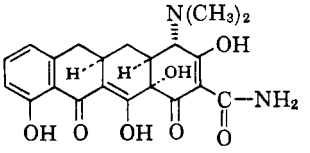
Tetracyclines. V.[1] A Total Synthesis of (±)-6-Deoxy-6-demethyltetracycline

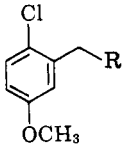
Sir:

6-Deoxy-6-demethyltetracycline (I) is the simplest degradation product of a tetracycline antibiotic which shows full biological activity.[2] This compound has been synthesized recently by Woodward, *et al.*[3] We wish to announce that we have finished a different total synthesis of this compound which for the first



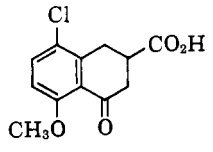
I

time allows tetracyclic compounds to be prepared on a large scale. Starting material for our synthesis was 1-chloro-2-bromomethyl-4-methoxybenzene (IIa).[4] This compound was condensed in methanol with dimethyl

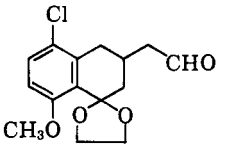


IIa, R = Br
b, R = $C(CO_2CH_3)_2CH_2CO_2CH_3$
c, R = $C(CO_2H)_2CH_2CO_2H$
d, R = $CH(CO_2H)CH_2CO_2H$

carbomethoxysuccinate in the presence of sodium methoxide. The corresponding condensation product IIb (m.p. 81–83°)[5] was saponified with sodium hydroxide to the tricarboxylic acid IIc (m.p. 172–174° dec.) and subsequently decarboxylated by heating to 160°. The resulting dicarboxylic acid IId (m.p. 136–138°) was isolated in 85% yield without isolation of IIb by running all reactions in one flask and simply drying and decarboxylating the crude IIc in an oven at 160°. Cyclization of IId with polyphosphoric acid (ρ 1.92) for 1 hr. at 80° led in almost quantitative yield to the tetralone III. This compound had previously been transformed into the aldehyde IV in excellent yield.[1]



III

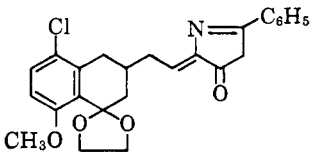


IV

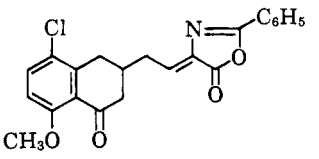
Condensation of the aldehyde of IV with hippuric acid in acetic anhydride with lead acetate as catalyst yielded the condensation product V (m.p. 196–198°; $\lambda\lambda_{max}$ mμ (ε); 233 (20,000) and 299 (25,800) in CH_3CN).

Careful deketalization of V in tetrahydrofuran and hydrochloric acid at room temperature resulted in the formation of VI (m.p. 155–158°; $\lambda\lambda_{max}$ mμ (ε): 222 (33,300), 242 (16,600), 255 (10,300), and 299 (26,100) in CH_3CN).

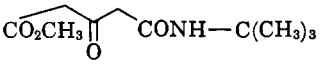
Dissolution of this compound in a mixture of tetrahydrofuran and ethyl ether and addition of methyl N-*t*-butyl-3-oxoglutaramate (VII) and then 2 equiv. of sodium hydride yielded, after a reaction time of 24 hr. at 35°, a mixture of the two C-4 epimeric tetracyclic compounds (VIII) in 82%[6] yield (m.p. 193–245° dec.; $\lambda\lambda_{max}$ mμ (ε): 220 (30,800), 303 (9,300), 463 (47,500), and 487 (38,500), in MeOH–0.1 *M* $Na_2B_4O_7$, after 2-hr. equilibration). Since the starting material for this unusual reaction[7] can be conveniently prepared on a large scale, the tetracyclic compounds VIII are available in substantial quantity.



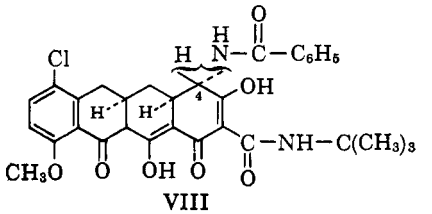
V



VI



VII



VIII

Thin layer chromatography of crude VIII (benzene–ethyl acetate, 4:1) showed, instead of the expected two spots, four spots. When, however, the crude material was held in the solvent mixture for 12 hr. prior to chromatography, only two spots appeared. This indicated clearly that initially we were dealing not only with the two C-4 epimers of VIII but also with different tautomers, which equilibrated on standing in the solution.[8] We were able to isolate one C-4 epimer of VIII in pure form (m.p. 241–247° dec.; $\lambda\lambda_{max}$ mμ (ε): 220 (29,700), 303 (9,500), 462 (50,000), and 488 (41,500) in MeOH–0.1 *M* $Na_2B_4O_7$ after 2-hr. equilibration).

In order to remove the N-benzoyl group crude VIII was treated with Meerwein's reagent[9] and subsequently in dioxane solution with 3% acetic acid in water to yield the pair of C-4 epimers (IXa) which crystallized

(1) Tetracyclines. IV. H. Muxfeldt, E. Jacobs, and K. Uhlig, *Chem. Ber.*, **95**, 2901 (1962).

(2) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *J. Am. Chem. Soc.*, **82**, 3381 (1960).

(3) L. H. Conover, K. Butler, J. D. Johnston, J. J. Korst, and R. B. Woodward, *ibid.*, **84**, 3222 (1962).

(4) J. H. Boothe, A. S. Kende, T. L. Fields, and R. G. Wilkinson, *ibid.*, **81**, 1006 (1959).

(5) All melting points were taken on a Kofler hot plate microscope. All analytical data (C, H, Cl, and, if necessary, OCH_3, N, S, and B) are in agreement with the structures proposed.

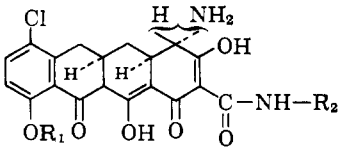
(6) The formation of C-4a epimers was excluded by examination of the ultraviolet and visible spectra of the crude reaction mixture. This result was anticipated in the light of earlier experiences; *cf.* H. Muxfeldt W. Rogalski, and K. Striegler, *Chem. Ber.*, **95**, 2581 (1962).

(7) This reaction is rather complex and involves a general reaction between azlactones and derivatives of acetonedicarboxylic acid discovered recently in this laboratory: H. Muxfeldt, *Angew. Chem.*, **74**, 825 (1962); H. Muxfeldt, W. Rogalski, F. G. Kathawala, G. Grethe, and J. Behling, Abstracts, IUPAC Symposium, Kyoto, Japan, April 1964, p. 142.

(8) In all formulas of tetracyclic compounds the degree and direction of enolization are drawn arbitrarily.

(9) H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. prakt. Chem.*, (2) **147**, 257 (1936).

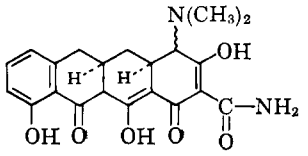
with $0.5B(OH)_3$ (m.p. 185–206° dec.; $\lambda\lambda_{max}$ mμ (ϵ): 240 (12,500), 272 (10,800), 300 (11,200), 464 (44,000), and 490 (34,900) in MeOH–0.1 *M* $Na_2B_4O_7$ after 2-hr. equilibration).



IXa, $R_1 = CH_3$; $R_2 = C(CH_3)_3$
b, $R_1 = R_2 = H$

Treatment of IXa with HBr in acetic acid on a steam bath resulted in the formation of the epimeric pair (IXb) which was crystallized as the hydrobromide (dec. above 255°; $\lambda\lambda_{max}$ mμ (ϵ): 272 (8,600), 287 (7,500), 471 (47,000), and 497 (34,100) in MeOH–0.1 *M* $Na_2B_4O_7$ after 2 hr.).

In order to alkylate the nitrogen in IXb, this compound was hydrogenated in methanol in the presence of 2 equiv. of triethylamine and an excess of formaldehyde with palladium-on-charcoal catalyst. By this procedure compound X was formed, crystallizing with 1 mole of dimethyl sulfoxide from dimethyl sulfoxide



X

and acetone (m.p. 216–223° dec.; $\lambda\lambda_{max}$ mμ (ϵ): 312 (6,100), 470 (46,800), and 496 (36,400) in MeOH–0.1 *M* $Na_2B_4O_7$ after 2 hr., 248 (16,000), 380 (12,600), 471 (20,200), and 495 (17,500) in MeOH–0.01 *N* NaOH after 14 min.). Both spectra are identical with spectra of optically active X, prepared by degradation of 6-demethyltetracycline, taken under exactly the same conditions.[10] The infrared absorption spectrum of synthetic X in KBr is identical with that of the known racemic synthetic X[3,11] but differs from optically active X prepared by degradation. Paper chromatographic behavior of synthetic X and X prepared by degradation is identical in several different solvent systems.

Compound X has already been transformed into racemic 6-deoxy-6-demethyltetracycline (I)[3] and can also be oxidized to this compound by the method developed in this laboratory[12] with platinum and oxygen.[13] It might be pointed out that resolution of the racemic mixture of either I or X seems to be extremely difficult, due to rapid equilibration at C-4. We have, therefore, resolved III. The transformation of optically active III into I will be the subject of a subsequent paper.

Acknowledgment. We thank Dr. Günter Grethe for the preparation of methyl N-*t*-butyl-3-oxoglutaramate and gratefully acknowledge financial support by the National Institutes of Health (Grant No. AI-04221-03 MCHA), the National Science Foundation (Grant No. 19 242), the Hofmann-LaRoche Anniversary Foundation, and Chas. Pfizer and Company, Inc.

(10) The spectrum of X in 0.01 *N* methanolic sodium hydroxide differs somewhat from the published spectrum.[3] This is due to the rapid change of the spectrum with time.[3]

(11) We wish to express our thanks to Dr. J. J. Korst for sending us his ultraviolet and infrared spectra. For the comparison of the infrared spectra a sample containing no dimethyl sulfoxide was used.

(12) H. Muxfeldt, G. Buhr, and R. Bangert, *Angew. Chem.*, **74**, 213 (1962); *Angew. Chem. Intern. Ed. Engl.*, **1**, 157 (1962).

(13) It has been reported erroneously and without our knowledge by a reporter in *Angew Chem.*, **76**, 791 (1964), that I has been synthesized by us in a different way.

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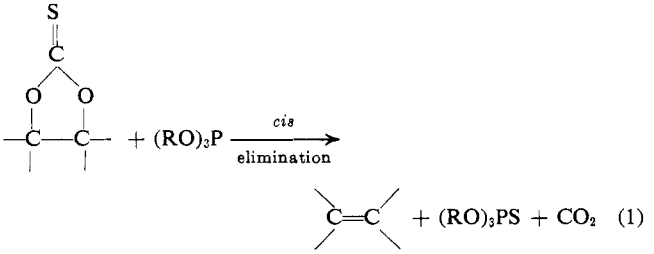
Stereospecific Syntheses of Olefins from 1,2-Thionocarbonates and 1,2-Trithiocarbonates. *trans*-Cycloheptene

Sir:

A new stereospecific and orientationally specific synthesis of olefins from 1,2-thionocarbonates which proceeds according to eq. 1 has recently been reported from this laboratory.[1] In this note we present some new results which illustrate the power of the method as



(1)

applied to the synthesis of relatively unstable olefins and a further generalization of the approach to the analogous elimination of $[CS_3]$ from 1,2-trithiocarbonates.

cis-1,4-Diphenyl-2-butene was synthesized stereospecifically from the thionocarbonate derivative of *meso*-1,4-diphenyl-2,3-butanediol[2,3] (96% yield) by heating at reflux with trimethyl phosphite for 50 hr. with no evidence for formation of the thermodynamically more stable 1,4-diphenyl-1-butene by isomerization. Similarly, pure *trans*-1,4-diphenyl-2-butene was prepared from the corresponding racemic butane-2,3-diol in 99% yield without isomeric contaminants. Bicyclohexylidene was obtained free of isomeric impurities in 95% yield from the thionocarbonate derivative[4] of cyclohexanone pinacol.

Treatment of *trans*-1,2-cyclooctene thionocarbonate with triisooctyl phosphite at 135° for 24 hr. using a steady stream of argon through the reaction mixture to effect rapid removal of the volatile product afforded *trans*-cyclooctene of >99% purity (by v.p.c. analysis)

(1) E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

(2) Satisfactory elemental analyses and molecular weight data were obtained for all new compounds reported here. In addition the structures assigned are fully indicated by infrared and n.m.r. spectra. Homogeneity was established by v.p.c. or thin layer chromatographic analysis.

(3) Prepared from the diol and N,N'-thiocarbonyldiimidazole; see ref. 1 and H. A. Staab and G. Walther, *Ann.*, **657**, 98 (1962).

(4) This derivative was prepared from the dipotassium salt of the pinacol by sequential treatment in dry dioxane with 1 equiv. of carbon disulfide at 70° for 15 min. and 1 equiv. of methyl iodide at 0° initially, with gradual heating in a bath at 70° for 5 min. (see ref. 1). The thiocarbonyldiimidazole procedure is unsatisfactory for hindered diols such as the pinacols derived from ketones.