$[\alpha]_{500}$ +77°, $[\alpha]_{375}$ +220° (peak), $[\alpha]_{320}$ +10° (trough), $[\alpha]_{250}$ +505°.

24-Oxosolacongestidine O-Acetate (4a).—A solution of 14 mg of **4**, 0.6 ml of anhydrous pyridine, and 0.45 ml of Ac_2O was allowed to stand at room temperature for 3 hr. To the reaction mixture was added ice–water to decompose excess Ac_2O, and the product was extracted with $CHCl_3$. The $CHCl_3$ extract gave 19 mg of amorphous mixture, which was chromatographed on tlc plates (benzene–AcOEt, 2:1). The substance eluted from the R_f 0.85 band (10 mg) was recrystallized from acetone to give prisms (**4a**): mp 200–203°; $\lambda_{max}^{CHCl_3}$ 5.81 (OAc), 5.92 (C=O); mass spectrum 455 (M^+, $C_{29}H_{45}NO_3$), 440, 427, 140, 139, 395, 111; the mass spectrum pattern was almost the same as that of alkamine **4**.

The other component (R_f 0.3) was identified as 24-oxosolacongestidine O,N-diacetate (**4b**). When the reaction time was prolonged for 14 hr, diacetate **4b** was formed predominantly.

24-Oxosolacongestidine O,N-Diacetate (4b).—**4** (90 mg) in 5 ml of Ac_2O was refluxed under N_2 for 1 hr. The reaction mixture, worked up in the conventional way, yielded 0.1 g of powder, which crystallized from Me_2CO to afford 22 mg of prisms (**4b**) of mp 184–187°; λ_{max}^{EtOH} 275 (log ϵ 3.60); end absorption [222 mμ (log ϵ 3.75)]; $\lambda_{max}^{CHCl_3}$ 5.81 (OAc), 5.94, 6.04, 6.30 (AcNC=CCO), 9.83 μ (CO).

Anal. Calcd for $C_{31}H_{47}NO_4$: C, 74.81; H, 9.52. Found: C, 74.50; H, 9.43.

Data follow: nmr 0.65 (18-CH_3), 0.79 (19-CH_3), 1.13 (d, J = 6.5 cps, *sec*-CH_3), 1.17 (d, J = 7 cps, *sec*-CH_3), 1.98 (OAc), 2.02 (NAc), 5.97 (d, J = 3 cps, C_{23}-H); mass spectrum 497 (M^+), 455, 454, 152, 140, 124.

Alkali Treatment of 24-Oxosolacongestidine.—A solution of 80 mg of **4** in 5 ml of 1% KOH–MeOH was refluxed at 130° (bath temperature) for 4 hr under N_2. After removal of the solvent, and addition of water, the $CHCl_3$ extract gave about 60 mg of amorphous powder[21] (mainly basic and neutral substances). Extraction of the aqueous layer with $CHCl_3$ after acidification with dilute H_2SO_4 yielded about 28 mg of brown powder (acid part). The acidic fraction was purified by tlc (benzene–AcOEt–MeOH, 15:15:4) to afford crystals (**4c**) of mp 255–265°. Treatment of the acid with CH_2N_2 in MeOH–Et_2O overnight afforded methyl ester[22] **4d**: mp 130–145°; $\lambda_{max}^{CHCl_3}$ 2.79, 2.95 (OH), 5.78 (OAc), 8.66, 9.78, 11.72 μ; mass spectrum 362 (M^+), 347, 329, 233, 215, 165, 147. The acid and the ester proved to be 3β-hydroxybisnorallocholanic acid and its methyl ester by comparison with an authentic sample (tlc, ir, glpc, and mass spectrum).

Registry No.—**1**, 984-82-7; **1a**, 19374-52-8; **1b**, 19374-53-9; **1c**, 19398-17-5; **1d**, 19398-18-6; **1e**, 19374-54-0; **1f**, 19374-55-1; **1g**, 19374-56-2; **1h**, 19374-57-3; **2**, 19374-58-4; 2 HCl, 19374-59-5; **3**, 19374-60-8; **4**, 19374-61-9; **4a**, 19398-19-7; **4b**, 19374-62-0.

(21) From the amorphous fraction, about 5 mg of unidentified crystals were obtained by tlc (benzene–AcOEt–MeOH, 15:15:2, R_f 0.6). Crystallization from MeOH–$CHCl_3$ yielded fine needles of mp 275–280°; mass spectra 411 (M^+, strong), 396, 139, 108; nmr 0.77 (18- and 19-CH_3), 2.05 3.55, 4.30, 6.79 ppm; λ_{max}^{MeOH} 254 mμ (ϵ 990), 299 (2520); λ_{max}^{Nujol} 6.12 (sharp, medium), 7.24, 8.03, 8.68, 10.30 μ.

(22) W. Bergman, D. H. Gould, and E. M. Low, *J. Org. Chem.*, **10**, 570 (1945): 3β-hydroxybisnorallocholanic acid, mp 274–276°; methyl ester, mp 151–152.5°. The same alkali treatment of an authentic specimen lowered its melting point to 240–255° (acid) and 125–140° (methyl ester).

Synthesis of Dihydrothiazines Related to Deacetylcephalosporin Lactones. An Alternate Total Synthesis of Deacetylcephalosporin Lactones

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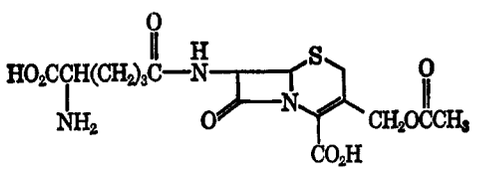
A unique synthesis of dihydrothiazines related to the cephalosporins is based upon the reaction of 2-amino-4-hydroxy-3-(tritylthiomethyl)crotonic acid lactone I with aldehydes to form an imine, followed by acid-catalyzed cyclization with the simultaneous loss of the trityl group. The synthesis has been used to produce a compound [XI, R = $C(CH_3)_3$] which is a known intermediate for the synthesis of deacetylcephalosporin lactones.

The cephalosporin antibiotics are widely recognized as interesting and useful broad spectrum antimicrobial agents. Cephalosporin C was discovered by Abraham



cephalosporin C

and Newton[1] as a result of their studies on the antibiotic components produced by a species of *Cephalosporium* isolated by Brotzu.[2] Classical degradative studies[3] culminated in a tentative structure assignment which received confirmation by X-ray crystallographic studies.[4] Cephalosporin C, the subject of these pioneering studies, was therefore unambiguously assigned its now accepted structure. A recent review[5] has cataloged with clarity and thoroughness the major points of interest in the developing area of cephalosporin antibiotics.

The Squibb Institute has been responsive to the challenge involved in the synthesis of the cephalosporins for some time.[6a] At the present date several approaches of various degrees of success have been described.[6] In common to all of these propositions is the construction of a 1,3-[6H]-dihydrothiazine system. The formation of model 1,3-dihydrothiazines structurally related to cephalosporins has been studied by a number of groups.[6,7]

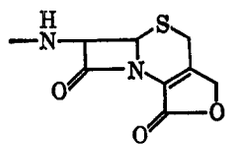
An approach to cephalosporin synthesis which depended upon the preparation of a deacetylcephalosporin lactone, a type represented by the following

(1) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **58**, 266 (1954).
(2) G. Brotzu, *Lav. Ist. Igiene Cagliari*, 1948.
(3) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **79**, 377 (1961).
(4) D. Hodgkin and E. N. Maslen, *ibid.*, **79**, 393 (1901).
(5) E. P. Abraham, *Quart. Rev.* (London), **21**, 231 (1967).

(6) (a) E. Galantay, H. Engel, A. Szabo, and J. Fried, *J. Org. Chem.*, **29**, 3560 (1964); (b) R. Heymés, G. Amiard, and G. Nominé, *C. R. Acad. Sci., Paris*, **263**, 170 (1966); (c) G. Stork and H. T. Cheung, *J. Amer. Chem. Soc.*, **87**, 3783 (1965); (d) R. B. Woodward, K. Heusler, J. Gosteli, P. Nalgeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *ibid.*, **88**, 852 (1966).

(7) See, *inter alia*, G. C. Barrett, V. V. Kane, and G. Lowe, *J. Chem. Soc.*, 783 (1964); D. M. Greene, A. G. Long, P. J. May, and A. F. Turner, *ibid.*, 766 (1964); A. I. Meyers and J. M. Greene, *J. Org. Chem.*, **31**, 556 (1966); J. C. Sheehan and J. A. Schneider, *ibid.*, **31**, 1635 (1966).

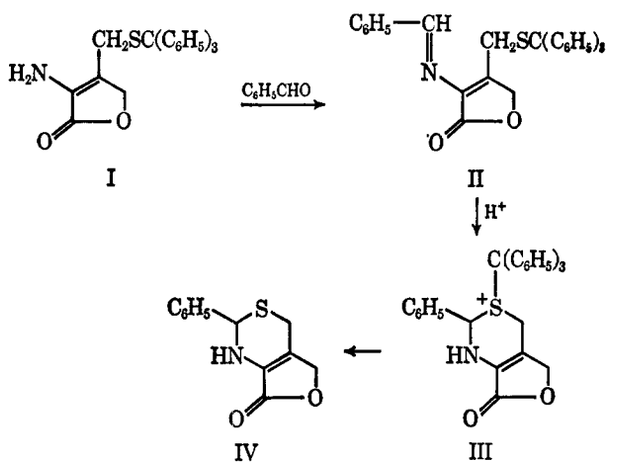
partial structure, had been suggested previously by Squibb scientists.[6a] It was anticipated that opening of



the lactone ring would lead to the formation of the 3-acetoxymethyl and 4-carboxy functions of the natural antibiotic. In a continuation of the earlier work we decided to study the possibilities of using 2-amino-4-hydroxy-3-(tritylthiomethyl)crotonic acid lactone (I) as a precursor of dihydrothiazine lactones.

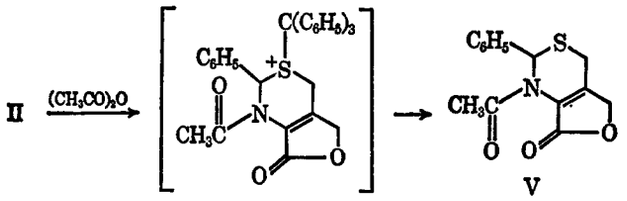
The nucleophilicity of the amino group of aminobutenolide I is low and salt formation with mineral acids does not occur under normal circumstances. However, reaction with aldehydes does occur and the corresponding imines can be obtained in generally high yield by refluxing a benzene solution of the reactants with concomitant removal of water. For example, reaction of amino lactone I with benzaldehyde produces an 88% yield of imine II (Scheme I). It was anticipated that imine II might be utilized directly in an acid-catalyzed reaction to produce dihydrothiazine lactone IV, with the intermediacy of cyclic sulfonium ion III. Indeed, when imine II was subjected to boiling with alcoholic hydrogen chloride the process of cyclization–detritylation occurred readily and the product dihydrothiazine IV crystallized from the solution in 60% yield. The material, mp 180–181°, analyzed correctly for $C_{12}H_{11}NO_2S$ and showed a characteristic lactone carbonyl absorption at 5.70 μ in the infrared spectrum. The ultraviolet spectrum revealed a maximum at 269 mμ (ϵ 4220). The pmr spectrum exhibited a quartet (J = 17.5 Hz) at τ 6.45 (CH_2S), singlet at 5.18 (CH_2O), doublet (J = 4.5 Hz) at 4.56 (benzylic H) and a broad absorption at 5.52 (NH) with a broad aromatic absorption at 2.6. The integrated ratios were in accord with the structure.

SCHEME I



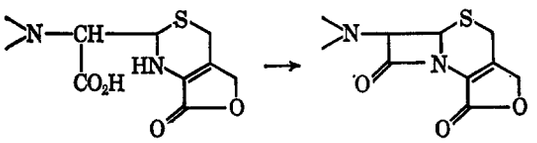
During our work a publication of Stork and Cheung[6c] appeared describing a clever synthesis of the N-acetyl derivative (V) of dihydrothiazine IV. We were able to effect a direct synthesis in 72% yield of the compound by heating imine II with acetic anhydride at 100°, the reaction presumably occurring by Scheme II.

SCHEME II



Our product (V) exhibited spectral values essentially identical with those published by Stork and Cheung. Having developed a reliable and convenient method of synthesis for dihydrothiazines related to the antibiotic, we turned our attention to the more complicated structures which might serve as intermediates in cephalosporin synthesis.

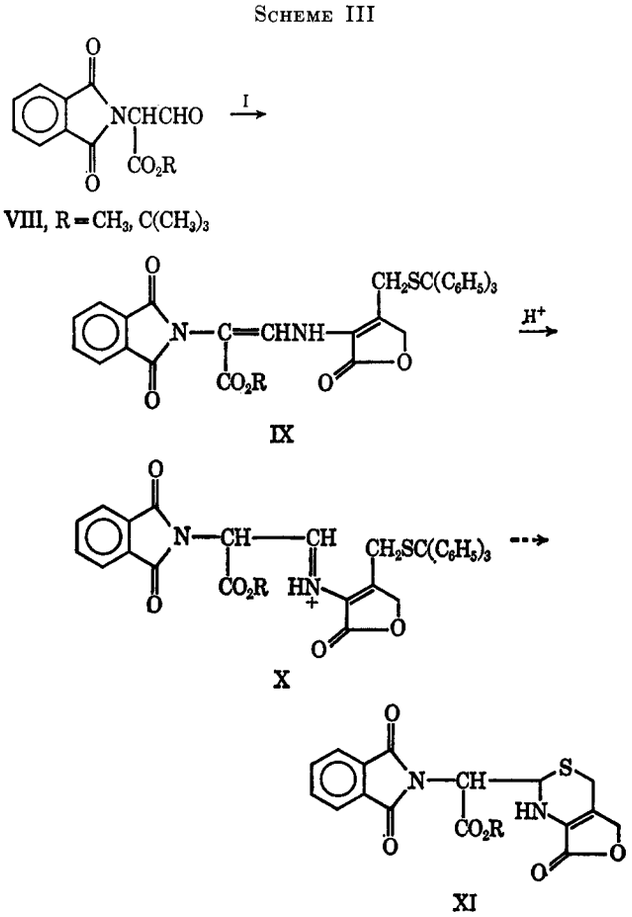
Consistent with the earlier design of the over-all synthetic plan[6a] was the preparation of an acid (VI)



which could logically serve as a precursor for β-lactam VII; there are numerous published methods for cyclizing β-amino acids (and their esters) to β-lactams.

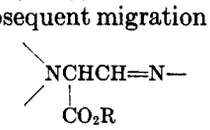
The reaction of α-phthalimidomalonaldehydic esters VIII with amino lactone I gave, as expected, an enamine type of product (IX) (Scheme III). The methyl

SCHEME III



ester (IX, R = CH_3) is readily obtained as *either* the *cis* or *trans*[8] forms depending upon the reaction conditions. In methanol containing a trace of acid, the reaction of methyl α-phthalimidomalonaldehydate (VIII, R = CH_3) with amino lactone I produces a precipitate of the predominantly *trans* form of amino ester IX in 84% yield. The pure material, mp 239–241°, exhibits a pmr spectrum (dimethyl sulfoxide solvent) in which the amino proton absorbs at τ 1.70 and the vinyl proton at 0.90 (J = 13.5 Hz). In contrast, reaction of the substrates in refluxing benzene containing *p*-toluenesulfonic acid produces mainly the *cis* isomer, mp 215–217°. The pmr spectrum absorption of the amino proton appears at τ 0.17 and the vinyl proton at 2.20 (J = 14 Hz). The assignment of the amino protons in both cases was confirmed by deuterium exchange. The downfield shift of the amino proton in the *cis* isomer is consistent with an internally hydrogen bonded structure and is used for the geometric assignment. This method of assignment has been neatly applied by Huisgen[9a] in similar situations. The position of the vinyl hydrogen absorption at a higher relative field in the *cis* isomer (in which this proton is *trans* to the carboxyl group) is consistent with independent correlations in other aminoacrylic esters.[9] The mobility of the *cis* ester possessing an internally hydrogen-bonded structure is greater than the *trans* on thin layer chromatography, an observation circumstantially in accord with the geometric assignments.

The clear stereochemical discrimination is difficult to rationalize on the basis of the formation of an initial aldimine structure (XII), since there is no compelling reason why the subsequent migration of the double bond

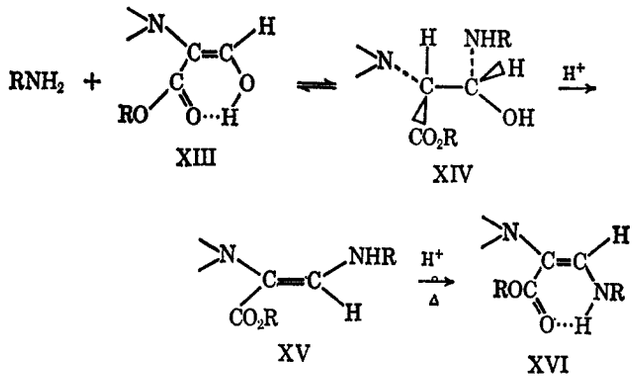


XII

should favor the exclusive formation of the *trans* form in acidic methanol. However, it would seem more appropriate to consider the reaction paths possible on the enol form of the malonaldehydic ester rather than the carbonyl form since pmr measurements in deuteriochloroform or dimethyl sulfoxide-d_6 show a 4:1 ratio favoring the enol. A concerted Michael addition to the hydrogen-bonded enol (XIII) would lead to an *erythro* intermediate (XIV) which upon concerted loss of water would be expected to produce *trans* isomer XV. In light of earlier findings[9a,10] with regard to the stability of β-aminocrotonic esters, it is to be expected that the kinetically produced *trans* isomer XV would be thermodynamically less stable than the *cis* isomer, which tends to be stabilized by hydrogen bonding. It is reasonable then that more energetic reaction conditions (refluxing benzene with *p*-toluenesulfonic acid) would facilitate the accumulation of the more stable *cis* isomer (XVI)[11] (Scheme IV).

The conversion of either the geometric isomers (IX,

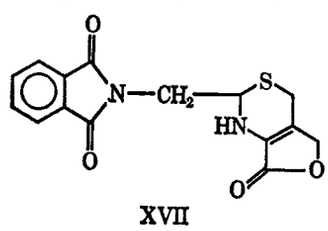
SCHEME IV



XIII XIV XV XVI

R = CH_3) into dihydrothiazines proceeded readily in nitromethane containing hydrogen chloride, a mixture of diastereomers (XI, R = CH_3) being obtained. From the mixtures a crystalline isomer, mp 211–215°, was easily separated. The structure of the material was determined to be of the *erythro* configuration by X-ray crystallographic analysis.[12] The *threo* racemate, corresponding to the natural cephalosporin configuration, remained a glass. However, both of the corresponding carboxylic acids were obtained as pure solids as a result of experiments with the *t*-butyl esters.

Reaction of *t*-butyl α-phthalimidomalonaldehydate [VIII, R = $C(CH_3)_3$] with amino lactone I gave the intermediate [IX, R = $C(CH_3)_3$] as an amorphous solid which does convert easily into the dihydrothiazine system. However, the ring formation may be attended by loss of the *t*-butyl group as well as the carboxyl group and the nature of the isolated product is very much a function of the conditions of reaction, particularly the temperature. A nearly quantitative conversion into the degradation product (XVII) is effected



XVII

by hydrogen chloride in nitromethane at room temperature. Conducting the same reaction at 0° permits only a trace of compound XVII to form, while a 65% yield of diastereomeric acids (XI, R = H) is obtained which can be quite readily separated owing to their differing solubilities and crystallization rates in chloroform. The isomeric acids decarboxylate on heating to 167–175 and 202–208°, respectively, with the final melting point coinciding with that of the decarboxylated compound XVII at 255° in both cases. The process of decarboxylation, crystal reorientation and final melting transitions are best followed and confirmed by differential thermal analysis.[13]

Esterification of the more stable acid (202–208°, $-CO_2$) with diazomethane gave a compound, mp 214–218°, identical (mixture melting point, infrared

(8) *cis* and *trans* here denote the relationship of the ester and β-amino groups.

(9) (a) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Ber.*, **99**, 2526 (1966); (b) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

(10) K. Herbig, R. Huisgen, and H. Huber, *Ber.*, **99**, 2546 (1966); W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).

(11) Thin layer chromatographic analysis of a warm (50°) benzene solution of the *trans* isomer with *p*-toluenesulfonic acid does show an accumulation of a preponderance of the *cis* isomer.

(12) We gratefully acknowledge the skillful cooperation of Professor J. Zanos Gougoutas and his collaborators of Harvard University who performed the structure determinations.

(13) These observations were made using a Du Pont 900 differential thermal analyzer through the courtesy and collaboration of Dr. Harold Jacobson of the Squibb Institute.

spectrum) with the ester previous discussed. The configuration of the less stable acid corresponds to the *threo* compound related to the natural cephalosporins.

When the temperature of the hydrogen chloride–nitromethane cyclization of the *t*-butyl ester [IX, R = $C(CH_3)_3$] is lowered to −20 to −25°, good yields of the *t*-butyl products (XI) may be obtained. Since the conversion of these materials into a racemate of cephalosporin lactones has been reported by French workers,[6b] an alternate total synthesis for the cephalosporin lactones is thus provided.

Experimental Section

All melting points are corrected. Proton magnetic resonance spectra were obtained on a Varian A-60 instrument by Dr. A. I. Cohen and values are reported in τ units using internal tetramethylsilane standard. Microanalytical data were obtained by Mr. J. Alicino and his staff.

2-(Benzylidenamino)-4-hydroxy-3-(tritylthiomethyl)crotonic Acid Lactone (II).—A solution of 1.00 g (2.58 mmol) of 2-amino-4-hydroxy-3-(tritylthiomethyl)crotonic acid lactone[6a] (I) and 550 mg (5.2 mmol) of redistilled benzaldehyde in 25 ml benzene was heated at reflux with a Dean–Stark water separator for 1 hr after which the (cooled) solution was evaporated at reduced pressure. The oily residue was triturated with 7 ml of isopropyl alcohol to induce crystallization and then allowed to stand overnight in the cold room. The crystalline mass was separated by filtration and washed with hexane. In this way 1.07 g (88%) of product, mp 136–143°, was obtained. A recrystallization from isopropyl alcohol gave 840 mg (68%), mp 143–145°. (In earlier experiments a lower melting, less stable polymorph, mp 119–120°, was obtained which proved to be convertible into the higher melting form by crystallizing from a seeded isopropyl alcohol solution.)

Anal. Calcd for $C_{31}H_{25}O_2NS$: C, 78.35; H, 5.30; N, 2.95; S, 6.75. Found: C, 78.85; H, 5.90; N, 2.75; S, 6.93.

3,6-Dihydro-5-(hydroxymethyl)-2-phenyl-2H-1,3-thiazine-4-carboxylic Acid Lactone (IV).—A solution of 100 mg (0.210 mmol) of benzylidene compound II in 5 ml of isopropyl alcohol was obtained by gentle heating and was then acidified to Congo red paper with methanolic hydrogen chloride. The solution was heated to boiling on a steam bath for 30 sec, then allowed to cool. A crystalline mass formed and was subsequently filtered off. The product was obtained as 30 mg (61%) of pure white crystals, mp 180–181°. The pmr spectrum ($CDCl_3$) showed a quartet (J = 17.7 Hz) at τ 6.45; a singlet at 5.18; a doublet (J = 4 Hz) at 4.56; a broad absorption at 5.52. Spin decoupling of the 5.52 absorption resulted in the coalescence of the doublet at 5.18 to a singlet. The ultraviolet spectrum shows $\lambda_{max}^{ethanol}$ 269 mμ (ϵ 4220); the infrared spectrum showed λ_{max}^{KBr} 3.03, 5.80, 5.97 μ.

Anal. Calcd for $C_{12}H_{11}O_2NS$: C, 61.85; H, 4.75. Found: C, 62.15; H, 5.04.

3-Acetyl-3,6-dihydro-5-(hydroxymethyl)-2-phenyl-2H-1,3-thiazine-4-carboxylic Acid Lactone (V).—A solution of 100 mg (0.210 mmol) of benzylidene compound II in 4 ml of acetic anhydride was heated on steam bath under nitrogen for 15 hr. The acetic anhydride was evaporated at reduced pressure leaving a pale yellow gum. The gum was dissolved in benzene and chromatographed on 5 g of Florisil (60–100 mesh). Elution with 50 ml of benzene removed triphenylcarbinol, identified by comparison of its infrared spectrum with that of an authentic sample; elution with chloroform then removed the product as 53 mg (93%) of pale yellow oil, $\lambda_{max}^{CHCl_3}$ 5.63, 5.91, 6.02 μ, values identical with those reported by Stork and Cheung[6c] for the material. Also in agreement was the pmr spectrum ($CDCl_3$) singlet at τ 6.03, quartet at 5.43 (J = 17.5 Hz), singlet at 2.98 and 7.01, aromatic hydrogens as broad singlet at 2.6. The material crystallized from hexane–carbon tetrachloride as 52 mg (72%) of colorless plates, mp 77–79° (lit.[6c] mp 77–78°).

3,6-Dihydro-5-(hydroxymethyl)-2-(phthalimidomethyl)-2H-1,3-thiazine-4-carboxylic Acid Lactone (XVII).—The starting material for this reaction was obtained by heating a solution of 289 mg (1 mmol) of *t*-butyl α-phthalimidomalonaldehydate and 387 mg (1 mmol) of aminobutenolide (I) in 25 ml of benzene under reflux for 4 hr, the water of reaction being removed by a Dean–Stark trap filled with Drierite. The solvent was then evaporated at reduced pressure; the residual gum formed a pale yellow amorphous solid upon trituration with hexane.

The crude intermediate was not purified further but was taken up in 50 ml of nitromethane and treated with a rapid stream of gaseous hydrogen chloride for 15 min at room temperature. Upon concentration of the reaction mixture at reduced pressure, 148 mg (47%) of the product, mp 251–254° dec, was obtained by allowing the residue to crystallize from acetonitrile. The ultraviolet absorption showed λ_{max}^{EtOH} 272 (ϵ 4490) as 218, 230, 239, 290 mμ. The pmr spectrum (CF_3CO_2H solvent) showed a quartet at τ 6.25 (J = 18 Hz), singlet at 4.88, doublet at 5.84, triplet at 4.93, in a ratio of 2:2:1:2:1; the NH absorption is masked owing to solvent exchange.

Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.90; H, 3.82; S, 10.12. Found: C, 56.80; H, 3.89; S, 10.08.

α-{[(2,5-Dihydro-2-oxo-4-(tritylthiomethyl)-3-furyl)amino]-methylene}-1,3-dioxo-2-isoindolineacetic acid *t*-butyl ester [IX, R = $C(CH_3)_3$] was prepared as described in a previous experiment, but the mixture of *cis–trans* isomers could not be purified well. The infrared red spectrum showed $\lambda_{max}^{CHCl_3}$ 2.9–3.0, broad, weak; 5.68, 5.81, 5.97 μ. The material was used in further experiments without purification.

α-{[(2,5-Dihydro-2-oxo-4-(tritylthiomethyl)-3-furyl)amino]-methylene}-1,3-dioxo-2-isoindolineacetic Acid Methyl Ester (IX, R = CH_3), *trans* Isomer.—A solution of 247 mg (1 mmol) of methyl α-phthalimidomalonaldehydate[14] and 387 mg (1 mmol) of amino lactone I in 15 ml of methanol and 5 ml of chloroform was acidified to Congo red with methanolic hydrogen chloride and stirred at room temperature; a precipitate gradually formed. After 1 hr, filtration gave 274 mg (44.5%) of white solid, mp 225–226°. A second crop, mp 214–221°, 238 mg (38.6%), was obtained from mother liquors by evaporating at reduced pressure and trituration with 5 ml of cold methanol. A purified sample (mp 236–238°) could be obtained by crystallization from acetonitrile. The material showed a major spot, R_f 0.33, and a very minor spot, R_f 0.57, on tlc ($CHCl_3$–SiO_2).

Anal. Calcd for $C_{36}H_{28}N_2O_6S$: C, 70.12; H, 4.58; N, 4.55; S, 5.20. Found: C, 69.86; H, 4.76; N, 4.53; S, 5.36.

***cis* Isomer.**—A solution of equimillimolar amounts of the reactants, used in part A, in 30 ml of benzene containing 30 mg of *p*-toluenesulfonic acid hydrate was heated to reflux for 1 hr using a Dean–Stark water separator and then evaporated at reduced pressure. The resulting pale yellow foam solidified upon trituration with 5 ml of cold acetonitrile giving 440 mg (72%) of product, mp 212–213°. A recrystallization of a small sample from acetonitrile gave pure material, mp 214–217°. The mother liquors (from the previous trituration) gave an additional 160 mg (20%), mp 211–215°. A total of 600 mg (97%) of product was obtained. The total material recrystallized from methanol as 485 mg (79%), mp 213–217°. This material on thin layer chromatography showed a major spot, R_f 0.57, and a minor spot, R_f 0.33.

Anal. Calcd for $C_{36}H_{28}N_2O_6S$: C, 70.12; H, 4.58; N, 4.55; S, 5.20. Found: C, 70.23; H, 4.56; N, 4.66; S, 5.33.

1,2,5,7-Tetrahydro-α-phthalimido-7-oxo-4H-furo[3,4-*d*][1,3]-thiazineacetic Acid Methyl Ester (XI, R = CH_3).—A suspension of 1.90 g (3.08 mmol) of *trans* isomer unsaturated ester (IX) in 250 ml of nitromethane was saturated with a rapid stream of hydrogen chloride for 15 min, a yellow solution being obtained. The reaction was stirred for a total of 1.5 hr at room temperature, then evaporated at reduced pressure. The residue was taken up in 10 ml of hot methanol. Cooling gave a small amount of product. Chromatography of the mother liquors on 60 g of Florisil gave, with chloroform, additional product. The combined product fractions crystallized from chloroform–methanol affording 532 mg (46%) of rhombic crystals, mp 211–215°.

Anal. Calcd for $C_{17}H_{14}N_2O_6S$: C, 54.54; H, 3.77; S, 8.56. Found: C, 54.77; H, 3.95; S, 8.54.

1,2,5,7-Tetrahydro-α-phthalimido-7-oxo-4H-furo[3,4-*d*][1,3]-thiazine Acetic Acid *t*-Butyl Ester [XI, R = $C(CH_3)_3$].—Under a nitrogen atmosphere, a solution of 20.0 g (51.6 mmol) of amino lactone I and 14.8 g (51.6 mmol) of *t*-butyl α-phthalimidomalonaldehydate[14] in 1.0 l. of benzene was refluxed for 4 hr, a Dean–Stark trap separating the water of reaction. The solution was evaporated at reduced pressure to provide the intermediate as a gum, which was then taken up in 600 ml of nitromethane and cooled to −20° by a Dry Ice–acetone bath. A

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rapid stream of gaseous hydrogen chloride was passed through the solution for 45 min, the temperature being maintained at or below −20° at all times. After this time a stream of nitrogen was passed through the reaction mixture to flush out the bulk of the hydrogen chloride. The solution was then diluted with 2 l. of chloroform, precooled to −20°, and evaporated at reduced pressure. The residue was taken up in 300 ml of benzene, washed with 250 ml of aqueous 10% sodium carbonate, dried over sodium sulfate, filtered and evaporated. This neutral material was chromatographed on 500 g of Florisil (60/100 mesh). Elution with 1:1 benzene–chloroform gave 9.7 g (52%) of diastereoisomeric product, which crystallized from chloroform–ether as needles, mp 189–190°. While careful chromatography on alumina or silica gel did not separate the isomers, repeated crystallization from chloroform–hexane gave a single racemate: mp 193°; uv max (C_2H_5OH) 268 mμ (ε 4700), 216 (41,700); ir ($CHCl_3$) 2.90 (NH), 5.70 (lactone C=O), 5.85 μ (ester C=O); pmr (pyridine-d_5) τ 1.9–2.6 (m, 4, aromatic), 3.83 (q, 1, J = 6, 10 Hz, CHS), 4.72 (d, 1, J = 10 Hz, CH—CO, 5.0 (m, 1, NH), 5.31 (s, 2, —OCH_2C=), 6.43 [q, 2, J = 18 Hz, SCH_2C(=C)—], 8.60 [s, 9, $OC(CH_3)_3$].

Anal. Calcd for $C_{20}H_{20}N_2O_6S$: C, 57.69; H, 4.80. Found: C, 57.44; H, 5.05.

1,2,5,7-Tetrahydro-α-phthalimido-7-oxo-4H-furo[3,4-*d*][1,3]-thiazine Acetic Acid (XI, R = H).—The crude intermediate, obtained by allowing 1.16 g (4 mmol) of aldehyde [VIII, R = $C(CH_3)_3$] and 1.55 g (4 mmol) of amino lactone I to react in refluxing benzene for 3 hr, was dissolved in 80 ml of nitromethane and cooled to −15°; hydrogen chloride was passed through the solution for 15 min at this temperature; the solution was immediately diluted with 400 ml of ice-cold chloroform and the resulting solution evaporated at reduced pressure below 25°. The residue was taken up in 200 ml of benzene, and extracted with two 60-ml portions of 10% aqueous sodium bicarbonate. The extracts were cooled to 0° and acidified with dilute hydrochloric acid to pH 3 in the presence of 80 ml of chloroform. The aqueous layer was extracted with two additional (80-ml portions of chloroform. The combined chloroform solutions were dried (Na_2SO_4), filtered, and evaporated at reduced pressure below 25°. The resulting crude acid mixture weighed 661 mg (46%) and was immediately dissolved in 10 ml of chloroform and placed in the cold room overnight, producing 239 mg (16.5%) of acid isomer A, mp 162–164° (−CO_2), 248–250° dec. A differential thermal analysis indicated rapid loss of gas (CO_2) with concomitant melting at 167°, resolidification at 175° and finally remelting at 258°, with subsequent decomposition.

Anal. Calcd for $C_{16}H_{12}N_2SO_6$: C, 53.30; H, 3.36; N, 7.78. Found: C, 53.51; H, 3.87; N, 7.66.

The mother liquor on standing deposited 158 mg (11%) of acid isomer B, mp 192–193° (−CO_2) and 245–247° dec. Differential thermal analysis showed major loss of CO_2 and melting at 202° with resolidification at 208° and final melting at 255° with subsequent decomposition. A small depression in the curve at 168° showed the presence of a minor amount of isomer A.

Anal. Calcd for $C_{16}H_{12}N_2SO_6$: C, 53.30; H, 3.36; N, 7.78. Found: C, 53.50; H, 3.32; N, 7.39.

Isomer B was converted in 90% yield by ethereal diazomethane into material of mp 195–212°; recrystallization from acetonitrile gave 70% of pure product, mp 214–218°, identical (mixture melting point, infrared) with the methyl ester previously obtained by direct cyclization.

Registry No.—II, 19289-43-1; IV, 19289-44-2; V, 4019-12-9; IX, R = Me (*trans*), 19289-54-4; IX, R = Me (*cis*), 19289-55-5; XI, R = Me, 19289-46-4; XI, R = *t*-Bu, 17493-47-9; XI, R = H, 17833-99-7; XVII, 19289-57-7.

Polychlorinated Ketones. I. Synthesis and Fragmentation of β,β-Bis(trichloromethyl)-β-propiolactone

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The uncatalyzed cycloaddition of ketene to hexachloroacetone at 190–200° has given β,β-bis(trichloromethyl)-β-propiolactone (I) in 85% yield. In the presence of catalytic amounts of anhydrous ferric chloride, I underwent facile fragmentation when heated above its melting point to give 1,1,4,4,4-pentachloro-1-buten-3-one (XI), carbon monoxide, and hydrogen chloride. Addition of chlorine to the double bond of XI afforded 1,1,1,3,4,4,4-heptachlorobutan-2-one (XVI) which was readily dehydrochlorinated in the presence of triethylamine to give 1,1,2,4,4,4-hexachloro-1-buten-3-one (XXIV). The structure of lactone I and ketones XI, XVI, and XXIV is supported by physical and chemical investigations.

In connection with our work concerning the polymerization of lactones,[3] we were interested in studying the influence of electronegative groups in the β position of β-lactones on their polymerizability. One of the most widely used methods for the preparation of β-lactones is the reaction of a ketene with a carbonyl compound which requires catalysts in most cases. This reaction and the chemistry of β-lactones have been studied and reviewed in some detail.[4,5] More recently, the cycloaddition of ketene to hexafluoroacetone (ether, −78°, P_2O_5) has been found to give β,β-bis(trifluoromethyl)-β-propiolactone.[6] Similarly, β-trichloromethyl-β-propiolactone (II) was obtained from ketene and chloral at −80° [inert solvents, $BF_3 \cdot O(C_2H_5)_2$].[7] It has also been found that II can be prepared more conveniently from ketene and chloral at room temperature in the absence of solvents and catalysts.[8]

We have now found that when ketene was allowed to react with hexachloroacetone in the absence of catalysts and solvents at 190–200° β,β-bis(trichloromethyl)-β-propiolactone (I) was isolated in 85% yield. Catalysis of the cycloaddition reaction proved unsuccessful. Lewis acids in the presence or absence of a solvent

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