H)] of N-*t*-butyl-5-chloro-1,4,4a,10-tetrahydro-3,9-dihydroxy-8-methoxy-1-oxo-2-anthramide (xi, R = *t*-C_4H_9) as small yellow rods, mp 179–182°. Two recrystallizations from acetone–isopropyl alcohol afforded yellow prisms, mp 189–192°, $\lambda\lambda_{max}$ mμ (ε) 261 (11,600), 275 sh (9900), 374 (24,200) in methanol–0.01 *N* HCl; $\lambda\lambda_{max}^{KBr}$ 3.08 and 6.2–6.5 (broad) μ.

Anal. Calcd for $C_{20}H_{22}O_5NCl$: C, 61.30; H, 5.66; N, 3.58; Cl, 9.05. Found: C, 61.27; H, 5.61; N, 3.48; Cl, 8.90.

2. Hydrolysis of the Cyclization Product xi (R = *t*-C_4H_9). This procedure is similar to that reported previously.[20] A solution of 2.00 g (5.1 mmoles) of the *t*-butyl amide xi (R = *t*-C_4H_9) in 60 ml of 30% hydrogen bromide in acetic acid was heated on the steam bath for 1 hr. Upon cooling to room temperature, the product began to crystallize. After 3 hr, the mixture was filtered, and the crystals were washed twice with acetic acid, then several times with ether, and air dried. There was obtained 1.35 g (82% yield) of product xii as yellow crystals, mp 238° dec. The analytical and spectral data on this substance were in agreement with those previously reported.[20]

5-Chloro-1,4,4a,10-tetrahydro-3,9-dihydroxy-8-methoxy-1-oxo-2-anthramide (xi, R = H). 1. The Acyl Malonamate x (R = H). To a magnetically stirred suspension of 1.00 g (3.72 mmoles) of tetraloneacetic acid ix (X = H), mp 192–195°,[20] in 50 ml of toluene (dried by distillation) was added 1.02 ml (0.740 g, 7.3 mmoles) of triethylamine. After the acid had dissolved, the solution was cooled in an ice bath and 0.91 g (7.3 mmoles) of isopropyl chloroformate, bp 101–102°, was added. The solution was kept in the ice bath for 2 hr with stirring, then warmed to room temperature, and 1.22 g of the magnesium derivative of ethyl malonamate (see below) was added. After being stirred overnight at room temperature, ethyl acetate was added, and the mixture was then washed twice with 3 *N* hydrochloric acid, twice with saturated sodium bicarbonate solution, once with water and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue, a colorless crystalline substance, was slurried in ether and filtered. After air drying, there was obtained 0.96 g (68% yield) of the desired acyl malonamate x (R = H) as colorless crystals, mp 157–159°. Recrystallization of a sample prepared in a similar experiment from tetrahydrofuran–methanol afforded clusters of colorless rods, mp 162–164°; $\lambda\lambda_{max}$ mμ (ε) 259 (19,200), 327 (4700) in methanol–0.01 *N* HCl; $\lambda\lambda_{max}^{CHCl_3}$ 2.83, 2.99, 5.94, and 6.30 (broad) μ.

Anal. Calcd for $C_{18}H_{20}O_6NCl$: C, 56.62; H, 5.28; N, 3.67. Found: C, 56.57; H, 5.25; N, 3.58.

In an experiment identical with that just described except that chloroform was used as solvent rather than toluene, 0.88 g (62% yield) of acyl malonamate x (R = H), mp 155–158°, was obtained.

2. Cyclization of the Acyl Malonamate. To 0.96 g (2.52 mmoles) of acyl malonamate x (R = H), mp 157–159°, dissolved in 50 ml of dimethylformamide under nitrogen was added 0.48 g (0.01 mole) of 50% sodium hydride in mineral oil. There was immediate evolution of hydrogen gas and the color of the mixture became yellow. After 5 min from the time of the hydride addition (the temperature had risen 4°), the mixture was heated slowly in an oil bath to 85° and kept at that temperature for 30 min. The mixture, orange and fluorescent, was then cooled, acidified with acetic acid, and poured into water, a yellow precipitate forming at this stage. The mixture was extracted with chloroform, a large volume being necessary to dissolve the yellow solid. The organic solution was then washed twice with water and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue, a yellow oily solid, after being washed with hexane several times to remove the mineral oil, was triturated with ethyl acetate, then filtered. There was obtained 0.69 g (82% yield) of triketo amide xi (R = H) as yellow crystals, mp 236–237° dec. A sample was recrystallized from tetrahydrofuran–isopropyl alcohol to give golden prisms, mp 246–249° dec; $\lambda\lambda_{max}$ mμ (ε) 262 (12,100), 372 (23,400) in methanol–0.01 *N* HCl; $\lambda\lambda_{max}^{KBr}$ 2.99, 6.15 sh, 6.30, and 6.55 μ. The analytical data on this substance were in agreement with those previously reported.[20]

Magnesium Derivatives of the Malonamic Esters. 1. Ethyl N-*t*-Butylmalonamate (37). This procedure is an adaptation of that reported previously for the magnesium derivative of diethyl malonate.[31] A mixture of 3.75 g (0.020 mole) of ethyl N-*t*-butylmalonamate (**37**), 0.487 g (0.020 g-atom) of magnesium powder, 3.65 ml of absolute ethanol, and 0.15 ml of carbon tetrachloride was stirred magnetically at room temperature. A vigorous reaction occurred which subsided after 20 min. To the thick slurry was added 10 ml of dry ether and the stirring continued. Within 30 min, the remainder of the magnesium had dissolved. The mixture was evaporated under reduced pressure to a foam which was crushed to a powder and dried under high vacuum. The substance was stored *in vacuo* prior to subsequent use in acylation reactions. Analytical data on this derivative were in fair agreement with a malonamate–magnesium–ethanol ratio of 1:1:1.

Anal. Calcd for $C_{11}H_{21}O_4NMg$: C, 51.7; H, 8.28; N, 5.48; OC_2H_5, 35.3; residue (as MgO), 15.8. Found: C, 49.8; H, 8.23; N, 5.51; OC_2H_5, 38.5; residue, 15.5.

2. Ethyl Malonamate. A mixture of 5.25 g (0.040 mole) of the amide, mp 43–44° (lit.[32] mp 50°), 0.973 g (0.040 g-atom) of magnesium turnings, 7.3 ml of absolute ethanol, and 0.3 ml of carbon tetrachloride was stirred magnetically at room temperature. Reaction was slow, and when the mixture became thick, 25 ml of ether was added. The mixture was refluxed overnight, the remainder of the magnesium dissolving during this time. The pale suspension was evaporated under reduced pressure to a white powder which was dried and stored *in vacuo* until subsequent use.

6-Demethyl-6,12a-dideoxytetracycline (41). 1. The Anhydride 36 (X = CO_2-*i*-C_3H_7). To a magnetically stirred mixture of solvent-free amino acid **36** (X = H) (1.035 g, 3.00 mmoles), mp 210° dec, in 50 ml of chloroform was added 0.92 ml (0.67 g, 6.6 mmoles) of triethylamine. After the acid had dissolved, the solution was cooled in an ice bath and 0.81 g (6.6 mmoles) of isopropyl chloroformate (freshly distilled, bp 100–102°) was added. After being stirred an additional 0.5 hr in an ice bath, the mixture was evaporated cold to a partially crystalline gum. An infrared spectrum taken immediately after the chloroform had been removed demonstrated the product to be good anhydride (no enol ester; see below), $\lambda\lambda_{max}^{CHCl_3}$ 5.51 and 5.70 μ.

In an identical experiment, the chloroform solution, after anhydride formation was complete, was washed four times with water and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to a crystalline solid. Trituration with ether followed by filtration afforded 0.93 g (72% yield) of the anhydride **36** (X = CO_2-*i*-C_3H_7) as pale yellow prisms, mp 128–130°. Recrystallization of a sample prepared in this manner from acetone–hexane gave pale yellow prisms, mp 132° dec; $\lambda\lambda_{max}^{CHCl_3}$ 5.51 and 5.70 μ.

Anal. Calcd for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.32; H, 6.77; N, 3.41.

2. The Acyl Malonamate 38. To the crude anhydride **36** (X = CO_2-*i*-C_3H_7), immediately after removal of the infrared sample, was added 3.84 g of the magnesium salt of ethyl N-*t*-butylmalonamate (**37**) (see above), followed by 20 ml of acetonitrile (freshly distilled from phosphorus pentoxide followed by distillation from anhydrous potassium carbonate). With stirring, a somewhat cloudy yellow solution was obtained in a few seconds. The mixture was stirred overnight after which time the acetonitrile was evaporated under reduced pressure at room temperature. The residual viscous gum was dissolved in 200 ml of chloroform and 50 ml of 1.5 *N* hydrochloric acid. The mixture was shaken; the layers were separated, and the organic solution was washed five times with 50-ml portions of 1.5 *N* hydrochloric acid, followed by five 200-ml portions of water (acid free). After an additional wash with saturated sodium chloride solution, the chloroform was dried over

(31) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).
(32) C. Oppenheimer, *Ber.*, **28**, 478 (1895).

anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. There was obtained 2.68 g of crude acyl malonamate **38** as thick oil. The ultraviolet spectrum in methanol–0.01 *N* hydrochloric acid exhibited increased absorption at 260 mμ, indicative of an acyl malonate moiety [see the spectral data for the model acyl malonamate x (R = H)]. Paper chromatography (toluene–acetic acid–water, benzene–acetic acid–water, pH 4.2 paper) of the crude product showed the presence of several substances, one of which was the ethyl ester **36** (X = C_2H_5) of the starting amino acid **36** (X = H).

The 1.5 *N* hydrochloric acid extracts from above were combined and extracted four times with 1-butanol. The butanol extracts were combined and washed once with water, then evaporated to a crystalline yellow solid. A small amount of methanol was added, and the mixture was allowed to stand for 2 hr, then filtered. The crystals were washed with methanol, then ether, and air dried. There was obtained 0.22 g of recovered amino acid **36** (X = H) as the hydrochloride salt. An additional 0.03 g of amino acid hydrochloride was obtained from the mother liquor by evaporation and crystallization from methanol (total acid recovery 0.25 g, 22%).

3. 2-N-*t*-Butylcarbamoyl-4-dimethylamino-3,4,4aα,5,5aα,6-hexahydro-1,11,12-trihydroxy-10-methoxy-3-oxonaphthacene (39). The entire sample (2.67 g) of crude acyl malonamate **38** obtained above was dissolved in 50 ml of dimethylformamide under nitrogen. To the magnetically stirred yellow solution was added 1.0 g of sodium hydride (50% in mineral oil), a vigorous reaction resulting. After 5 min, the initial reaction having subsided, five drops of methanol were added, and the flask was immediately placed in a 155° oil bath. When the temperature of the reaction mixture reached 85°, the bubbling increased and a vigorous reaction occurred at 95–100° (3 min in bath). Within a minute, the reaction had subsided, and the mixture was becoming orange. A visible spectrum at this point indicated no increased absorption above 400 mμ. After 6 min in the bath, 0.20 g of the 50% sodium hydride was added, a vigorous reaction ensuing which quickly subsided. One minute after the second hydride addition, an additional 0.20 g of the hydride was again added to the orange-red mixture. Again, vigorous bubbling occurred which rapidly decreased. At this stage, the temperature was 122° and the mixture had a deep red color. One minute after the third hydride addition the mixture was cooled rapidly in an ice bath and poured into 15 ml of acetic acid with stirring, a highly fluorescent solution being obtained. A visible spectrum of this solution had intense absorption at 430 mμ (the ε value approximated that of the 340-mμ maximum). To the fluorescent solution was added 200 ml of chloroform and 200 ml of water. The mixture was shaken and separated, and the water layer was extracted once with 50 ml of chloroform. The combined organic layers were washed with six 200-ml portions of water and once with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After filtration, the chloroform was evaporated under reduced pressure to yield **39** as a thick dark oil which partially crystallized on trituration with a glass rod. This crude material was used directly in the hydrolysis procedure described below.

Though unnecessary, it was possible at this stage to isolate the cyclization product **39** in either of two ways. (1) The partially crystalline gum was washed several times with cold hexane by decantation and methanol was added to the residue. The mixture was filtered and the crystals were washed with cold methanol and dried. Since the substance had some solubility in hexane, more crystalline material could be obtained by slow evaporation of the combined hexane washes. (2) The gum was chromatographed on silicic acid, 50% carbon tetrachloride in chloroform being used to put the substance onto the column. The desired intense yellow-green fluorescent material was eluted with chloroform–1% methanol in chloroform. The eluate was evaporated to dryness under reduced pressure and crystals were obtained from methanol.

In an experiment identical with that just described, there was obtained 0.101 g [9% yield, allowing for the recovery of 20% of the starting amino acid **36** (X = H)] of the cyclization product **39**, mp 209–211° dec, after silicic acid chromatography and isolation from methanol. This sample was recrystallized from chloroform–methanol to give orange-yellow needles, mp 215–216° dec; $\lambda\lambda_{max}$ mμ (ε) (initial), 254 (12,900), 325 (9300), 420 sh (21,600), 436 (26,700), 456 sh (22,400) in methanol–0.01 *N* HCl; $\lambda\lambda_{max}^{CHCl_3}$ 6.25 and 6.35–6.95 (broad) μ.

Anal. Calcd for $C_{26}H_{32}O_6N_2$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.95; H, 6.80; N, 6.04.

4. Hydrolysis of the Tetracyclic Compound 39. a. The Crude Cyclization Product. The thick partially crystalline oil from above was dissolved in 15 ml of 48% hydrobromic acid (the mineral oil from the sodium hydride was not soluble in the acid). Nitrogen was slowly bubbled through the mixture for 3 min and then, while continuing the nitrogen, the mixture was heated on the steam bath for 20 min. The dark solution was cooled in an ice bath and poured into 100 ml of water, some amorphous material precipitating. The water mixture was washed three times with hexane to remove the mineral oil, care being taken not to remove any of the amorphous solid. The mixture was adjusted to pH 5 with 10% sodium hydroxide solution (48 ml), and then extracted five times with 1-butanol (the amorphous solid dissolved in the 1-butanol). The organic extracts were combined and washed three times with water, then evaporated under reduced pressure to a dark solid. The crude product was purified by partition chromatography on a Super-Cel–formic acid column (18 × 350 mm) (see below). The material was applied to the top of the column with a minimal amount (*ca.* 5 ml) of stationary phase and mobile phase was then forced through under nitrogen pressure. The first material eluted had no absorption above 400 mμ in the visible spectrum and was discarded. After *ca.* 500 ml of mobile phase had been pressured through the column, a bright fluorescent yellow band had moved down from the very dark nonfluorescent material near the top of the column. When the fluorescent band was *ca.* half-way down the column, separation appeared complete. The column was then dismantled, excess mobile phase removed from the top, and the entire Super-Cel column extruded from the top opening of the column by pressure applied at the bottom. The intense yellow fluorescent band was then cut from the column and the Super-Cel slurried in methanol, filtered, and washed until the filtrate was no longer colored. The methanol filtrate was evaporated to a dark gum under reduced pressure. Some methanol and toluene were added to the gum and the evaporation process repeated to remove all formic acid. There was obtained 0.145 g of crude product as an amorphous solid. The substance was slurried in 2 ml of methanol and warmed several minutes on the steam bath. Crystallization occurred and was allowed to continue overnight at 5°. The mixture was filtered and the crystals were washed with methanol, then ether, and air dried. There was obtained 0.077 g of **41** as small orange-red crystals, the ultraviolet and infrared spectra being indistinguishable from those of the analytical sample. From the mother liquor by evaporation and crystallization from methanol was obtained an additional 0.007 g [total yield 0.084 g; 9.0% based on recovery of 22% of the starting amino acid **36** (X = H)] of orange-red crystals with good spectral characteristics.

In a similar experiment, a 15% yield [based on a recovery of 30% of the starting acid **36** (X = H)] of the 12a-deoxy substance **41** was obtained. It is believed the wide yield variation is due mainly to the considerable difficulty in duplicating the stringent conditions necessary in the cyclization reaction.

b. Crystalline Cyclization Product. A 0.100-g sample (0.224 mmole) of the cyclization product **39**, mp 214–216° dec, was added to 5 ml of 48% hydrobromic acid. Nitrogen was bubbled slowly through the mixture for 5 min, then the flask was heated on a steam bath, the nitrogen treatment continuing. After 2 min a clear solution was obtained. The product, as the hydrobromide salt, began to crystallize after 7 min and the heating was continued for an additional 10 min. The mixture was cooled, poured into 100 ml of water, and filtered. The clusters of yellow needles were washed with water, then acetone, and air dried. There was obtained 0.085 g (78% yield) of the desired product **41** as the hydrobromide–hemihydrate.

Anal. Calcd for $C_{21}H_{22}O_6N_2 \cdot HBr \cdot 0.5H_2O$: C, 51.64; H, 4.95; N, 5.74; Br, 16.4. Found: C, 51.79; H, 4.95; N, 5.34; Br, 16.7.

This hydrobromide salt differed tautomerically from the free base of **41** as shown by the ultraviolet and visible spectra. In methanol–0.01 *N* HCl, the substance had an initial spectrum very similar to the equilibrium spectrum of the free base. In methanol–0.01 *N* NaOH, little long-wavelength absorption (above 400 mμ) was observed and an intense peak was noted at 375 mμ. Both the acid and the base spectra changed on standing, ultimately being identical with the equilibrium spectra obtained from the free base (see Figures 2 and 3).

A 0.385-g sample (0.79 mmole) of the hydrobromide hemihydrate of **41** obtained in experiments similar to that described above was suspended in 30 ml of methanol. Water (5 ml) was added followed by triethylamine dropwise to pH 7.5–8.0, when the solid almost completely dissolved. The free base then began to precipitate as small orange crystals. After crystallization was complete, the mixture was filtered, and the crystals were washed with methanol.

There was obtained 0.29 g (92% yield) of base having ultraviolet and visible spectra identical with those of the analytical sample. Several samples, obtained in this manner and also by partition chromatography of crude material, were combined and chromatographed on a Super-Cel–formic acid column (see below), the orange crystals being isolated from methanol as described previously, mp 223–224° dec, $\lambda\lambda_{max}$ mμ (ε) (initial) 260 (12,900), 326 (10,300), 408 sh (16,600), 429 (23,600), 451 (20,100) in methanol–0.01 *N* HCl; 247 (13,600), 262 sh (13,000), 378 (9500), 447 sh (17,900), 470 (24,500), 495 (22,900) in methanol–0.01 *N* NaOH (see Figures 2 and 3); $\lambda\lambda_{max}^{KBr}$ 2.95, 6.26, and 6.45 μ. In addition to the ultraviolet and visible spectra, the paper chromatographic behavior [ethyl acetate–nitromethane–chloroform (40:25:7), ethyl acetate–chloroform–pyridine (40:15:5), pyridine–toluene (3:20) saturated with water, pH 4.2 paper; chloroform–nitromethane–pyridine (10:20:3), pH 3.5 paper] of synthetic **41** was identical with that of optically active **41**.[23]

Anal. Calcd for $C_{21}H_{22}O_6N_2$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.27; H, 5.51; N, 6.73.

Preparation of the Super-Cel–Formic Acid Partition Column Used in the Purification of Compounds 41 and 7. A mixture of chloroform, formic acid, ethyl formate, and water in a volume ratio of 2:1:1:1 was equilibrated in a separatory funnel. The lower layer, containing the bulk of the chloroform, was drawn off to be subsequently used as the mobile phase. The upper aqueous layer, the stationary phase, was added in portions to Super-Cel until a slurry of medium consistency was obtained. The slurry was poured into a suitable chromatography column and nitrogen pressure was applied to the top, excess stationary phase being eluted from the bottom of the column. The column was packed in this manner until firm, care being taken not to allow the column to dry at the top at any time during the packing process. The material to be chromatographed was dissolved in a *minimal* amount of either the mobile or the stationary phase for application to the column.

The Ethyl Ester 36 (X = C_2H_5). To a slurry of 0.250 g (0.725 mmole) of amino acid **36** (X = H), mp 210° dec, in 25 ml of chloroform was added 0.11 ml (0.79 mmole) of triethylamine. The resulting clear solution was cooled in an ice bath and 0.09 g (0.73 mmole) of isopropyl chloroformate, bp 101°, was added. After 35 min an infrared spectrum indicated complete anhydride formation (see above). After an additional 15 min the mixture was evaporated cold under reduced pressure to a gummy solid. To this solid, immediately after the chloroform evaporation, was added 10 ml of absolute ethanol. The solution was warmed on the steam bath for 5 min and then allowed to stand at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue, a partially crystalline gum, was dissolved in chloroform. The solution was washed three times with water and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was crystallized from ether, and the crystals were washed with a small volume of ether. After air drying, there was obtained 0.097 g of yellow crystals, mp 126–128°. From the mother liquor, after evaporation and crystallization from ether, there was obtained an additional 0.032 g (total yield 48%) of yellow crystals, mp 124–127°, having an infrared spectrum identical with the first crop material. Both crops were combined and recrystallized three times from ethyl acetate–hexane to give clusters of yellow needles and rods, mp 129–130°; $\lambda\lambda_{max}$ mμ (ε) 264 (4900), 339 (14,600) in methanol–0.01 *N* HCl; 264 (5500), 342 (14,900) in methanol–0.01 *N* NaOH; $\lambda\lambda_{max}^{CHCl_3}$ 5.79 and 6.30 μ.

Anal. Calcd for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.29; H, 7.22; N, 3.62.

The Enol Ester Methyl Ester 40 (X = CH_3). The anhydride was prepared as above from 0.75 g (2.17 mmoles) of amino acid **36** (X = H), mp 210° dec, 0.90 ml (6.5 mmoles) of triethylamine, and 0.81 g (6.6 mmoles) of isopropyl chloroformate, bp 99–100°, in 75 ml of chloroform. After 1 hr, the chloroform was evaporated in the cold under reduced pressure to a partially crystalline gum, the ultraviolet spectrum of which, taken immediately, showed absorption due only to the starting diketone. The infrared spectrum had normal anhydride absorption at 5.51 and 5.70 μ. The substance was allowed to stand *in vacuo* overnight, after which time the ultraviolet spectrum showed intense absorption at *ca.* 285 mμ. In addition, the long-wavelength absorption was shifted to 330 mμ. Further, the infrared spectrum[29] had changes consistent with the formation of enol ester imposed upon the characteristic anhydride absorption; $\lambda\lambda_{max}^{CHCl_3}$ 5.52, 5.70 (increased intensity with respect to the anhydride), 5.98, 6.20, and 6.27 μ.

The crude enol ester anhydride **40** (X = CO_2-*i*-C_3H_7) was dissolved in methanol and allowed to stand overnight, after which time the solvent was evaporated, the residue being crystalline. The substance was dissolved in chloroform, and the solution was washed four times with water and once with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residual gum crystallized when treated with ether. After filtration and washing of the crystals with ether, there was obtained 0.58 g (60% yield) of the product **40** (X = CH_3), mp 124–131°. An additional 0.02 g of product, mp 121–124°, was obtained from the mother liquor by evaporation and crystallization from ether. A sample of the main crop was recrystallized twice from ether and once from ethyl acetate–hexane to give clusters of pale yellow rods and prisms, mp 132–134°, no color with alcoholic ferric chloride; $\lambda\lambda_{max}$ mμ (ε) 284 (10,700), 330 (8900) in methanol; $\lambda\lambda_{max}^{KBr}$ 5.69, 5.75, 5.95, 6.18, 6.25, and 6.33 μ. The ultraviolet spectrum in methanol–0.01 *N* NaOH was initially the same as that obtained in methanol. However, on standing 3 days in this solvent, the enol derivative was cleaved and a normal dione spectrum was obtained.

Anal. Calcd for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; N, 3.14. Found: C, 65.02; H, 7.05; N, 3.19.

6-Demethyl-6-deoxytetracycline (7). A 0.250-g sample (0.627 mmole) of *dl*-6-demethyl-6,12a-dideoxytetracycline (**41**) was dissolved in 25 ml of dimethylformamide. The resulting amber solution was stirred magnetically and nitrogen was bubbled through for 5 min, after which time 0.308 g (0.83 mmole) of cereous chloride heptahydrate was added. After the salt had dissolved, 55 ml of methanol was added, followed by 17 ml of a pH 10.4 buffer (prepared by mixing 9 ml of a 0.1 *N* glycine–0.1 *N* sodium chloride solution with 8 ml of a 0.1 *N* sodium hydroxide solution). The nitrogen was stopped and oxygen was then bubbled through the mixture for 15 min, the color changing from light amber to a dark brown. The oxygen was turned off and nitrogen was again bubbled through for 5 min to displace any dissolved oxygen. Concentrated hydrochloric acid (9.5 ml) was added, and the mixture was evaporated under reduced pressure. To the gummy solid residue was added 5 ml of concentrated hydrochloric acid, 60 ml of 1-butanol (saturated with 1 *N* hydrochloric acid), and 50 ml of water. The mixture was shaken, the layers separated, and the butanol solution was extracted with 25 ml of 1 *N* hydrochloric acid (saturated with butanol). The acid extracts were combined and extracted three times with butanol (saturated with 1 *N* hydrochloric acid). Throughout these extractions, some yellow solid was present in the aqueous phase. After the extraction procedure was completed, the aqueous solution was filtered, and the yellow solid was dried. There was obtained 0.071 g, papergrams of which indicated the presence of only a trace of desired product **7**. The butanol extracts were combined and passed through a Super-Cel partition column (1-butanol–1 *N* hydrochloric acid, 28 × 250 mm) to ensure complete removal of the cerium. The aqueous acid was the stationary phase. The column was eluted until the eluate no longer was colored, and the eluate was then evaporated under reduced pressure to a yellow solid. Toluene was added to the residue and then evaporated under reduced pressure. This procedure was repeated to obtain a butanol-free residue. Paper chromatograms at this stage indicated the desired oxidation product **7** to be only the C_4-normal epimer.

The solid was chromatographed on a Super-Cel–formic acid partition column (28 × 300 mm, see above) to separate oxidized compounds from unreacted starting material and degradation products. The column was eluted with the mobil (lower) phase until a fluorescent yellow band containing unreacted starting material had separated from the slower moving oxygenated product. The Super-Cel was extruded from the column by the application of nitrogen pressure and divided into three sections, so chosen because of the separation of bands on the column. The organic material was recovered from each portion of Super-Cel by slurrying in methanol, filtering, and evaporating the filtrates under reduced pressure. There was obtained: (a) from the lower portion of the column, a gum which crystallized upon the addition of methanol and yielded, after filtration and drying, 0.025 g (10% recovery) of starting 12a-deoxy compound **41**; (b) from the center of the column, 0.087 g of an amorphous solid consisting mainly of desired **7** and 6,N-didemethyl-6-deoxytetracycline[25] and their C_4 epimers; (c) from the top of the column, 0.064 g of a dark gum which contained no desired material.

On some Super-Cel–formic acid columns, in similar experiments, a small yellow band appeared between that containing the desired oxidized material and the dark band at the top of the column.

Isolation of the material in this small band was accomplished as above, affording a very small amount of a solid material, $\lambda\lambda_{max}$ mμ (ϵ) 265 (11,900), 328 (10,300) in methanol–0.01 *N* HCl; 260 (10,700), 350 (7900) in methanol–0.01 *N* NaOH. From the spectral data, the possibility exists that this substance is an 11a-hydroxylated material.

It was necessary to convert the C_4 epimer of **7** into the C_4-normal compound since partial epimerization at that center occurred in the presence of formic acid. This procedure is essentially that developed by Noseworthy.[26] The amorphous solid (0.087 g) containing the desired tetracycline **7** and its C_4 epimer was dissolved in 1-butanol with a few drops of 1.5 *N* hydrochloric acid. Finely divided anhydrous calcium chloride (0.070 g) was added followed by 0.5 ml of water, a clear solution being obtained with gentle warming. The solution was adjusted to apparent pH 8.5 with a 10% solution of ethanolamine in 1-butanol. At pH 2–3 a precipitate was obtained which dissolved when the pH was raised to 8.5. The solution was refluxed under nitrogen for 3.5 hr, a precipitate forming after 10 min. The mixture was cooled and 3 ml of 1 *N* hydrochloric acid (saturated with butanol) was added. The mixture was shaken, the layers separated, and the butanol was washed once with 1 *N* hydrochloric acid (saturated with butanol). The combined acid washes were extracted three times with 5 ml of 1-butanol (saturated with 1 *N* hydrochloric acid). The organic solutions were combined and passed through a Super-Cel partition column (1-butanol–1 *N* hydrochloric acid, 28 × 250 mm) to remove any remaining calcium salts. The butanol eluate, collected until it no longer contained any tetracycline, was evaporated under reduced pressure to a yellow solid.

The mixture of oxidation products, now void of the C_4 epimer of **7**, was separated into its components by means of a simple countercurrent apparatus consisting of 11 50-ml separatory funnels. A mixture of methanol–water–chloroform–carbon tetrachloride (4:4:3:1 by volume) was equilibrated and allowed to separate. To each of funnels 1–8 was added 25 ml of the stationary (upper) phase of the solvent mixture. To funnels 9–11 was added 25 ml of 1.5 *N* hydrochloric acid. A 25-ml portion of the mobil (lower) phase of the solvent mixture was then added to funnel 1 followed by the yellow solid containing the desired tetracycline **7**. After the solid had dissolved, the pH of the upper phase was adjusted to 8.0 with 5% ammonium hydroxide. The mixture was equilibrated, and the lower phase was transferred to funnel 2. The equilibration and transfer processes were then repeated until the mobil phase had passed through funnel 11. The passage of 25 ml of mobil phase through the funnels was then repeated five additional times. The solutions in funnels 1–3 were then combined and acidified. Papergrams showed the presence of 6,N-didemethyl-6-deoxytetracycline[25] and none of the desired **7**. The contents of funnels 9–11 were combined and extracted four times with 1-butanol. The organic extracts were combined and evaporated under reduced pressure to a yellow solid. Toluene was added, followed by evaporation under reduced pressure to ensure complete removal of the butanol. After two toluene treatments, there was obtained 0.043 g of an amorphous yellow solid, papergrams of which showed the substance to be quite pure 6-demethyl-6-deoxytetracycline (**7**).

The amorphous products thus obtained from two such oxidations and isolation procedures were combined in methanol, treated with Darco, filtered, and evaporated under reduced pressure to a glass (75 mg). Hydrochloric acid (3 *N*, 0.75 ml) was added followed by a few drops of methanol. Upon trituration with a glass rod, the desired product **7** began to crystallize. Before crystallization was complete, a few additional drops of 3 *N* hydrochloric acid was added. After several hours, the mixture was filtered and the crystals were washed with 3 *N* hydrochloric acid, then acetone, and air dried. There was obtained 33 mg (6.4% yield, allowing for the recovery of 10% of the starting 12a-deoxy compound **41**) of the hydrochloride salt of **7** as yellow prisms. Material obtained at this stage from four oxidation experiments (61 mg) was combined, dissolved in methanol, treated with Darco, filtered through Super-Cel and refiltered, and the filtrate evaporated. The residue was dissolved in water containing a few drops of methanol and one drop of 6 *N* hydrochloric acid (total volume 6 ml). A very small amount of material was insoluble at this stage, so the mixture was filtered. The clear, pale yellow filtrate was warmed, and 6 *N* hydrochloric acid was added with swirling to incipient cloudiness. Crystallization began quickly and was allowed to continue for several hours. The mixture was filtered, and the crystals were washed with 1.5 *N* hydrochloric acid, then acetone, and air dried. There was obtained 32 mg of the hemihydrate[33] of *dl*-6-demethyl-6-deoxytetracycline hydrochloride (**7**) as pale yellow prisms and rods, mp 225–226° dec; $\lambda\lambda_{max}$ mμ (ϵ) 267 (19,300), 347 (15,500) in methanol–0.01 *N* HCl; 248 (16,600), 262 sh (15,600), 284 sh (10,100), 383 (18,200) in methanol–0.01 *N* NaOH (see Figure 4); $\lambda\lambda_{max}^{KBr}$ 2.99, 3.13, 6.04, 6.20, and 6.30 μ. The *in vitro* antibacterial activity (turbimetric assay against *K. pneumoniae*) of synthetic **7** was exactly half that of optically active **7**. The paper chromatographic behavior of **7** is depicted in Figure 5.

Anal. Calcd for $C_{21}H_{22}O_7N_2 \cdot HCl \cdot 0.5H_2O$: C, 54.84; H, 5.26; N, 6.09; Cl, 7.71; CH_3O, 0.00. Found: C, 55.04, 54.94; H, 5.37, 5.46; N, 5.66; Cl, 7.54; CH_3O, 0.00.

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(33) The hydrochloride of optically active 6-demethyl-6-deoxytetracycline (**7**) has been reported as a hemihydrate.[10]