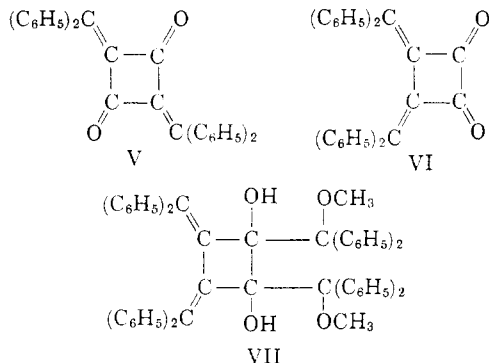


ever, by lithium aluminum hydride yielded tris-(diphenylmethylene)-cyclobutanol (IV).<sup>10</sup>

Diozonolysis of II in chloroform-methanol at  $-55^\circ$  gave 2,4-bis-(diphenylmethylene)-1,3-cyclobutanedione (V, 10–12%), 3,4-bis-(diphenylmethylene)-1,2-cyclobutanedione (VI, 2%), benzophenone, and 3,4-bis-(diphenylmethylene)-1,2-bis-(methoxydiphenylmethyl)-1,2-cyclobutanediol (VII, 35%). The structure of V is based on its analysis, the normal n.m.r. of its phenyl groups (2.68 $\tau$ ),



its *unsplit* carbonyl absorption (5.73 $\mu$ ), its intense ultraviolet absorption, and its stability to semicarbazide, 2,4-dinitrophenylhydrazine, hydrogen peroxide, *o*-phenylenediamine, and heat. Reduction of V by lithium aluminum hydride gave 2,4-bis(diphenylmethylene)-1,3-cyclobutanediol (VIII, 43%),<sup>12</sup>

Vicinal diketone VI<sup>13</sup> is a yellow fluorescent solid which exhibits split carbonyl absorption (5.78 and 5.88  $\mu$ ) as do related *cis*- $\alpha$ -diketones.<sup>14</sup> The instability of VI as compared to II is indicated by its reactivity with ethanol at 25–30 $^\circ$  and its decomposition upon recrystallization from hexane or ethyl acetate. Additional study of VI has been limited by its unavailability.

Dimethoxydiol VII is the principal product (35%) of diozonolysis of II in methanol-chloroform; VII apparently is formed *via* epoxidation

(10) White crystals, m.p. 205–206 $^\circ$ ; *anal.* calcd. for  $C_{43}H_{32}O$ : C, 91.49; H, 5.68. Found: C, 91.54; H, 5.78.

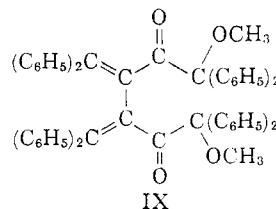
(11) White crystals, m.p. 252.5–253 $^\circ$ ; *anal.* calcd. for  $C_{30}H_{20}O_2$ : C, 87.35; H, 4.89. Found: C, 87.50; H, 4.76. Strong infrared absorption of V occurs at 13.9  $\mu$  (analogous to that in III; there was no absorption for ketene or allene groups); its ultraviolet absorption (cyclohexane) occurred at 224 (32,500), 256 (5,220), 308 (230), 324 (300) and 362 (280).

(12) White needles, m.p. 285.5–286.5 $^\circ$ . *Anal.* Calcd. for  $C_{30}H_{24}O_2$ : C, 86.51; H, 5.81. Found: C, 86.50; H, 6.10; ultraviolet absorption (95% ethanol) at 201 (1330), 264 (1300) and 272 (870).

(13) M.p. 182–183 $^\circ$ ; *anal.* calcd. for  $C_{30}H_{20}O_2$ : C, 87.35; H, 4.89. Found: C, 87.21; H, 5.19; ultraviolet absorption (cyclohexane) at 258 sh (11,000), 307 (5,540), 376 max. (7,300) and 392 sh (6,780).

(14) (a) Bicyclo[2.2.1]heptane-2,3-dione,<sup>14b</sup> 3,4-dibenzylidene-1,2-cycloalkanediones ( $n$  = ring size of 7 to 14),<sup>14c</sup> diphenylcyclobutanediolquinone<sup>14d</sup> and benzocyclobutanediolquinone<sup>14e</sup> are yellow and exhibit split carbonyl absorption whereas biacetyl shows only an *unsplit* sharp peak. (b) K. Alder, H. K. Schafer, H. Esser, H. Krieger and R. Reubke, *Ann.*, **593**, 23 (1955). (c) N. J. Leonard, J. C. Little and A. J. Kresge, *J. Am. Chem. Soc.*, **79**, 6436 (1957). (d) A. T. Blomquist and E. A. LaLancette, *ibid.*, **83**, 1387 (1961). (e) R. Pohl, private communication. (f) The carbonyl stretching frequencies in V and VI are at 5.73 and 5.78–5.88  $\mu$ , respectively, whereas that of diphenylcyclobutanediolquinone, benzocyclobutanediolquinone and related cyclobutenones occur at  $\sim 5.6$   $\mu$ . One wonders if there are 1,3- and 2,4-transannular interactions in V and VI (and in II) giving them tetrahedronic character.

and methanolysis at two benzhydrylidene centers.<sup>15a</sup> The structure of VII is based on its analysis, methoxyl content and its oxidative-cleavage by lead tetraacetate to 3,4-bis-(diphenylmethylene)-1,6-dimethoxy-1,1,6,6-tetraphenyl-2,5-hexanedione (IX, 51%).<sup>15b</sup> The positions of the *vicinal* hy-



droxyl groups in VIII agree with the observation that benzophenone is not obtained from the oxidation. The structure assigned to X is consistent with its analysis, methoxyl content, and spectra.

Synthesis of II<sup>16,17</sup> and photochemical reactions of other butatrienes are being studied.<sup>17</sup>

(15) (a) White crystals, m.p. 256–259 $^\circ$ ; *anal.* calcd. for  $C_{44}H_{34}O_4$ : C, 86.11; H, 5.98;  $CH_3O$ , 7.67. Found: C, 86.10; H, 6.01;  $CH_3O$ , 7.54. Ultraviolet absorption (cyclohexane): 245 sh (18,500), 265 sh (10,000). (b) White plates, m.p. 196–197 $^\circ$ ; *anal.* calcd. for  $C_{44}H_{34}O_4$ : C, 86.36; H, 5.78;  $CH_3O$ , 7.69. Found: C, 86.34; H, 5.93;  $CH_3O$ , 7.79;  $>C=O$  stretching, 5.84  $\mu$ ; ultraviolet absorption (cyclohexane): 315 (1030).

(16) Private communication from Dr. G. W. Griffin, Yale University, New Haven, Conn.

CHEMISTRY DEPARTMENT  
THE OHIO STATE UNIVERSITY  
COLUMBUS, OHIO  
CENTRAL RESEARCH DEPARTMENT  
MINNESOTA MINING AND MANUFACTURING CO.  
ST. PAUL, MINN.

R. O. UHLER  
H. SHECHTER<sup>17</sup>  
G. V. D. TIERS

RECEIVED JULY 9, 1962

# THE CHEMISTRY OF PHOTODIMERS OF MALEIC AND FUMARIC ACID DERIVATIVES. IV.<sup>1</sup> TETRAMETHYLENOCYCLOBUTANE

Sir:

We wish to report the successful formation of tetramethylenecyclobutane (Ia) from a variety of precursors. This hydrocarbon has been predicted by the HMO treatment to possess substantial delocalization energy<sup>2</sup> and represents a possible precursor for substituted cyclobutadienes.<sup>3</sup> Only one previous description of a compound related to Ia, namely, octaphenyltetramethylenecyclobutane (Ib) is recorded. The latter compound was prepared by photodimerization of tetraphenylbutatriene.<sup>4</sup>

Pyrolysis of the amine oxide IIb (*cis*, *trans*, *cis*) at 250 $^\circ$  (1 mm. nitrogen) affords Ia which was collected in hexane at  $-70^\circ$ . The hexane solution of Ia then was distilled ( $< 0^\circ$ , 0.02 mm.)<sup>5</sup> to remove polymers and incompletely pyrolyzed products such as IVa retaining polar amine oxide groups.

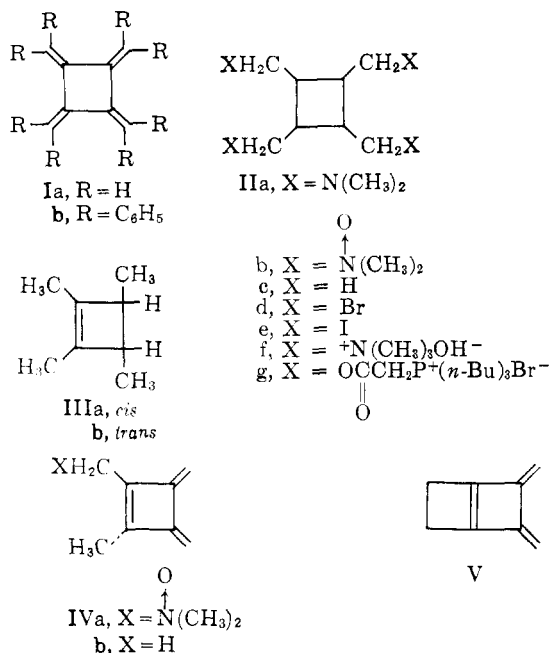
(1) For the last two papers in this series see G. W. Griffin, R. B. Hager and D. F. Veber, *J. Am. Chem. Soc.*, **84**, 1008 (1962), and G. W. Griffin, J. E. Basinski and L. I. Peterson, *ibid.*, **84**, 1012 (1962).

(2) J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, *ibid.*, **74**, 4579 (1952).

(3) A. T. Blomquist and Y. C. Meinwald, *ibid.*, **81**, 667 (1959).

(4) H. Shechter and R. O. Uhler, *Dissertation Abstr.*, **21**, 765 (1960).

(5) Prior to distillation this solution was washed with 0.5 N HCl to remove dimethylhydroxylamine formed during pyrolysis.



The distillate, when cooled to  $-70^{\circ}$ , deposits the tetramethylenecyclobutane in the form of white crystals which redissolve in the hexane without apparent polymerization on warming to room temperature. Insoluble polymers will form, however, if Ia is allowed to stand in the crystalline state even at  $-70^{\circ}$  for relatively short periods. That the pyrolysis product of Ia is indeed tetramethylenecyclobutane is shown by the results of hydrogenation, as well as infrared, ultraviolet and mass spectral analysis.

The mass spectrum of Ia determined in hexane exhibits the expected peak at  $m/e = 104$  (parent), which is not present in the spectrum of the solvent.

As expected,<sup>6</sup> hydrogenation of the distilled hexane solution of Ia, employing platinum-on-charcoal catalyst, afforded *cis,cis,cis*-1,2,3,4-tetramethylcyclobutane (IIc) which was isolated by gas chromatography on a Carbowax 20M preparative column.<sup>7</sup> The infrared spectrum<sup>8</sup> of IIc is identical with that of the hydrocarbon obtained by Criegee in the catalytic reduction of *cis*-1,2,3,4-tetramethylcyclobutene (IIIa) and assigned the *cis,cis,cis*-configuration.<sup>9</sup> The mass spectrum of IIc shows the expected parent peak at  $m/e = 112$  and a fragment peak of about equal intensity at  $m/e = 56$ .

Dilute solutions of tetramethylenecyclobutane also may be generated in ethanol from a variety of 1,2,3,4-tetrahalomethylcyclobutanes of different stereochemistry by treatment with sodium ethoxide. For example, both *cis,trans,cis*-1,2,3,4-tetrabromomethylcyclobutane (IIId) and *trans,trans,trans*-tetraiodomethylcyclobutane (IIe) are converted

slowly to Ia by reaction with sodium ethoxide in ethanol at room temperature.<sup>10</sup>

The ultraviolet spectra of Ia, obtained from two different sources, are reproduced in Fig. 1. Absorption occurs at 324 (0.08), 310 (0.25), 294 (0.84), 280 (1.40), 270 (1.54), 261 (1.40) and 208 (10.00) m $\mu$ . The figures in parentheses indicate the intensities relative to a reference band at 208 m $\mu$  (possibly false and thus not shown in Fig. 1) which has

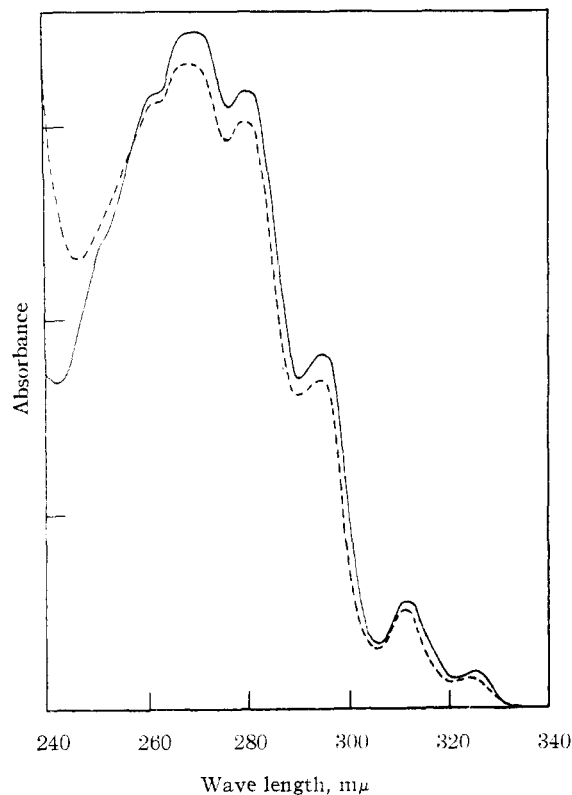


Fig. 1.—Ultraviolet spectra of tetramethylenecyclobutane generated from the amine oxide IIb (solid line, hexane) and the tetraiodide IIe (dashed line, ethanol). The scale on the ordinate has been omitted since exact concentrations are unknown.

a minimum extinction coefficient of 49,500. This figure must represent a minimum value for the extinction coefficient since it was determined by assuming quantitative conversion of a weighed sample of *trans,trans,trans*-1,2,3,4-tetraiodomethylcyclobutane to Ia. The absence of intense absorption in the 245–248 m $\mu$  region, reported to be characteristic of dimethylenecyclobutenes,<sup>11</sup> provides added assurance that IVa and IVb, as well as the highly unlikely structure V, can be excluded from serious consideration as alternate possibilities, even though they might conceivably be formed under the reaction conditions and would account for the experimental observations.

(6) R. L. Burwell, Jr., *Chem. Reviews*, **57**, 895 (1957).

(7) Wilkens Instrument and Research, Inc., Walnut Creek, California.

(8) The infrared spectrum in carbon tetrachloride of IIc (*cis,cis,cis*) exhibits significant absorption bands at 2971 (s), 2922 (s), 2880 (s), 1465 (m), 1450 (m), 1388 (m), 1372 (m), 1332 (w), 1316 (w), 1015 (m-w), 1000 (m-w), 965 (w) and 705 (w) cm<sup>-1</sup>.

(9) R. Criegee and K. Noll, *Ann.*, **627**, 1 (1959).

(10) The preparation of IIId and IIe will be reported in a later communication.

(11) J. K. Williams and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 4269 (1959); A. T. Blomquist and P. M. Maitlis, *Proc. Chem. Soc.*, 332 (1961).

The infrared spectrum of a dilute solution of tetramethylenecyclobutane in carbon tetrachloride shows a sharp intense peak at  $880\text{ cm}^{-1}$  which is near the characteristic region for the hydrogen out of plane deformations in terminal disubstituted olefins.<sup>12</sup> This band is replaced by one at  $855\text{ cm}^{-1}$  when the carbon tetrachloride solution is allowed to stand for 24 hours at room temperature. The latter band may arise from terminal methylenic groups in low molecular weight polymers. Other characteristic bands in the infrared spectrum of tetramethylenecyclobutane appear at  $3095\text{ (w)}$ ,  $1705\text{ (w)}$  and  $1400\text{ (m-w)}$   $\text{cm}^{-1}$ . The absorption band at  $1705\text{ cm}^{-1}$  also diminishes on polymerization while new bands appear at  $1675$ ,  $1730$  and  $1640\text{ cm}^{-1}$ .

Difficulties were encountered in all attempts to determine accurately the degree of unsaturation in Ia, by hydrogenation, because of problems associated with establishing accurately the concentration of the tetramethylenecyclobutane in dilute solution. Catalytic deuteration and mass spectral analysis were seen as a possible means of circumventing this problem. All experiments in this direction, however, were complicated by deuterium-hydrogen exchange. Similar exchange under a variety of solvent and catalyst conditions was noted in control experiments with cyclooctatetraene.

On warming to room temperature in air, or on prolonged storage at  $0^\circ$ , there deposited from a hexane solution of Ia polymeric material whose combustion analysis indicated incorporation of oxygen. Similar observations have been made by Blomquist on dimethylenecyclobutene, a related system.<sup>11</sup> Furthermore, the tendency to polymerize is in qualitative agreement with calculations of the "free valence index" for Ia.<sup>2</sup> A value of 0.88 was predicted at the termini of the methylene groups. For comparison, the predicted index for *p*-xylylene is 0.92, and while the latter is stable in the gas phase, it also polymerizes rapidly in solution.<sup>2,13</sup>

Pyrolysis of the tetraquaternary salt III<sup>1</sup> at temperatures between  $120$ – $250^\circ$  provided low yields of a mixture which, from its ultraviolet spectrum, appears to contain Ia possibly contaminated with a dimethylenecyclobutene such as IVb. Similarly, the phosphonium salt IIg affords Ia on pyrolysis at  $155^\circ$ .<sup>14</sup> The product (Ia) which, from its ultraviolet spectrum, appears homogeneous, is obtained in only trace amounts from this precursor. Other studies on the physical and chemical properties of Ia are in progress.

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CONTRIBUTION NO. 1697 FROM GARY W. GRIFFIN  
THE STERLING CHEMISTRY LABORATORY  
YALE UNIVERSITY, NEW HAVEN, CONN.

LAURENCE I. PETERSON

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(12) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, New York, N. Y., 1958, p. 51.

(13) C. A. Coulson, *Discussions Faraday Soc.*, **2**, 7 (1947); *J. Chim. Phys.*, **45**, 243 (1948).

(14) D. B. Deane, C. J. Rossi and J. J. Vill, *J. Am. Chem. Soc.*, **83** 3334 (1961).

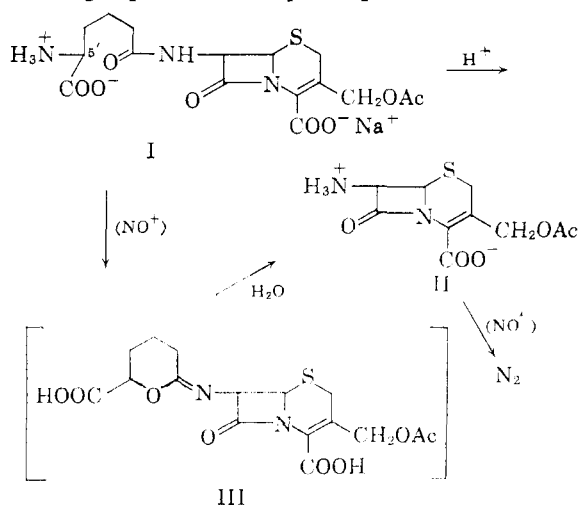
# CHEMISTRY OF CEPHALOSPORIN ANTIBIOTICS. I. 7-AMINOCEPHALOSPORANIC ACID FROM CEPHALOSPORIN C

Sir:

Cephalosporin C (I),<sup>1</sup> an antibiotic isolated in 1956<sup>2</sup> from a species of *Cephalosporium*, possesses greater acid and penicillinase stability than other  $\beta$ -lactam containing antibiotics but much weaker antibacterial action. The antimicrobial activity can be enhanced greatly by N-acylation of 7-aminocephalosporanic acid (7-ACA, II) which has been obtained in a low yield by mild acid hydrolysis of cephalosporin C.<sup>3</sup> However, 7-ACA has not been sufficiently available to evaluate fully this interesting new class of antibiotics.<sup>4</sup>

We wish to report a convenient method of converting cephalosporin C to 7-ACA.

It was felt that the yield of 7-ACA from an acid or base catalyzed hydrolysis is limited by the lability of the molecule under these conditions. A mild, selective cleavage of the aminoadipyl amide might result from a reaction in which an intramolecular interaction of the amide with the  $C_6'$  center in cephalosporin C could occur.<sup>5</sup> Deamination of cephalosporin C causes a cleavage of the amide under mild conditions since treatment of the antibiotic as the sodium salt with excess nitrous acid in acetic acid-water solution gives two moles of nitrogen per mole of cephalosporin C; the second

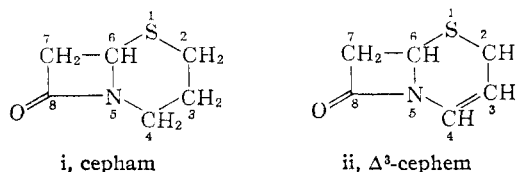


(1) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **79**, 377 (1961); D. C. Hodgkin and E. N. Maslem, *ibid.*, **79**, 393 (1961).

(2) G. G. F. Newton and E. P. Abraham, *ibid.*, **62**, 651 (1956).

(3) B. Loder, G. G. F. Newton and E. P. Abraham, *ibid.*, **79**, 408 (1961).

(4) As a convenience in naming new members of this series, we suggest, in collaboration with Dr. E. P. Abraham, the terms cepham and cephem for the structures i and ii.



This system is in accord with that generally accepted for the penicillins, see footnote 2, J. C. Sheehan, K. R. Henery-Logan and D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3293 (1953).

(5) For a review of facile cleavages of amide bonds by reactions which involve neighboring group participation see L. A. Cohen and B. Witkop, *Angew. Chem.*, **73**, 253 (1961).