1 hour to open the lactone. The solution was then chilled to −15°, and 0.54 g. (5% excess over 5 mmoles) of ethyl chloroformate was added, with shaking. After it had stood for 5 minutes in the cold, the solution was saturated with dry ammonia and then allowed to warm to room temperature during 1 hour. The solvent was evaporated, and the residue broken up and shaken well with a mixture of ethyl acetate and 1% aqueous sodium bicarbonate. The insoluble material (1.05 g.) was filtered off, washed well with ethyl acetate and water, and dried. The product was insoluble in hot ethyl acetate, and only very slightly soluble in hot dioxane or tetrahydrofuran, but it was quite soluble in the latter two solvents when they contained some water. For purification the product was dissolved in hot 90% tetrahydrofuran, filtered, and caused to crystallize by addition of more water and chilling; needles m.p. 207–209° dec. For analysis, it was necessary to dry the compound for 7 hours at 100°.

Anal. Calcd. for $C_{23}H_{28}N_4O_7$: C, 58.46; H, 5.97; N, 11.86. Found: C, 58.46; H, 6.06; N, 11.92.

Hydroxydiaminopimelic Diamide Diacetate, Isomer A.—A solution of 0.5 g. of N,N′-dicarbobenzoxy HDAP diamide, isomer A, in 25 ml. of acetic acid was shaken for 19 hours with 0.15 g. of 5% palladium-on-carbon catalyst under a hydrogen pressure of 45 p.s.i. The catalyst was removed by filtration, and the solvent evaporated. Last traces of acetic acid were removed by three evaporations from ethanol solution, leaving a colorless glass. Paper electrophoresis at *p*H 5 showed HDAP diamide, essentially free of contamination by any other ninhydrin-positive substances. The product was dissolved in water, filtered to remove some insoluble material, and lyophilyzed, leaving a hygroscopic glass.

Anal. Calcd. for $C_{11}H_{24}N_4O_7$: C, 40.70; H, 7.45; N, 17.25. Found: C, 40.71; H, 7.90; N, 16.40.

A sample was hydrolyzed for 3 hours in refluxing 6 *N* hydrochloric acid. Electrophoresis now showed only amino acid. After removal of hydrochloric acid, the amino acid was converted to the DNP derivative by the usual procedure. Paper chromatography of the latter revealed only one substance, having the same R_f as DNP isomer A run alongside.

Behavior of HDAP Diamide toward Hog Kidney Amidase.—Hog kidney amidase was prepared according to the directions of Birnbaum,[18] and assayed for activity with L-leucinamide. This enzyme preparation hydrolyzed 260 μmoles of leucinamide/mg. protein/hour when incubated in "Tris" buffer, *p*H 8, at 37°. The course of the hydrolysis was followed by paper electrophoresis of aliquots which had been acidified with *N* acetic acid and heated for 10 minutes at 100° to inactivate the enzyme. HDAP diamide, when incubated with the enzyme under these conditions, was hydrolyzed at the rate of 0.36 μmole/mg. protein/hour, and the ultimate product was a mixture of equal parts of monoamide and free amino acid. Without enzyme, the diamide hydrolyzed at the rate of 0.10 μmole/hour to the monoamide, which was stable.

Behavior of HDAP toward the DAP Decarboxylase of *Aerobacter aerogenes*.—The isomers of HDAP were tested with the crude DAP decarboxylase of *A. aerogenes*[19] by the qualitative procedure of Dewey, *et al.*[7] Paper electrophoresis of the assay tubes after inactivation of the enzyme showed that while both *meso*- and L-DAP were decarboxylated to lysine, HDAP was not decarboxylated.

Behavior of HDAP toward the D-Amino Acid Oxidase of *Neurospora crassa*.—*N. crassa*, strain 25a,[20] was grown in the medium of Bender and Krebs,[6] and the crude D-amino acid oxidase was prepared from the mycelium by their procedure. The enzyme was assayed by incubation with substrate in pyrophosphate buffer, *p*H 8.4, and examination of the resulting mixture by paper chromatography. While D-alanine and D-glutamic acid were oxidized, none of the isomers of HDAP was attacked by this enzyme.

(18) S. M. Birnbaum, in S. P. Colowick and N. O. Kaplan, "Methods In Enzymology," Vol. II, Academic Press, Inc., New York, N. Y., 1955, p. 397.

(19) Freeze-dried cells of *A. aerogenes*, rich in this enzyme, kindly supplied by Dr. H. T. Huang of Chas. Pfizer and Co.

(20) We thank Dr. E. L. Tatum for this culture.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO., PEARL RIVER, N. Y.]

Total Synthesis of Tetracyclines. IV. Synthesis of an Anhydrotetracycline Derivative

BY ANDREW S. KENDE, THOMAS L. FIELDS, JAMES H. BOOTHE AND S. KUSHNER

RECEIVED AUGUST 24, 1960

Synthetic 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetic acid (14) has been converted in seven steps to the *syn* isomer (20) of methyl 5-benzyloxy-8-chloro-1,2,3,4,4a,9,9a,10-octahydro-4,10-dioxo-2-anthraceneacetate. Subsequent elaboration of this intermediate into biologically active (±)-dedimethylamino-12a-deoxy-6-demethylanhydro-7-chlorotetracycline (39), and comparison of the latter with a sample of dextrorotatory 39 derived by degradation are described.

The yellow crystalline antibiotic Aureomycin,[1] isolated by Duggar in 1948 from the actinomycete *Streptomyces aureofaciens*,[2] was the first example of an important class of naturally occurring antibacterial substances.[3] The recognition of its powerful activity against a broad spectrum of pathogenic microörganisms, followed in 1950 by the isolation of a similar substance, Terramycin,[4] from *Streptomyces rimosus*,[5] stimulated intense efforts toward the structure elucidation of these complex natural products. Success was achieved in 1952, when a brilliant investigation involving alkaline, acidic and reductive degradation and full use of spectrophotometric and pK_a determinations culminated in the establishment of Terramycin as 5-hydroxytetracycline (1).[6] Research upon aureomycin led in turn to announcement of its structure as 7-chlorotetracycline (2).[7] Subsequent investigations have resulted in the identification of a number of

(1) Aureomycin is the registered trademark of the American Cyanamid Co. for the antibiotic chlorotetracycline.

(2) B. M. Duggar, *Ann. N. Y. Acad. Sci.*, **51**, 177 (1948); U. S. Patent 2,482,055.

(3) A concise review of the chemistry of the principal members of this group of antibiotics is given by P. Regna in "Antibiotics: Their Chemistry and Non-Medical Uses," H. Goldberg ed., D. Van Nostrand Co., Inc., Princeton, N. J., 1959, pp. 77–96.

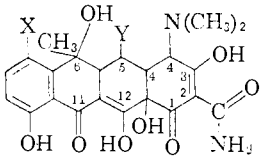
(4) Terramycin is the registered trademark of Charles Pfizer and Co. for the antibiotic oxytetracycline.

(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).

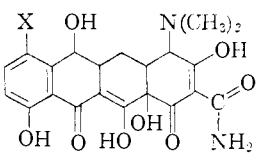
(6) (a) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **74**, 3708 (1952); (b) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75**, 5455 (1953).

(7) (a) C. R. Stephens, L. H. Conover, F. A. Hochstein, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **74**, 4976 (1952); (b) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952); (c) C. R. Stephens, L. H. Conover, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

related *Streptomyces* antibiotics, including the parent compound tetracycline (3)[8] and the substances 6-demethyltetracycline (4) and 6-demethyl-7-chlorotetracycline (5).[9]



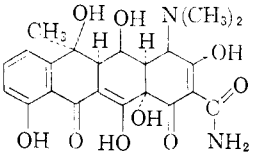
1, X = H, Y = OH
2, X = Cl, Y = H
3, X = H, Y = H



4, X = H
5, X = Cl

Despite the numerous chemical transformations delineated early in the course of the structure determinations, approaches to the total synthesis of the tetracycline antibiotics have only recently begun to appear in the literature. The problem is rendered formidable by the complex array of functional groups located upon the characteristic hydronaphthacene ring system. The presence of a chain of six potential carbonyl groups each β- to another, not without analogy in the chemistry of mold metabolites, is indicative of the probable role of polyacetic acid fragments in the biogenesis of these substances.[10] Upon this polycarbonyl framework Nature has imposed a variety of substituents which result in a minimum of five asymmetric carbon atoms within the molecule, thereby posing a major stereochemical challenge to total synthesis.

The stereochemistry of the tetracyclines has been examined by standard chemical methods and more recently by the increasingly powerful tool of X-ray crystallography. Interpretation of certain key degradative reactions involving 5-hydroxytetracycline (1) and its derivatives has resulted in the tentative proposal of formula 6 to represent the relative stereochemistry of that molecule.[11] The detailed X-ray diffraction study of 7-chlorotetracycline hydrochloride by Hirokawa, Okaya, Lovell and Pepinsky has confirmed the gross structure 2 and has provided stereoformula 7 to represent the relative configurations of the five asymmetric centers.[12] Although the orientation of the dimethylamino group is still *sub judice*, the close agreement in the relevant chemical and biological properties of the various tetracycline antibiotics suggests that these compounds are identical with respect to essential stereochemical features.



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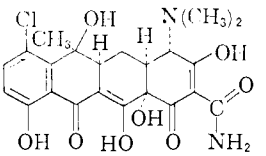
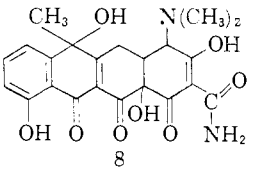


7

It appears established that the presence of the dimethylamino group at C-4 and the hydrogen atom at C-5a, both in the correct (natural) configuration, is essential for full biological activity. Thus the equilibration of 4-normal to 4-epitetracyclines, which takes place readily at intermediate *p*H by enolization across the 3,4-positions, results in a sharp fall in the antibacterial activities of all the tetracyclines described above.[13] Indirect epimerization at position 5a, as effected by reduction of 5a,11a-dehydrotetracycline (8), likewise results in substantial loss of biological activity.[14] On the other hand, catalytic hydrogenolysis of the C-6 hydroxyl in either the tetracyclines or 6-demethyltetracyclines has no significant effect upon the activities of those compounds.[15,16] Thus the compound 6-deoxy-6-demethyl-7-chlorotetracycline (9), derived from 6-demethyl-7-chlorotetracycline (5) by selective reduction of the 6-hydroxyl group,[16] not only possesses the powerful antibacterial activity of 7-chlorotetracycline but also the desirable feature for synthesis of having only four asymmetric centers.



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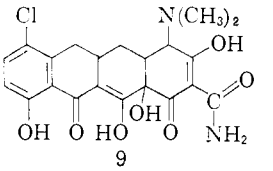


9

The total synthesis of a compound such as 9 may be arbitrarily subdivided into three problems: construction of the appropriate polycarbonyl hydronaphthacene framework, the incorporation of the dimethylamino group and the stereospecific introduction of the 12a-hydroxyl substituent. A signal contribution to the last phase of this sequence has been achieved by Holmlund and coworkers, who have effected the transformation (10) → (11) for several tetracyclines and dedimethylaminotetracyclines by aeration of the corresponding 12a-deoxy compounds in the presence of certain inorganic catalysts, such as sodium nitrite.[17] Introduction of the 12a-hydroxyl in the desired configuration by the action of organic peracids on a monomethyl ether of dedimethylamino-12a-deoxyanhydrotetracycline (12) has been

(8) (a) J. H. Boothe, J. Morton, J. P. Petisi, R. G. Wilkinson and J. H. Williams, THIS JOURNAL, **75**, 4621 (1953); (b) L. H. Conover, W. T. Moreland, A. R. English, C. R. Stephens and F. J. Pilgrim, *ibid.*, **75**, 4622 (1953).

(9) (a) J. R. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen and A. P. Doerschuk, *ibid.*, **79**, 4561 (1957); (b) J. S. Webb, R. W. Broschard, D. B. Cosulich, W. J. Stein and C. F. Wolf, *ibid.*, **79**, 4563 (1957); (c) J. H. Boothe, A. Green, J. P. Petisi, R. G. Wilkinson and C. W. Waller, *ibid.*, **79**, 4564 (1957).

(10) J. F. Snell, A. J. Birch and P. L. Thomson, *ibid.*, **82**, 2402 (1960); A. J. Birch, *Fortschr. Chem. Org. Naturstoffe (Vienna)*, **14**, 186 (1957); R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957). Of particular relevance are the structurally related Streptomyces metabolites of the pyrromycin group, *cf.* L. Ettlinger, *et al.*, *Chem. Ber.*, **92**, 1867 (1959); H. Brockmann and W. Lenk, *ibid.*, **92**, 1880, 1904; W. D. Ollis and I. O. Sutherland, *Tetrahedron Letters*, **16**, 17 (1959).

(11) (a) Reference 6b, p. 5467, footnote 41; (b) R. B. Woodward, Colloquium at Glasgow University, Dec. 1, 1956.

(12) S. Hirokawa, Y. Okaya, F. M. Lovell and R. Pepinsky, Abst. of Amer. Cryst. Assoc. Meeting, Cornell University, July, 1959, p. 44.

(13) (a) A. P. Doerschuk, B. A. Bitler and J. R. D. McCormick, THIS JOURNAL, **77**, 4687 (1955); (b) C. R. Stephens, L. H. Conover, P. N. Gordon, F. C. Pennington, R. L. Wagner, K. J. Brunings and F. J. Pilgrim, *ibid.*, **78**, 1515 (1956); (c) J. R. D. McCormick, S. M. Fox, L. L. Smith, B. A. Bitler, J. Reichenthal, V. E. Orlgoni, W. H. Muller, R. Winterbottom and A. P. Doerschuk, *ibid.*, **78**, 3547 (1956).

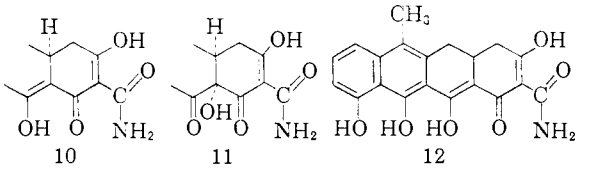
(14) J. R. D. McCormick, P. A. Miller, J. A. Growich, N. O. Sjolander and A. P. Doerschuk, *ibid.*, **80**, 5572 (1958).

(15) C. R. Stephens, K. Murai, H. Rennhard, L. H. Conover and K. J. Brunings, *ibid.*, **80**, 5324 (1958).

(16) J. R. D. McCormick and E. Jensen, private communication.

(17) C. E. Holmlund, W. W. Andres and A. J. Shay, THIS JOURNAL, **81**, 4748 (1959).

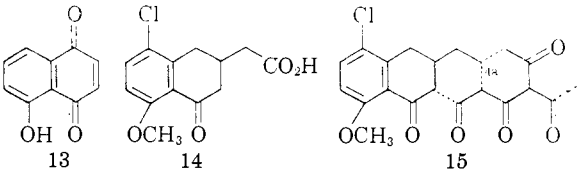
reported[18]; however, the generality of this method is uncertain in view of the apparent failure of other workers to observe the desired hydroxylation using perbenzoic acid on 12a-deoxytetracycline.[19]



10 11 12

The versatility of the Diels–Alder reaction for the elaboration of complex polycyclic natural products has led to its use in preliminary efforts toward construction of the hydronaphthacene ring system. Inhoffen and co-workers have described the addition of 1-acetoxybutadiene to derivatives of juglone (13) and have explored the behavior of the adducts toward organometallic reagents.[20] Shemyakin and colleagues have in turn examined the corresponding reactions involving juglone and butadiene or 2-methoxybutadiene.[21] Barltrop and Burstall have shown that the addition of suitable dienes to 2,5-diacetoxybenzoquinone can lead to intermediates of interest as prototypes of the tetracycline A and B rings.[22] It seemed clear from these explorations that the number and nature of the substituents required for the construction of the tetracycline antibiotics would militate against the facile utilization of the Diels–Alder approach. In our view, an attractive pathway would, in so far as practicable, emulate the postulated type of biogenetic mechanism by employing various forms of the generalized Claisen condensation to achieve the tetracyclic target. This paper describes such an approach, which has resulted in the first total synthesis of a biologically active tetracyclic derivative of anhydrotetracycline.[23]

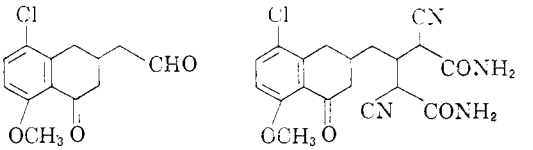
Our experimental point of departure was the methoxytetraloneacetic acid 14 available in 28% over-all yield from 3-methyl-4-chloroanisole by the procedure described in a previous publication.[24] Elaboration of acid 14 into a tetracycline nucleus requires the formal addition of a seven carbon unit containing four carbonyl functions (*cf.* formula 15). In view of the oxidation state desired of the potential carbon atom 4a, a reductive step involving the carboxyl carbon of 14 seemed necessary at some stage of the synthesis. This was effected at the outset through conversion of the acid 14 first to the acid chloride and thence



13 14 15

to the aldehyde 16 by Rosenmund reduction, employing toluene as solvent and unpoisoned palladium on barium sulfate as catalyst.

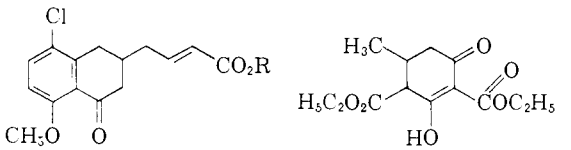
Exploratory reactions with the crystalline aldehyde 16 clearly demonstrated the selective reactivity of the aldehydic carbonyl toward amine-catalyzed condensations with certain active methylene compounds.[25] This property was exploited through the piperidine-catalyzed condensation of the aldehyde with excess cyanoacetamide in ethanol, which led to the highly insoluble crystalline solvate of diastereomeric dicyanodiamides (17).[26] Hydrolysis of this product with concentrated hydrochloric acid in acetic acid was accompanied by



16 17

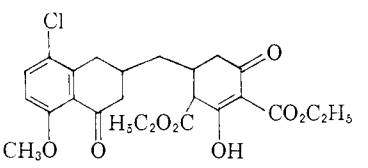
demethylation and gave the phenolic glutaric acid 18 in 74% yield.[27]

The diacid was realkylated with benzyl chloride in boiling alkali, and the resulting benzyl ether carefully esterified to give the benzyloxy diester 19. This intermediate underwent intramolecular acyla-



i, R = H
ii, R = CH_3

iii



iv

(18) H. Muxfeldt and A. Kreutzer, *Naturwissenschaften*, **46**, 204 (1959).

(19) (a) C. R. Stephens, Gordon Research Conference, Medicinal Chemistry, August, 1957; (b) A. Green and J. H. Boothe, THIS JOURNAL, **82**, 3590 (1960).

(20) H. H. Inhoffen, H. Muxfeldt, H. Schaefer and H. Kramer, *Croat. Chem. Acta*, **29**, 329 (1957).

(21) M. M. Shemyakin, M. N. Kolosov, M. G. Karapetyan and E. S. Chaman, *Doklady Akad. Nauk. SSSR (Khim.)*, **112**, 669 (1957); **128**, 113 (1959).

(22) J. A. Barltrop and M. L. Burstall, *J. Chem. Soc.*, 2183 (1959).

(23) J. H. Boothe, A. S. Kende, T. L. Fields and R. G. Wilkinson, THIS JOURNAL, **81**, 1006 (1959). An independent total synthesis of (±)-12a-deoxydedimethylaminoanhydrochlorotetracycline, employing terminal stages analogous to those reported by the above authors, has subsequently been described by H. Muxfeldt, *Chem. Ber.*, **92**, 3122 (1959).

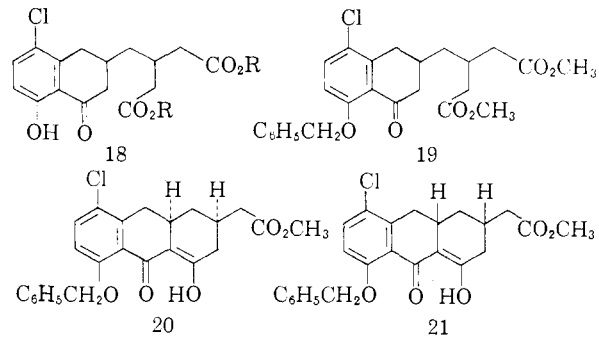
(24) R. G. Wilkinson, T. L. Fields and J. H. Boothe, *J. Org. Chem.*, in press.

(25) Thus the aldehyde 16 readily underwent Doebner condensation with malonic acid in the presence of piperidine to give the unsaturated acid i; esterification gave ii. The latter compound was of interest in view of our observation that ethyl crotonate reacted with diethyl β-ketoglutarate in the presence of sodium hydride to give the model compound iii. The construction of a tetracyclic system by a comparable reaction of ii with diethyl β-ketoglutarate, to proceed by way of an analogous intermediate, iv, could not be realized.

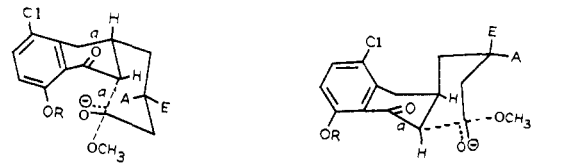
(26) *Cf.* R. E. Kent and S. M. McElvain, in E. C. Horning, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 591.

(27) The rapid dealkylation of the alkoxytetralone system in the dicyanodiamide 17 is a particular instance of the frequently facile cleavage of phenolic ethers flanked by a carbonyl group; G. K. Hughes, N. K. Matheson, A. T. Norman and E. Ritchie, *Austral. J. Sci. Res. Ser. A*, **5**, 207 (1952); W. J. Horton and J. T. Spence, THIS JOURNAL, **80**, 2453 (1958); W. J. Horton and B. W. Rossiter, *J. Org. Chem.*, **23**, 488 (1958). The increased rate of such dealkylations has been attributed (Horton and Spence, above) to the greater basicity of the ether oxygen atom as a result of hydrogen bonding in the conjugate acid i.

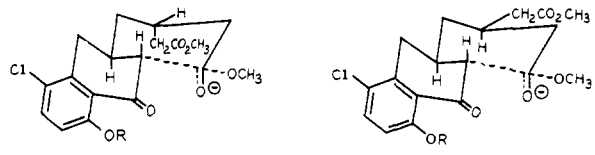
ion in the presence of excess sodium hydride[28] in boiling toluene to give a good yield of tricyclic material, as indicated by the distinct bathochromic shift of the ultraviolet absorption maximum. From the reaction product there was obtained after purification *ca.* 40% of a single crystalline enol which may be assigned stereoformula 20 on the following grounds. Closure of the symmetrical diester side chain of 19 could occur in two stereochemical senses, to give final products 20 and 21, which differ with respect to the configuration of the acetate side chain relative to the tertiary hydrogen at C-9a. Consideration of the over-all rate and extent of ring closure under the present reaction conditions suggests that the reaction is largely kinetically controlled.[29] Therefore the relative transition state energies leading to the *syn* (20) as opposed to the *anti* (21) series must determine the final proportion of these products. Although the precise structures of the respective transition states are difficult to specify, they must possess to a considerable extent the geometry of the incipient cyclohexanone ring. A total of six chair conformations for this ring may be drawn, leading to transition states resembling structures 22 through 27. It is clear that, in the absence of special stereoelectronic requirements for ring closure,[30]



structures 22 through 25 would be sterically unfavorable since each possesses a minimum of two 1,3-diaxial carbon–hydrogen interactions.

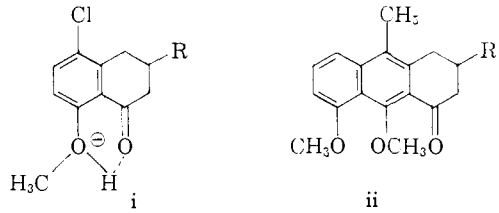


22, A = H, E = $CH_2CO_2CH_3$ 24, A = H, E = $CH_2CO_2CH_3$
23, A = $CH_2CO_2CH_3$, E = H 25, A = $CH_2CO_2CH_3$, E = H



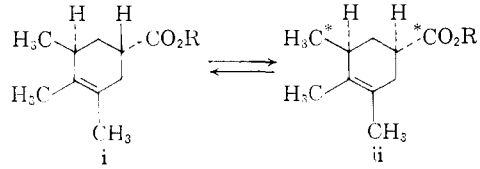
Of the remaining structures, conformation 26, leading to *anti* product 21, exhibits one 1,3-diaxial carbon–hydrogen and one 1,3-diaxial carbon–oxygen interaction whereas conformation 27 possesses neither. This would predict the more rapid formation by way of 27, of the intermediate *trans-syn*-

Systems in which there is further (steric) assistance to intermediates of type i, such as the anthracene series ii, are observed to undergo loss of the central O-methyl even more readily (unpublished observations from this Laboratory).

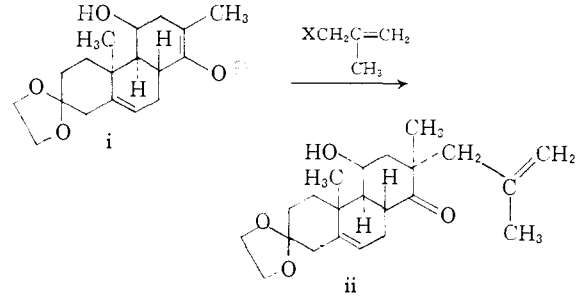


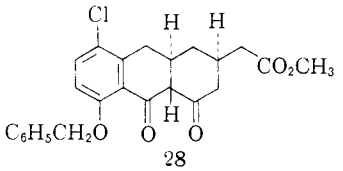
(28) The advantages of sodium hydride over other reagents for the Claisen condensation have been discussed by F. W. Swamer and C. R. Hauser, THIS JOURNAL, **68**, 2647 (1946).

(29) G. B. Kline, *ibid.*, **81**, 2251 (1959), has presented an interesting illustration of a carbanion acylation proceeding by kinetic control in the presence of sodium hydride but directed by thermodynamic factors when carried out using ethanolic sodium ethoxide; see also R. B. Woodward and R. H. Eastman, *ibid.*, **68**, 2229 (1946). It is noteworthy that our configuration assignment would not necessarily be obviated by the possibility that equilibrium may have been attained. In the latter case the product distribution would be a function of the relative stabilities of the *syn*- and *anti*-enolates. Here the situation with respect to the newly formed rings closely resembles the system i ⇄ ii studied by V. F. Kucherov, V. M. Andreev and I. N. Nazarov, *Izvest. Akad. Nauk SSSR (Khim.)*, 1058 (1959). For this equilibrium the *cis* isomer ii, in which both starred substituents can be equatorial or *quasi*-equatorial, is known to be decisively more stable than the *trans* isomer ii. On similar grounds the *syn*-enolate 29 would be expected to have greater stability than the corresponding *anti* isomer, so that the *syn* configuration would be predicted for the predominant product on either kinetic or thermodynamic grounds.



(30) It may be argued that intramolecular acylation of the bicydic enolate anion derived from 19 would tend to proceed in such a manner that the incoming ester group approaches axially with respect to the enolate system in order to maximize orbital overlap. Although such stereoelectronic preference has been demonstrated for certain cationoid α-brominations and α-protonations of enols [E. J. Corey, THIS JOURNAL, **76**, 175 (1954); E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956)] its extension to the present case is exceedingly tenuous. Thus the work of L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth [*ibid.*, **75**, 2112 (1953)] which showed that the major alkylation product of the enolate i gives ii by equatorial attack suggests that relatively minor steric factors, such as that provided by the transannular hydroxyl group, reverse the assumed stereoelectronic requirement for axial attack. Since in the present work the transition states for axial acylation, 22 and 23, each possess the minimum equivalent of two 1,3-diaxial C–H interactions plus a severe diaxial CH_2–oxygen interaction it is probable that these steric factors would outweigh any stereoelectronic tendency of the type discussed. More recent evidence on the alkylation of 6-ketosteroid enolates [J. H. Fried, A. N. Nutile and G. E. Arth, *ibid.*, **82**, 5704 (1960)] is in full agreement with hypothesis.

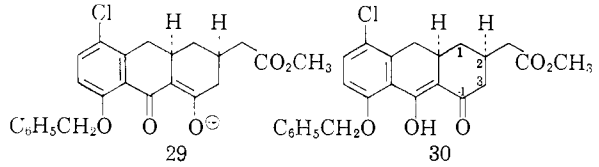




28

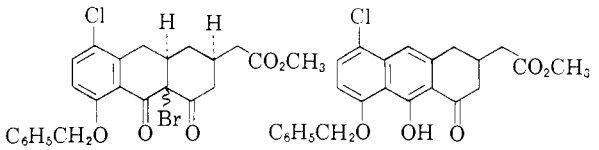
diketone 28, which by irreversible proton loss would lead to *syn*-enolate 29 as the predominant reaction product.

The absence of infrared carbonyl absorption between 5.85 and 6.00 μ in solution spectra of the tricyclic product pointed to the existence of this substance entirely in the chelated enolic form 20, or as the tautomer 30.[31]



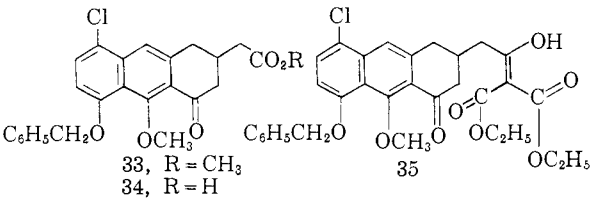
29 30

It was anticipated that elaboration of this compound into a tetracyclic system by Claisen-type condensation involving an enolate anion at position 3 might prove difficult because of the tendency to form instead the characteristically stable β-diketone anion 29. Moreover, an experimental problem arose in that alkaline hydrolysis of 20 led to facile cleavage of the β-dicarbonyl system which effectively competed with ester hydrolysis. For the present, these problems were by-passed by an aromatization sequence which directed the synthesis into the anhydrotetracycline series. Reaction of 20 with bromine in the presence of sodium acetate[32] gave a bromodiketone (31), which was dehydrobrominated by boiling collidine to give the highly fluorescent phenol 32. This product, which possessed the characteristic chromophore of the anhydrotetracyclines, was O-alkylated using dimethyl sulfate and potassium carbonate in toluene to give the



31 32

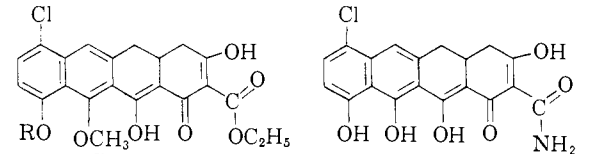
ester 33, which in turn gave the crystalline acid 34 on mild alkaline hydrolysis.[33] Such alkylation results in the disruption of the intramolecular hydrogen bond between the phenolic proton and the carbonyl oxygen, with a consequent 20–30 mμ hypsochromic shift in the long wave length band in the ultraviolet, and a corresponding shortening of the infrared carbonyl band from near 6.15 to about 5.95 μ.[34]



33, R = CH_3
34, R = H

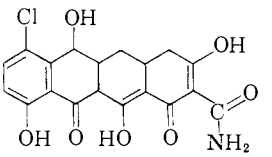
35

With the achievement of the tricyclic acid 34 the stage was set for closure of the fourth ring by the acylmalonate technique developed in an earlier investigation.[24] Treatment of 34 with ethyl chloroformate and triethylamine, followed by reaction of the resulting mixed anhydride with magnesioethoxy diethyl malonate, gave the acylmalonate 35. This substance could be cyclized by the action of sodium hydride in toluene under rigorously controlled conditions to give 30–35% of the desired tetracyclic ester 36 in the form of golden needles, m.p. 169–171°.[35] This product exhibited no carbonyl absorption below 6.0 μ, gave naphthacene on zinc dust distillation, and underwent ready hydrogenolytic debenzylation to the corresponding phenol 37.



36; R = $CH_2C_6H_5$
37; R = H

38



39

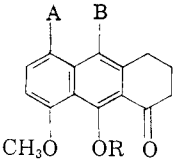
Attempts to convert the synthetic esters 36 or 37 into the corresponding carboxamides by treatment with methanolic or liquid ammonia under a variety

(31) The simple analog 1,8-diketodecahydronaphthalene, recently synthesized by H. Stetter and U. Milbers [*Chem. Ber.*, **91**, 977 (1958)], similarly exists entirely in the conjugate-chelated enolic form.

(32) Sodium acetate was employed to prevent rearrangement of the bromine in bromoketone 31 to the 3-position [*cf.* E. J. Corey, THIS JOURNAL, **75**, 3297 (1953), and references cited therein under footnote 6, p. 3298].

(33) The reaction sequence proceeding from the phenolic glutaric acid 18 to the tricyclic ester 33 has also been carried out using a methyl ether instead of a benzyl ether as the protecting group (see Experimental). In this "methoxy series" the yields and crystallinity of intermediates were inferior to those of the main series, and this factor, together with subsequent synthetic complications, led to the abandonment of the "methoxy series" at the tricyclic stage.

(34) The 15–20 mμ hypsochromic shift exhibited in methanol solution by the long wave length ultraviolet maxima of 8-hydroxytetralones upon ether formation finds ready analogy in the literature [R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1347 (1940)]. In a like manner the infrared carbonyl peaks of 8-hydroxytetralones shift from within the range 6.10–6.25 μ to *ca.* 5.95 μ for their ethers. We have observed entirely comparable effects in the tricyclic systems i–iii tabulated below. It is noteworthy that a series of compounds reported by H. Muxfeldt (ref. 23, *loc. cit.*) to possess system iv appear to show anomalous maxima (see table).



	A	B	Ultraviolet, mμ $\lambda^{R=H}$	Ultraviolet, mμ $\lambda^{R=CH_3}$	Infrared, μ $\lambda_{CO}^{R=H}$	Infrared, μ $\lambda_{CO}^{R=CH_3}$
	H	H	403	377	6.14	5.96
ii	Cl	H	400	376	6.22	5.93
iii	H	CH_3	402	375	6.15	5.95
iv	Cl	CH_3	431	418	..	6.19

(35) The use of sodium hydride in an inert solvent renders remote the possibility that an initial closure to the tetracyclic ester 36 had been followed by rapid reverse Dieckmann cleavage with subsequent

of conditions were without conspicuous success.[36] The desired transformation was eventually accomplished by fusion of ester 36 with ammonium formate at 135–140° in a nitrogen atmosphere.[37] The crude reaction product was directly dealkylated by a boiling solution of concentrated hydrochloric acid in acetic acid to give on crystallization orange needles of the synthetic (±)-amide 38.

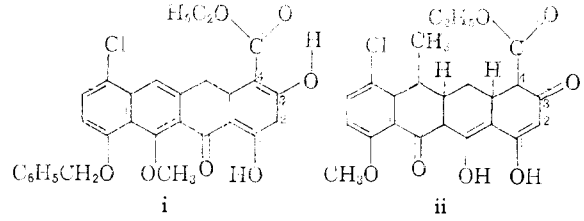
The natural antibiotic 6-demethyl-7-chlorotetracycline (5) was reduced with zinc dust in aqueous acetic acid to give the known 12a-deoxy-dedimethylamino compound 39.[9b] Dehydration of the latter with hydrobromic acid in acetic acid afforded the dextrorotatory anhydro derivative 40, which was purified by recrystallization. Comparison of this anhydrotetracycline derivative 40 with the racemic synthetic amide 38 by means of their infrared and ultraviolet spectra, chromatographic behavior and solubility properties clearly indicated the chemical identity of the two substances. Determination of *in vitro* antibacterial activity toward *S. aureus* by turbidimetric assay gave half-maximum inhibitory concentration of 0.065 ± 0.010 and 0.074 ± 0.010 μg. per ml. for the racemic and dextrorotatory amides, respectively.[38]

Acknowledgment.—We are indebted to Dr. E. F. Ullman for helpful discussions of various aspects of this work. We are grateful to Dr. R. G. Wilkinson for making available his experimental observations prior to publication. We wish to thank Mr. C. Pidacks and Mr. R. D. Mills for the chromatographic studies, Mr. W. Fulmor and his associates for spectroscopic determinations, and Mr. L. Brancone and staff for microanalyses.

Experimental[39]

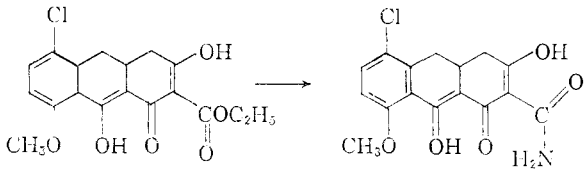
8-Chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetyl Chloride.—Oxalyl chloride (5 ml.) in anhydrous benzene (50 ml.) was added over a 30-minute period to a refluxing suspension of 5.4 g. (0.02 mole) of 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetic acid[24] in 50 ml. of dry benzene. The reaction mixture was refluxed an additional 30 minutes, allowed to cool, and concentrated to a sirup *in vacuo*. A potion of the crude acid chloride was taken up in 40 ml. of ether and concentrated *in vacuo* to a dark yellow solid. The solid was slurried in

recyclization to the 4-carbethoxy isomer i. Moreover, the absence of carbonyl absorption below 6.0 μ in the reaction product favors the 2-carbethoxy structure 36 since the compound ii, reported by H. Muxfeldt, W. Rogalski and K. Striegler, [*Angew. Chem.*, **72**, 170 (1960)], exhibits carbonyl absorption at 5.82 μ (H. Muxfeldt, private comm.).



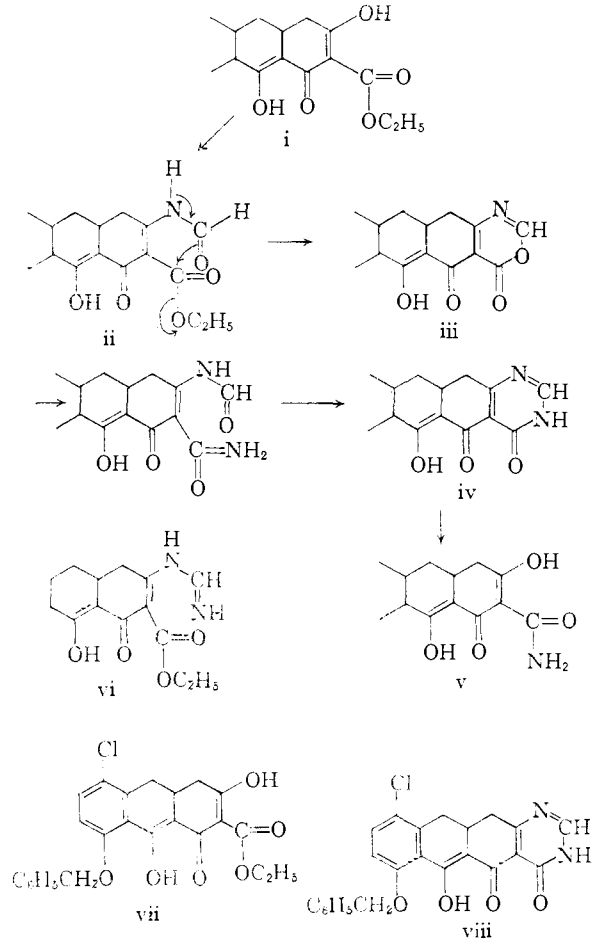
i ii

(36) In contrast, the tricyclic ester i was smoothly converted by methanolic ammonia at 80° for 5 hours into an enamine-carboxamide which gave the desired amide ii upon acid hydrolysis.[34]



i ii

(37) Work in these laboratories has shown that conversion of certain ketoesters having the structural groupings (i) into the corresponding carboxamides V can readily be achieved by brief fusion with ammonium formate at 130–145° followed by strong acid hydrolysis. Under these conditions neither ethyl benzoate nor ethyl salicylate react with ammonium formate. For this reason the reaction is believed to proceed through an intermediate formyl enamine ii which is subsequently transformed to a pyrimidone derivative (iv) by the action of ammonia. Acid hydrolysis of the latter could give the desired amide v with loss of formic acid and ammonia [*cf.* J. A. Carbon, THIS JOURNAL, in press]. The proposed formation of a formyl enamine (ii) finds analogy in the Leuckart reaction [M. L. Moore, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., pp. 303–306] while the subsequent conversion to a pyrimidone finds precedent in the work of Bredereck and his group [*Chem. Ber.*, **90**, 942 (1957); **91**, 2830, 2832 (1958)]. In the present system it is unclear whether the pyrimidone arises simply through the amidine vi or if instead there occurs a thermal cyclization of the formyl enamine ii to the oxazinone iii followed by aminolysis and recyclization to the pyrimidone [*cf.* the N-acylanthranilic acids studied by R. Anschütz, O. Schmidt and A. Greiffenberg, *Chem. Ber.*, **35**, 3481 (1902)]. In any case, it is noteworthy that when compound (vii) is fused at 140° with ammonium formate and the product isolated prior to acid hydrolysis there is obtained a neutral amorphous solid having analytical and spectroscopic properties clearly consistent with the postulated pyrimidone structure viii.



i ii iii iv v vi vii viii

(38) Antibacterial assays were carried out by Mr. A. Dornbush and associates by the turbidimetric technique described by E. Pelcak and A. Dornbush, *Ann. N. Y. Acad. Sci.*, **51**, 218 (1948).

(39) Melting points were taken in soft glass capillaries and are uncorrected. Unless otherwise specified infrared spectra were taken of potassium bromide disks using a Perkin-Elmer model 21 double-beam recording spectrophotometer equipped with sodium chloride prism. Ultraviolet spectra were determined on a Cary recording spectrophotometer, model 11, with methanol as solvent except as indicated.

50 ml. of ether, collected on a filter, and washed twice with ether. The acid chloride was so obtained as a cream-colored crystalline solid, m.p. 80–82°, having infrared maxima at 5.52 (COCl) and 5.91 μ (tetralone C=O).

Anal. Calcd. for $C_{13}H_{12}Cl_2O_3$: C, 54.54; H, 4.23; OCH_3, 10.84. Found: C, 54.60; H, 4.54; OCH_3, 10.74.

8-Chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetaldehyde (16).—A suspension of 21.6 g. (0.08 mole) of the 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetic acid (14) in 500 ml. of benzene was converted to the acid chloride as described above. The crude acid chloride was dissolved in 1 liter of toluene and transferred to a 3-liter round-bottom flask equipped with a reflux condenser, sealed mechanical stirrer and gas inlet tube. The system was flushed with nitrogen and 4.0 g. of 5% palladium-on-barium sulfate was added. Hydrogen was bubbled through the system at a vigorous rate and the solution was brought to reflux. After 149 minutes 65% of the theory of hydrogen chloride had been evolved. An additional 4.0 g. of 5% palladium-on-barium sulfate was added. After a further reflux period of 24 minutes more than 95% of the theory of hydrogen chloride had been evolved. The reaction was cooled, flushed with nitrogen and the catalyst was filtered off. The clear filtrate was washed three times with 100-ml. portions of 1 *N* sodium bicarbonate and three times with 100-ml. portions of water. The toluene layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to a brown oil. The crude aldehyde was dissolved in 50 ml. of benzene and concentrated to a dark brown solid. This was slurried in 100 ml. of ether, and the light tan crystals thereby obtained were collected on a filter and air-dried. The yield of 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetaldehyde, m.p. 88–90°, was 16.55 g. (82%). The analytical sample, recrystallized from ether, had m.p. 89–91°; its infrared spectrum showed maxima at 3.67 (aldehyde CH), 5.80 (aldehyde C=O), 5.94 μ (tetralone C=O). The ultraviolet spectrum is given in Fig. 1.

Anal. Calcd. for $C_{15}H_{15}ClO_3$: C, 61.78; H, 5.18; Cl, 14.02. Found: C, 61.63; H, 5.40; Cl, 13.92.

4-(8-Chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthyl)-2-butenoic Acid.—Malonic acid (0.416 g., 0.004 mole) and the naphthaleneacetaldehyde (16), m.p. 88–90° (1.01 g., 0.004 mole), were dissolved in 24 ml. of pyridine.[40] Three drops of piperidine was added and the solution was allowed to stand at room temperature overnight, followed by reflux under nitrogen for 7 hours. The cooled reaction mixture was poured into 60 ml. of 1 *N* sodium carbonate. This mixture was extracted with a portion of 1:1 ether–ethyl acetate, and the aqueous layer was acidified with dilute hydrochloric acid. The light tan solid which precipitated upon acidification was collected by filtration and dried under vacuum over P_2O_5. The crude acid (0.99 g.) was recrystallized from toluene to give 0.55 g. of product, m.p. 168–180° dec. The analytical sample, recrystallized twice more from toluene, was a cream-colored solid, m.p. 182–184° dec.

Anal. Calcd. for $C_{15}H_{15}ClO_4$: C, 61.1; H, 5.12; Cl, 12.03. Found: C, 61.38, 61.36; H, 5.48, 5.60; Cl, 12.13.

Methyl 4-(8-Chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthyl)-2-butenoate.—A mixture of 4-(8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthyl)-2-butenoic acid (540 mg., 0.00183 mole), 15 ml. of absolute methanol, 15 ml. of chloroform and 3 drops of concd. sulfuric acid was refluxed for 16 hours under a Soxhlet apparatus containing 1 g. of anhydrous magnesium sulfate in the thimble.[41] The cooled mixture was concentrated *in vacuo* to 3 ml., diluted with 40 ml. of ether, washed twice with 1 *N* sodium carbonate and twice with water. The ether layer was dried over anhydrous magnesium sulfate, filtered and concentrated to an oil. The crude ester (460 mg.) was dissolved in 3 ml. of ether and, upon chilling, cream colored needles deposited. The yield of pure methyl 4-(8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthyl)-2-butenoate was

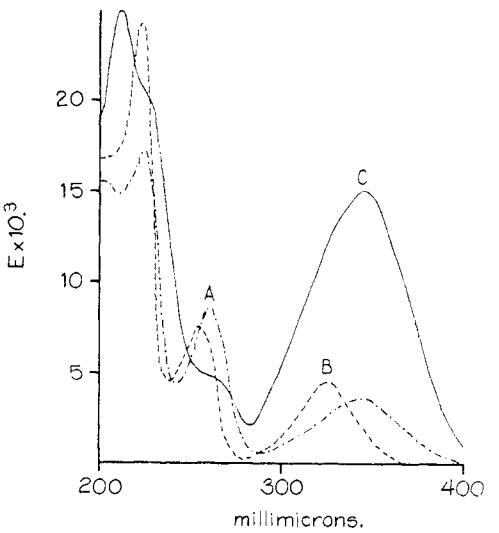


Fig. 1.—Ultraviolet spectra of methanol solutions of: A, 3-(8-chloro-1,2,3,4-tetrahydro-5-hydroxy-4-oxo-2-naphthylmethyl)-glutaric acid (18); B, 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneacetaldehyde (16); C, methyl 5-benzyloxy-8-chloro-1,2,3,4,4a,9,9a,10-octahydro-4,10-dioxo-2-anthraceneacetate (*syn* isomer, 20).

278 mg. (50%), m.p. 65–67°. Infrared carbonyl absorption was at 5.80 (ester) and 5.96 μ (tetralone).

Anal. Calcd. for $C_{16}H_{17}ClO_4$: Cl, 11.50; OMe, 20.10. Found: Cl, 11.61; OMe, 19.66.

Dimethyl 1-Hydroxy-3-oxo-5-methylcyclohexene-2,4-dicarboxylate (or Tautomer).—A three-neck round-bottom flask was equipped with a sealed stirrer, a dropping funnel and a reflux condenser capped by a nitrogen inlet. Dry benzene (50 ml.) and sodium hydride (1.44 g., 0.06 mole) were successively introduced, and the suspension stirred under a nitrogen atmosphere. To the stirred suspension was added dropwise, over a period of 30 minutes, a solution of dimethyl β-oxoglutarate (5.2 g., 0.03 mole) and methanol (0.2 ml.) in dry benzene (10 ml.). A clear solution was thereby obtained. To this solution was added ethyl crotonate (3.5 g., 0.03 mole) in dry benzene (10 ml.). No detectable reaction occurred.

The solution was kept at gentle reflux under a nitrogen atmosphere for 16 hours. A flesh-colored powdery precipitate was formed. Approximately 5 ml. of dry methanol was added to destroy any residual hydride and the mixture cautiously acidified by addition of 6 *N* hydrochloric acid.

The suspension was diluted with ether and stirred thoroughly while in the flask. The two-phase mixture was poured into a separatory funnel and the product taken up by successive ether extracts. The combined organic layers were washed with water and dried over sodium sulfate. Evaporation of solvent gave an oil which crystallized on trituration with ether–petroleum ether to a colorless solid, m.p. 64–69° (2.14 g.). Repeated recrystallizations from ether were necessary to obtain a constant m.p. of 89–91°. This product (0.66 g., 30% yield) gave a strong red-brown coloration with methanolic ferric chloride. An aqueous solution of the pure product gave no precipitate with formaldehyde solution or with copper acetate solution.

The analytical sample was recrystallized from benzene–ether and was dried at 78° in oil-pump vacuum for 1 hour.

Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.5; H, 5.83; OCH_3, 25.6. Found: C, 54.84; H, 5.98, 6.14; OCH_3, 25.12, 25.59.

The product possessed infrared maxima at 5.73 (ester), 6.0, 6.29 and 7.93 μ. The ultraviolet absorption spectrum varied with solvent and *p*H[42]; in acidified methanol,

(40) J. R. Johnson, Organic Reactions, Vol. I, John Wiley and Sons, Inc., New York, N. Y., pp. 234, 252.

(41) This efficient method of esterification is described by B. R. Baker, M. V. Querry, S. R. Safir and S. Bernstein, *J. Org. Chem.*, **12**, 138 (1947).

(42) The variation of the ultraviolet absorption of β-dicarbonyl systems with *p*H and solvent has been discussed by H. Bastron, R. E. Davis and L. W. Butz, *J. Org. Chem.*, **8**, 522 (1943); E. R. Blout, V. W. Eager and D. C. Silverman, THIS JOURNAL, **68**, 566 (1946); W. R. Chan and C. H. Hassall, *J. Chem. Soc.*, 3495 (1956).

λ_{max} 222 and 254 mμ (ε 9,000 and 14,100); in 0.1 *N* aqueous sodium hydroxide, λ_{max} 273 mμ (ε 23,600). Conover gives λ_{max} 258 and λ_{max} 270 mμ for dihydro-*p*-orsellinamide in acidified and alkaline methanol, respectively[43]; Tomino cites 258 mμ (log ε 4.25) for the same amide in methanol.[44]

2,2'-Dicyano-3-(8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthylmethyl)-glutaramide (17).—Cyanoacetamide (8.0 g., 0.095 mole) and 8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthaleneactaldehyde (8.0 g., 0.032 mole) were dissolved in absolute ethanol (300 ml.) with the aid of heat. The solution was cooled, filtered, 5 drops of piperidine was added, and the liquid set aside at room temperature for 24 hours. The white crystals (11.7 g., 92%) which deposited were collected by suction filtration, washed with ether, and air-dried. This highly insoluble product had m.p. 140–155°, but the m.p. of other batches prepared in a similar manner varied from 105 to 160°, despite reproducible analytical data. The infrared spectrum showed maxima at 2.9 and 3.1 (NH), 4.45 (CN), 5.9–5.95 (tetralone C=O), 6.2–6.3, 7.8, 8.0, 9.15, 9.4 and 10.2 μ. The ultraviolet spectrum was that of the methoxytetralone system.

Because of its extreme insolubility, a sample was submitted for analysis without further purification after drying at 60° for 3 hours at 0.1 mm.

Anal. Calcd. for $C_{19}H_{19}O_4N_4Cl \cdot C_2H_5OH$: C, 56.13; H, 5.62; N, 12.49. Found: C, 55.61; H, 5.62; N, 12.54.

3-(8-Chloro-1,2,3,4-tetrahydro-5-hydroxy-4-oxo-2-naphthylmethyl)-glutaric Acid (18).—The dicyanodiamide 17 (10.0 g., 0.25 mole) was slurried in a mixture of concentrated hydrochloric acid (405 ml.) and glacial acetic acid (135 ml.). Upon reflux a clear yellow solution formed which gradually turned bright red, then brown. After 12 hours at reflux the reaction was cooled and filtered. The filtrate was concentrated at reduced pressure to approximately two-thirds volume. The light yellow crystals which separated on cooling were collected on a filter, washed thoroughly with water and dried *in vacuo* over phosphorus pentoxide and potassium hydroxide pellets. The yield of the glutaric acid 18 was 5.9 g. (70%), m.p. 177–180°. Recrystallization from ethyl acetate raised the melting point to 181.5–182°. The ultraviolet spectrum is given in Fig. 1.

The product exhibited infrared maxima at 3.0–3.3, 5.85, 6.10 (chelated tetralone C=O) and 8.20 μ.

Anal. Calcd. for $C_{16}H_{17}ClO_6$: C, 56.40; H, 5.03; Cl, 10.42. Found: C, 56.45; H, 5.30; Cl, 10.36.

3-(5-Benzyloxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-naphthylmethyl)-glutaric Acid.—A solution of the phenolic glutaric acid (0.92 g. 0.0027 mole) in 25 ml. of 1 *N* sodium hydroxide was placed in a flask equipped with a reflux condenser and nitrogen inlet. Benzyl chloride (1.8 g., 0.0142 mole) was added and the mixture refluxed for 2 hours under a nitrogen atmosphere. During this period the disappearance of phenolic hydroxyl may be followed by the diminution of the phenolate absorption at 378 mμ in dilute alkali and the growth of a peak at 327 mμ characteristic of the alkoxytetralone system. After 2 hours of reflux the reaction was cooled and washed with five 20-ml. portions of ether. The aqueous layer was separated, acidified, and the tan oily solid which formed was extracted into ethyl acetate. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated to a light tan solid *in vacuo*. The crude benzyloxyglutaric acid (1.10 g.), m.p. 167–173°, was used for the subsequent step without further purification.

The analytical sample was obtained from ethyl acetate as a colorless microcrystalline solid, m.p. 174–176°; $\lambda_{max}^{CH_3OH}$ 222,254 and 325 mμ, ε 29,400, 7300 and 4100.

Anal. Calcd. for $C_{23}H_{23}O_6Cl$: C, 64.05; H, 5.38; Cl, 8.25. Found: C, 64.68; H, 6.17; Cl, 8.22.

Dimethyl 3-(8-Chloro-1,2,3,4-tetrahydro-5-benzyloxy-4-oxo-2-naphthylmethyl)-glutarate (19).—The benzyloxy acid (9.0 g.), anhydrous methanol (450 ml.) and ten drops of concentrated sulfuric acid were brought to reflux in a flask equipped with a reflux condenser and a drying tube. After 160 minutes the reaction mixture was allowed to cool, the bulk of the methanol was removed at room temperature under reduced pressure, and the remaining solution was poured into a large volume of ethyl acetate. The organic liquid was washed twice with sodium bicarbonate solution, then dried over magnesium sulfate. Evaporation of solvent *in vacuo* gave 9.0 g. of clear tan oil having infrared maxima at 5.75 μ (ester C=O) and 5.91 μ (tetralone C=O). This product was suitable for cyclization without further purification.

A sample of the benzyloxy diester was recrystallized four times from ether to give colorless crystals of the analytical sample, m.p. 62–63°.

Anal. Calcd. for $C_{25}H_{27}O_6Cl$: C, 65.43; H, 5.92. Found: C, 65.10; H, 6.04.

Dimethyl 3-(8-Chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthylmethyl)-glutarate.—A mixture of 3-(8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthylmethyl)-glutaric acid (2.10 g.) and dry methanol (400 ml.) containing dry hydrogen chloride gas was allowed to stand in a stoppered flask for 18 hours. The resulting solution was refluxed, with the exclusion of moisture, for 90 minutes and allowed to cool. The volume of solvent was reduced *in vacuo* to *ca.* 50 ml., a large volume of 1:1 benzene–ethyl acetate was added, the liquid was poured into salt solution and the organic layer separated. The organic portion was washed with water, then with sodium bicarbonate solution and again with water. The solution was dried over anhydrous magnesium sulfate and the solvent was evaporated to give 2.10 g. of the oily phenolic dimethyl ester.

Powdered potassium carbonate (5.0 g.), freshly baked at 140° for 16 hours, was added to dry reagent acetone (70 ml.) in a 3-neck flask equipped with sealed stirrer, stopper, and an efficient reflux condenser capped by a nitrogen inlet. To this suspension was added an acetone solution (30 ml.) of the oily phenolic diester, followed by methyl iodide (5 ml.). The suspension was stirred vigorously and brought to gentle reflux under a nitrogen atmosphere.

The progress of the methylation was followed by the shift of the ultraviolet maximum in base from 378 (phenoxide) to 327 mμ. After 5 hours of reflux the above reaction mixture showed only partial diminution of the phenoxide absorption. The suspension was filtered, the solvent removed and replaced by benzene, and the benzene solution was filtered and the filtrate evaporated to give the partially methylated material. A second methylation was now performed on this crude material using 175 ml. of dry acetone, 9.0 g. of fresh carbonate and 10 ml. of methyl iodide according to the procedure above. When methylation was essentially complete this second alkylation was worked up by the benzene extraction just described. Trituration of the product with ether gave the crystalline methoxydiester (1.65 g., 70%), m.p. 89–91°. The analytical sample was recrystallized from ether–petr. ether, giving colorless crystals, m.p. 91–92°. The substance possessed infrared maxima at 5.73 (ester C=O) and 5.92 μ (tetralone C=O), and exhibited the expected alkoxytetralone chromophore in the ultraviolet.

Anal. Calcd. for $C_{19}H_{23}O_6Cl$: C, 59.53; H, 6.06; OCH_3, 24.26. Found: C, 59.39; H, 6.31; OCH_3, 23.94.

***syn*-Methyl 4-Hydroxy-5-benzyloxy-8-chloro-1,2,3,9,9a,-10-hexahydro-10-oxo-2-anthraceneacetate (20).**—To a solution of the benzyloxydiester 19 (9.00 g.) in sodium-dried reagent toluene (600 ml.) was added "sodium hydride in oil"[45] (4.0 g., 52% NaH by weight) and two drops of anhydrous methanol. The mixture was brought to reflux under a nitrogen atmosphere and efficient stirring was maintained. The reaction mixture soon changed from nearly colorless to a deep yellow. Spectrophotometric assay indicated approximately 50% ring closure in 45 minutes; at the end of 4 hours, closure was over 95% complete. Reflux was maintained for a total of 4 hours, after which the mixture was allowed to stir at room temperature overnight. Methanol (10 ml.) was added to destroy any excess hydride, and the reaction mixture was carefully poured into ice-cold 2 *N* sulfuric acid. The organic layer was diluted with ethyl acetate, washed three times with water, dried over magnesium sulfate, and evaporated under reduced pressure. On standing the oily product solidified to give 6.6 g. of semi-crystalline enol 20, m.p. 105–112°. A 100-mg. portion was re-

(43) L. H. Conover, in "Symposium on Antibiotics and Mold Metabolites," Special Publication No. 5, The Chemical Society (London), 1956, p. 48.

(44) Koichi Tomino, *Yakugaku Zasshi* (*J. of Pharmacology, Tokyo*), **78**, 1425 (1958); *C. A.*, **53**, 8018 (1959).

(45) A product of Metal Hydrides, Inc., Beverly, Mass.

crystallized from ether to give material, m.p. 118–121° (51 mg.), which gave satisfactory analytical data; the melting point was unchanged upon further recrystallization. The ultraviolet spectrum is given in Fig. 1.

Anal. Calcd. for $C_{24}H_{23}ClO_5$: C, 67.53; H, 5.41; Cl, 8.31. Found: C, 67.47; H, 5.58; Cl, 8.85.

Methyl 5-Methoxy-4-hydroxy 8-chloro-1,2,3,9,9a,10-hexahydro-10-oxo-2-anthraceneacetate.—A solution of crystalline dimethyl 3-(8-chloro-1,2,3,4-tetrahydro-5-methoxy-4-oxo-2-naphthylmethyl)-glutarate (4.53 g.) in anhydrous toluene (180 ml.) was placed in a flask equipped with a stirrer, reflux condenser and nitrogen inlet. Sodium hydride (0.70 g.) was added, followed by a drop of methanol, and the suspension stirred at reflux under a nitrogen atmosphere for 16 hours. Excess hydride was destroyed by addition of dry methanol and the reaction mixture cautiously poured into cold 1 *N* sulfuric acid. Workup as with 20 above gave a brown oil which was purified by filtration through a silica gel column (30 g., Davidson). The oil was placed on the column in benzene solution and eluted with five 100-ml. portions of 4:1 ethyl acetate–benzene. By this procedure was obtained 3.72 g. of an amber oil, $\lambda_{max}^{CH_3OH}$ 343 mμ, having no tetralone absorption near 5.95 μ.

On standing in ether–ethyl acetate at 0° this oil slowly deposited 0.64 g. of yellow crystals, m.p. 199–202°. Recrystallization from ethyl acetate raised the m.p. to 229–230.5°; the pale yellow crystals were dried at 100° in vacuum prior to analysis. This substance, possibly a diastereomer of 4-hydroxy-5-methoxy-8-chloro-1,2,3,9,9a,-10-hexahydro-10-oxo-2-anthraceneacetic acid, had λ_{max} 219, 266 and 347 mμ, ε 14,100, 4040 and 14,000. The substance was soluble in sodium carbonate solution.

Anal. Calcd. for $C_{17}H_{17}ClO_5$: C, 60.74; H, 5.09; OCH_3-(1), 9.20. Found: C, 60.25, 60.35; H, 5.47, 5.57; OCH_3, 10.30.

The mother liquor from the above separation was evaporated *in vacuo* to give 2.80 g. (67%) of the mixture of diastereomeric methoxydiketone esters, which could not be obtained crystalline and was used as such for the aromatization sequence.

Methyl 5-Benzyloxy-10-hydroxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-anthraceneacetate (32).—Crystalline methyl 5-benzyloxy-4-hydroxy-8-chloro-1,2,3,9,9a,10-hexahydro-10-oxo-2-anthraceneacetate (20), m.p. 105–112° (6.5 g.), was dissolved in a mixture of ethyl acetate (40 ml.) and glacial acetic acid (80 ml.). Anhydrous sodium acetate powder (1.75 g.) was added and the mixture stirred magnetically until a solution was obtained. The reaction vessel was cooled to 0–5° and to the contents were slowly added, with stirring, 16 ml. of a 1 *M* solution of bromine in glacial acetic acid. After addition of the bromine solution, an aliquot of the reaction possessed an ultraviolet absorption ratio (ε360/ε335) of 0.55 in 0.1 *N* alkali. The entire reaction mixture was poured into benzene, the benzene solution washed with salt solution containing a little sodium sulfite, then with four successive portions of water. The benzene layer was dried over magnesium sulfate and the solvent removed to give the crude bromoketone 31 as a pale pink foam (7.0 g.).

The bromoketone was dissolved in 45 ml. of freshly distilled collidine and the solution heated under nitrogen at reflux for 12 minutes. The cooled supernatant was separated from solid collidine hydrobromide by decantation, the solid washed with ether–benzene and the ether and collidine solutions combined. The extracts were diluted with ether and washed with ice-cold 3 *N* sulfuric acid until the collidine odor was no longer present. The organic layer was dried over magnesium sulfate and the solvent evaporated under reduced pressure. There remained 5.5 g. (84%) of the crystalline phenol 32, tan solid with a vivid green-yellow fluorescence. The analytical sample was obtained from ether; m.p. 132–134°. The ultraviolet absorption spectrum is given in Fig. 2.

Anal. Calcd. for $C_{24}H_{21}O_5Cl$: C, 67.84; H, 4.98. Found: C, 67.45; H, 5.47.

Methyl 5,10-Dimethoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-anthraceneacetate.—A portion of the crude methoxy diketone (1.85 g., 0.053 mole) in ethyl acetate solution (10 ml.) was added to glacial acetic acid (40 ml.) containing anhydrous sodium acetate (0.55 g.). The solution was cooled to *ca.* 10°, and to it was added dropwise with magnetic stirring a solution of bromine in acetic acid (0.5 *M* Br_2, 11 ml.). At this point the ultraviolet spectrum of an aliquot indicated the absence of the 358 mμ chromopore in alkali characteristic of the methoxy diketone.

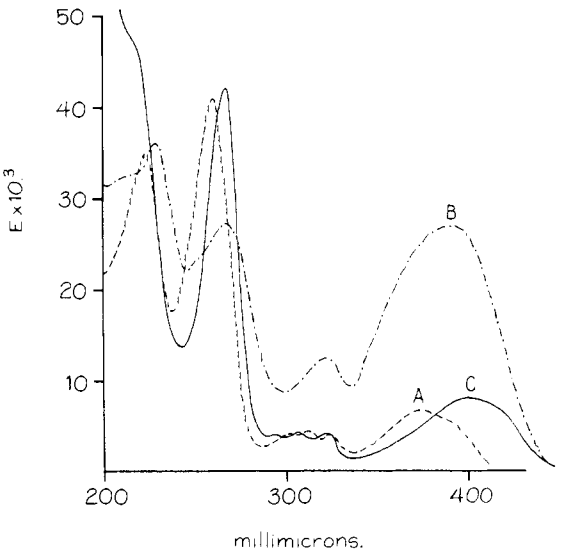


Fig. 2.—Ultraviolet spectra of methanol solutions of: A, methyl 5-benzyloxy-10-methoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-anthraceneacetate (33); B, tetracyclic ester, 36; C, methyl 5-benzyloxy-10-hydroxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-anthraceneacetate (32).

The reaction mixture was poured into saturated salt solution and extracted with benzene–ethyl acetate (2:1). The organic layer was washed with water, sodium sulfate solution, then water, followed by several washes with sodium bicarbonate solution. A final wash with water was followed by drying over sodium sulfate and evaporation of solvent *in vacuo* to give 1.77 g. of the amber, gummy bromodiketone.

This product was dissolved in 24 ml. of collidine that had been freshly distilled from calcium hydride. The solution was brought to reflux in a nitrogen atmosphere. A black solid soon began to precipitate. After 12 minutes, reflux was discontinued and the cooled reaction mixture diluted with a little benzene. The liquid was decanted from the precipitated solid and the latter washed with fresh benzene. The combined liquids were then poured into ice-cold 3 *N* H_2SO_4 and thoroughly shaken until the odor of collidine had been destroyed. The aqueous wash was discarded, the organic layers diluted with ethyl acetate, and the highly fluorescent solution washed with water and dried over sodium sulfate. Removal of solvent on the water-pump gave 1.21 g. of the phenolic methoxy ketone ester having λ_{max} 409 and 266 mμ. This product, which could not be obtained crystalline, was further characterized by infrared maxima at 5.74 (ester), 6.15 (ketone) and a sharp strong band at 7.25 μ believed characteristic of such tetrahydroanthracene ketones bearing free hydroxyl next to the carbonyl.

The phenol (1.21 g.) in anhydrous toluene (60 ml.) was placed in a flask equipped with an effective magnetic stirring bar and reflux condenser. To the solution were added anhydrous, micronized potassium carbonate (7.0 g., dried at 130° for 48 hours) and dimethyl sulfate (0.70 ml.). The solution was brought to reflux under a nitrogen atmosphere and stirred vigorously. After 3.5 hours the ultraviolet maximum had shifted to just below 380 mμ. The reaction mixture was cooled and the supernatant solution filtered. This solution was then chromatographed directly on 50 g. of Merck alumina. The column was washed with benzene to elute residual dimethyl sulfate. After about 150 ml. had been collected, the eluant was changed to 4:1 benzene–ethyl acetate. The yellow zone was thus collected and concentrated to a semi-crystalline cream-colored solid (0.73 g.).

Recrystallization of this solid from a small volume of ether gave cream-colored crystals of the dimethoxy ketone ester (485 mg.), m.p. 103–105°. The analytical sample was recrystallized again from ether, m.p. 105–106°. Infrared

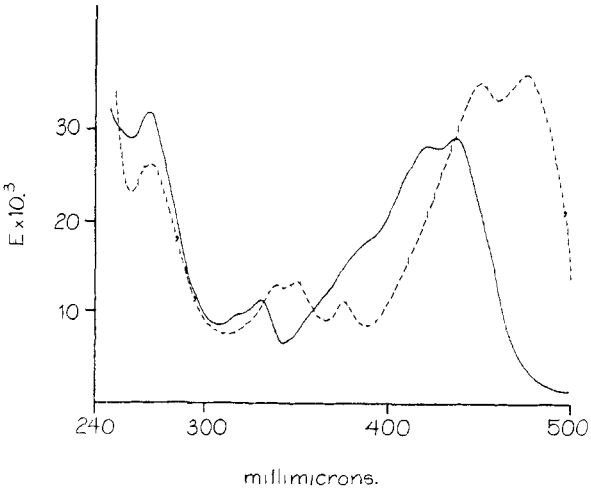


Fig. 3.—Ultraviolet spectrum of synthetic (±)-amide 39: in acidified methanol, —; in 0.001 *N* methanolic NaOH after standing 10 min., -------.

carbonyl maxima were at 5.79 and 5.95 μ; in the ultraviolet, λ_{max} 222, 260 and 376 mμ, ϵ 29,800, 38,000 and 5,400, respectively.

Anal. Calcd. for $C_{19}H_{19}ClO_5$; C, 62.89; H, 5.29; OCH_3, 25.61. Found: C, 62.95; H, 5.61; OCH_3, 26.00.

Methyl 5-Benzyloxy-10-methoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-anthraceneacetate (33).—A solution of 4.75 g. of benzyloxy-phenol 32 and dimethyl sulfate (3.2 ml.) in anhydrous toluene (160 ml.) was placed in a 500-ml. flask equipped with an efficient magnetic stirrer and reflux condenser. Micronized anhydrous potassium carbonate (33 g., previously dried 12 hours at 130°) was added and the stirred suspension held at reflux for 6 hours. The cooled mixture was filtered through a sintered glass suction funnel and the filter cake (K_2CO_3) washed with benzene. The combined filtrates were reduced to 30 ml. *in vacuo* and chromatographed on 100 g. of Merck alumina. Eluates corresponding to (A) benzene to benzene–10% ethyl acetate and (B) benzene–25% ethyl acetate to benzene–50% ethyl acetate were separately collected. Concentration and recrystallization of the residues from ether gave, from A, 0.80 g. of yellow needles, m.p. 129–130°; from B, 1.24 g. of tan needles, m.p. 127–128°; mixed m.p. 127–128.5°; the infrared spectra of A and B were identical.

The analytical sample was prepared from B by recrystallization from ether and drying *in vacuo* at 65°; the m.p. was 127.5–128.5°. The infrared spectrum exhibited carbonyl maxima at 5.77 (ester) and 5.94 μ (ketone). The ultraviolet spectrum is given in Fig. 2.

Anal. Calcd. for $C_{25}H_{23}O_5Cl$: C, 68.36; H, 5.29; OCH_3, 14.1. Found: C, 68.49; H, 5.56; OCH_3, 14.65.

5-Benzyloxy-10-methoxy-8-chloro-1,2,3,4-tetrahydro-4-oxo-2-anthracene-acetic Acid (34).—A solution of 2.5 g. of potassium hydroxide, 4 ml. of water and 35 ml. of methanol was brought to reflux and allowed to cool in a nitrogen atmosphere. To the cold solution was added 1.17 g. of methyl ester 33 and the suspension brought to reflux under nitrogen. After 1 hour of reflux the solution was evaporated *in vacuo* to approximately one-half the original volume. The reaction mixture was poured into excess cold dilute sulfuric acid and the organic product extracted into ethyl acetate. The ethyl acetate was washed twice with water and dried over magnesium sulfate. Evaporation of solvent led to 1.09 g. (96%) of crystalline tricyclic acid, tan needles melting at 169–171°.

The analytical sample was recrystallized three times from ethyl acetate to give straw-colored needles, m.p. 175–176°. Solvent of crystallization was removed by drying at 100° in vacuum for 4 hours.

Anal. Calcd. for $C_{24}H_{21}O_5Cl$: C, 67.81; H, 4.96; OCH_3, 7.31. Found: C, 67.72; H, 5.06; OCH_3, 7.27.

Preparation of the Tetracyclic Ester 36.—A suspension of 1.01 g. (2.3 millimoles) of recrystallized tricyclic acid 34 in 50 ml. of anhydrous (sodium-dried) toluene was stirred magnetically at room temperature under a dry nitrogen atmosphere. Addition of triethylamine (0.38 ml., 2.75 millimoles) effected solution of the acid. The mixture was cooled to −10° and ethyl chloroformate (0.26 ml., 2.75 millimoles) was added. The stirring at −10° under nitrogen was maintained for 15 minutes, at which time was added 5.5 ml. of 0.45 *M* magnesioethoxy diethyl malonate[46] in toluene. The reaction mixture was allowed to stand at room temperature for 18 hours; it was then poured into excess cold 2 *N* sulfuric acid. The acylmalonate was extracted into benzene, the benzene extracts washed with sodium bicarbonate (which removes traces of starting acid but does not take up this acylmalonate) and water, dried over magnesium sulfate, and evaporated to leave 1.39 g. of product. The crude acylmalonate was a yellow gum having infrared maxima at 5.75–5.80 and 5.94 μ, and ultraviolet spectrum essentially identical with that of the starting system.

The acylmalonate (1.39 g.) was dissolved in 20 ml. of toluene and evaporated to dryness *in vacuo*, then held at 95° at 1 mm. vacuum for 1 hour. The dried acylmalonate was dissolved in 35 ml. of sodium-dried reagent toluene and the solution placed in a rigorously dried round-bottom flask equipped with reflux condenser, small magnetic stirrer and nitrogen inlet. To the solution was added "sodium hydride in oil"[45] (1.20 g. of a solid suspension *ca.* 52% NaH by weight) and the stirred mixture refluxed under a nitrogen atmosphere for 20 minutes. During this period the ultraviolet spectrum of a given aliquot changed

	310 mμ	377 mμ	410 mμ	
O.D. (start)	0.40	0.53	0.20	(λ_{max} 379 mμ)
O.D. (20 min.)	0.62	1.30	1.01	(λ_{max} 390 mμ)

The reaction mixture, which had turned from the original very pale yellow to a strong golden-brown color, was cooled to room temperature and then cooled further in ice-water. The remaining sodium hydride was destroyed by the cautious dropwise addition of glacial acetic acid (3 ml.) followed by the very slow addition of absolute ethanol. The resulting solution was poured into cold dilute sulfuric acid, the organic components extracted into ethyl acetate, and the extracts washed with sodium bicarbonate and water. After drying over magnesium sulfate the ethyl acetate was evaporated to leave an oil (which contains *ca.* 0.6 g. of mineral oil from the NaH suspension). The oil was taken up in 35 ml. of dry ether and the solution scratched until crystallization commenced. On standing of the solution in the ice-box overnight there were obtained 415 mg. (35%) of golden yellow crystals, m.p. 170–172°.

The analytical sample was recrystallized from ethyl acetate and dried at 100° for 4 hours in vacuum; golden needles, m.p. 169–171°.

Anal. Calcd. for $C_{29}H_{25}O_7Cl$: C, 66.88; H, 4.84; OCH_3, 11.90. Found: C, 66.85; H, 5.08; OCH_3, 11.11.

Yields and melting points of tetracyclic product varied adversely with increasing reaction time, as tabulated

Run		M.p., °C.	Yield, %
2	40 min. reflux	168–171	31
3	45 min. reflux	131–134	25
4	80 min. reflux	128–134	14
5	8 hours reflux	110–128	Trace

The infrared spectrum of analytically-pure tetracyclic ester showed in chloroform solution no significant absorption below 6.0 μ. Zinc dust distillation of the tetracyclic ester gave naphthacene in a yield comparable to that obtained from authentic dedimethylamino-12a-deoxy-6-demethyl-anhydro-7-chlorotetracycline.

Catalytic reduction of 104 mg. of the tetracyclic ester in 25 ml. of methyl Cellosolve containing 0.5 ml. of acetic acid and 50 mg. of 10% Pd-on-charcoal catalyst gave the corresponding debenzylated ester 37, m.p. 159–161°. The ultraviolet absorption of the latter in 0.1 *N* NaOH had λ_{max} 272, 363 and 433 mμ (log ϵ 4.37, 4.26 and 4.25); this compound was not further characterized.

(±)-Dedimethylamino-12a-deoxy-6-demethylanhydro-7-chlorotetracycline (38).—To a small test-tube was added 90 mg. of crystalline tetracyclic ester 36 and this was covered with 2.0 g. of ammonium formate (crystals, Fisher, reagent grade). The test-tube was partially immersed in a r.b. flask containing xylene, and the xylene bath heated to gentle

(46) H. Lund, *Chem. Ber.*, **67**, 935 (1934); D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).

reflux under a nitrogen atmosphere for 3 hours. During the heating the organic portion gradually rose to the top of the molten formate as a dark-brown, hard layer. The reaction was allowed to cool, the contents of the test tube were digested first with water and then repeatedly with ethyl acetate to extract the organic component. All of the washings and extracts were poured into a separatory funnel, large volumes of water and ethyl acetate were added, and the dark brown reaction product shaken into solution. The ethyl acetate layer was washed twice with water, filtered through sodium sulfate, and evaporated to dryness *in vacuo* to give 75 mg. of a brown powder.

This crude amidation product was added to a mixture of 7.5 ml. of glacial acetic acid, 7.5 ml. of concd. HCl and 5 drops of water, and the solution refluxed for 50 minutes. The hot mixture was poured into water in a separatory funnel, the flask washed with ethyl acetate, and the washings combined with the diluted aqueous mixture. A large volume of ethyl acetate was added and the product isolated as above to give 44 mg. of an orange-brown solid. Repeated recrystallization from a small volume of dimethylformamide gave 7 mg. of orange-brown needles of the (±)-amide, dec. *ca.* 250°. The infrared spectrum, the ultraviolet spectrum (Fig. 3), biological activity toward *S. aureus*, and the chromatographic behavior[47] of this synthetic amide 38 were identical with the corresponding properties of dextrorotatory amide 40 derived (*vide infra*) from the natural antibiotic 6-demethylchlorotetracycline.

(47) Chromatography was carried out on a column of Cellte (registered trade-mark for diatomaceous silica produced by Johns-Manville Corp.) using the solvent system ethyl acetate–ethylene glycol–0.5% aqueous sodium carbonate (150:75:40).

(+)-**Dedimethylamino-12a-deoxy-6-demethyl-anhydro-7-chlorotetracycline (40).**—A solution of 3.75 g. of sodium acetate in 322 ml. of acetic acid and 138 ml. of water was stirred with nitrogen passing through, and 23 g. of 6-demethyl-7-chlorotetracycline hydrochloride was added. After a clear solution was obtained, zinc dust (27 g. total) was added in portions every hour for 7 hours. The excess zinc was then removed by filtration annd the filtrate was added with stirring to 6 l. of 0.1 *N* hydrochloric acid. The precipitated dedimethylamino-12a-deoxy-6-demethyl-7-chlorotetracycline (39) was filtered, washed well with water and after drying weighed 15.5 g.

To a solution of 5 g. of this crude intermediate in 100 ml. of acetic acid was added 10 ml. of 31% hydrobromic acid in acetic acid, and the mixture was warmed at 60–70° for 20 minutes. After cooling, the dark reddish precipitate was filtered, washed with acetic acid, then ether, and dried (3.67 g.). This material was crystallized twice from dimethylformamide (first from 70 ml. and then from 40 ml.) and yielded 1.58 g. of pure product, $[\alpha]^{25}D$ + 1670° (*c* 0.029 in dimethylformamide). The formation of different types of crystals during these crystallizations was shown to be related to the speed of cooling of the hot solution.

Anal. Calcd. for $C_{19}H_{14}O_6ClN$: C, 58.85; H, 3.64; N, 3.60; Cl, 9.15. Found: C, 59.15; H, 3.89; N, 3.87; Cl, 8.89.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL.]

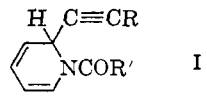
Reaction of Silver Acetylide with Acylpyridinium Salts: N-Benzoyl-2-phenylethynyl-1,2-dihydropyridine[1]

BY TOSHIO AGAWA[2] AND SIDNEY I. MILLER

RECEIVED APRIL 7, 1960

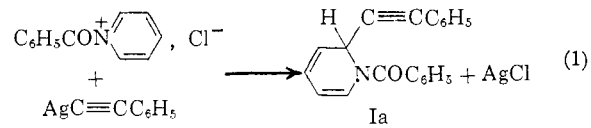
The reaction between certain halides, pyridine and silver acetylides leads to the system N-acyl-2-alkynyl-1,2-dihydropyridine(I) as well as acylacetylenes as co-products. Basic hydrolysis of I gives the alkenylpyridines (III), RCH=CH(2-C_5H_4N), while potassium hypobromite and possibly acid hydrolysis gives the alkynes, RC≡C(2-C_5H_4N): these constitute new paths to these unsaturated compounds. Reaction of the diene I with maleic anhydride leads to the isoquinuclidine system (2-azabicyclo[2·2·2]-7-octene) from which the azabicyclo[2·2·2]octadiene can be made.

We wish to report on a novel system



I

formed by nucleophilic attack on a pyridinium salt. Typically, the reaction is

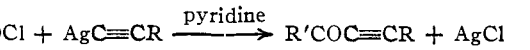


(1)

Ia

The product, N-benzoyl-2-phenylethynyl-1,2-dihydropyridine (Ia), shows the properties of a diene, an amide, an alkyne and of an active hydrogen compound. Since there is no immediate precedent for 1, it is worthwhile to point out two other possible reaction paths.

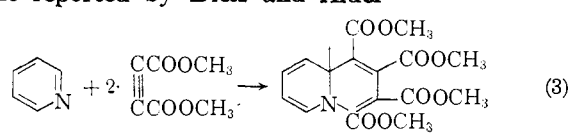
Originally we hoped to exploit our finding that silver phenylacetylide is soluble in pyridine by effecting coupling reactions with halides, *e.g.*



(2)

Recently, Davis and Sheiber found that certain silver acetylides, *e.g.*, 1-butyl, were soluble and that others, *e.g.*, methyl or phenyl, were insoluble in carbon tetrachloride, chloroform and benzene.[3] In solution they found that these acetylides react according to 2, although in some instances aluminum chloride was a necessary co-reactant. In the present study we found that reaction 2 is a minor reaction path in the solvent pyridine, at least for the silver phenyl- or butylacetylides.

To account for the absence of 2, we first speculated that our reaction might be related to a curious one reported by Diels and Alder[4]



(3)

II

Attempts to effect a reaction between benzoylphenylacetylene or phenyl 1-hexnyl ketone and

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(2) Present address: Faculty of Engineering, Osaka University, Osaka, Japan.

(3) R. B. Davis and D. H. Scheiber, THIS JOURNAL, **78**, 1675 (1956).

(4) (a) O. Diels and K. Alder, *Ann.*, **498**, 16 (1932); **505**, 103 (1933); (b) R. M. Acheson and G. A. Taylor, *Proc. Chem. Soc.*, 186 (1959).