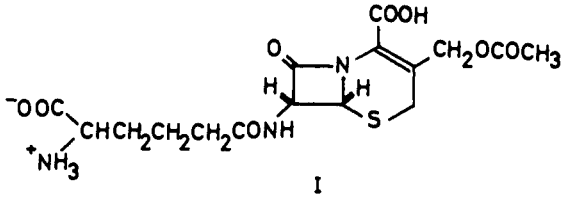
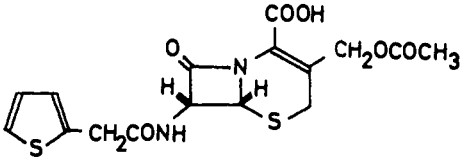
## The Total Synthesis of Cephalosporin C[1]

*Sir:*

Cephalosporin C (I), a product of the metabolism of



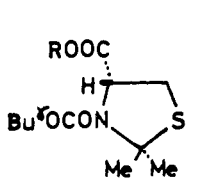
I



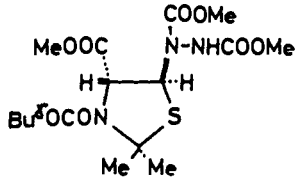
II

*Cephalosporium acremonium*, was isolated by Newton and Abraham in 1955,[2] and its structure was established in 1961 through chemical[3] and X-ray crystallographic[4] studies. The unusual antimicrobial properties of cephalosporin C and especially of substances prepared from the natural product by chemical modification, of which cephalothin (II)[5] may serve as an example, have attracted widespread interest. We now wish to record the first total syntheses of cephalothin and cephalosporin C.

L-(+)-Cysteine was converted into L-(−)-2,2-dimethylthiazolidine-4-carboxylic acid,[6] which with pyridine and *t*-butyloxycarbonyl chloride, prepared *in situ* from *t*-butyl alcohol, phosgene, and pyridine in methylene chloride at −74°, gave L-(−)-N-*t*-butyloxycarbonyl-2,2-dimethylthiazolidine-4-carboxylic acid[7] (III,

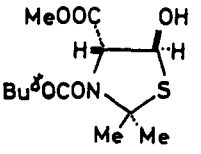


III

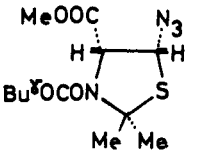


IV

R = H), mp 114–114.5°, $[\alpha]^{20}D$ −85° (*c* 1.34, $CHCl_3$). The corresponding ester[7] III (R = Me), mp 18.5–21°, $[\alpha]^{20}D$ −77° (*c* 1.50, $CHCl_3$), prepared from the acid with diazomethane, reacted with excess dimethyl azodicarboxylate at 105° during 45 hr to give the hydrazo diester[7] IV, mp 136–137.5°, $[\alpha]^{20}D$ +98° (*c* 1.45, $CHCl_3$). Oxidation of IV with 2.2 moles of lead tetraacetate in boiling benzene for 2 hr, followed by treatment of the reaction mixture with excess anhydrous sodium acetate in boiling dry methanol for 24 hr, gave the *trans* hydroxy ester[7] V, mp 101–102°, $[\alpha]^{20}D$ +48°

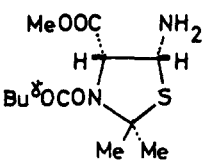


V

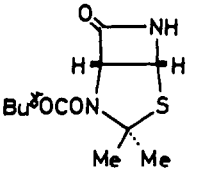


VI

(*c* 1.14, $CHCl_3$).[8] The latter was transformed by treatment in dimethylformamide with excess diisopropylethylamine and methanesulfonyl chloride, followed by concentrated aqueous sodium azide, to the *cis* azido ester[7] VI, mp 55–56°, $[\alpha]^{20}D$ −525° (*c* 1.01, $CHCl_3$), which was reduced in methanol by aluminum amalgam at −15° during 24 hr to the *cis* amino ester[7] VII, mp 64–65.5°,



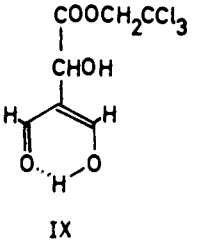
VII



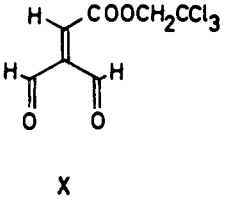
VIII

$[\alpha]^{20}D$ −113° (*c* 0.80, $CHCl_3$), whose structure was confirmed by a complete X-ray crystallographic study.[8] With triisobutylaluminum in toluene, the amino ester afforded the β-lactam[7] VIII, mp 120.5°, $[\alpha]^{20}D$ −274° (*c* 0.52, $CHCl_3$), the structure of which was also confirmed by X-ray crystallographic analysis;[8] it is worthy of note that this remarkable substance contains the basic structural elements common to cephalosporin C, its transformation products, and the penicillins.

In a parallel series of reactions, di-β,β,β-trichloroethyl *d*-tartrate,[7] mp 101.5–103.5°, $[\alpha]^{20}D$ +9° (*c* 1.04, $CHCl_3$), from *d*-tartaric acid and excess β,β,β-trichloroethanol in boiling toluene in the presence of *p*-toluenesulfonic acid, was oxidized by sodium metaperiodate in aqueous methanol to β,β,β-trichloroethyl glyoxylate hydrate,[7] mp 94.5–95.5°, which was condensed in aqueous solution with the sodium salt of malondialdehyde to give the aldol[7] IX, mp 114–116°,



IX



X

$\lambda\lambda_{max}$ 247 mμ (ε 19,100, EtOH–$H^+$), 269 mμ (27,600, EtOH–$OH^-$). When IX in 1,2-dimethoxyethane solution was added to distilling *n*-octane, dehydration occurred with formation of the highly reactive dialdehyde X, $\lambda_{max}$ 234 mμ (cyclohexane), which was utilized directly, without purification.

Condensation of the β-lactam VIII with the dialdehyde X in *n*-octane at 80° during 16 hr afforded the adduct[7]

(1) The material presented in this communication provided the basis for the Nobel Lecture delivered by one of us in Stockholm on Dec 11, 1965.

(2) G. G. F. Newton and E. P. Abraham, *Nature*, **175**, 548 (1955); *Biochem. J.*, **62**, 651 (1956).

(3) E. P. Abraham and G. G. F. Newton, *ibid.*, **79**, 377 (1961).

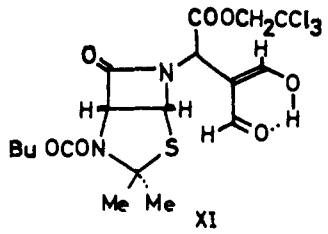
(4) D. C. Hodgkin and E. N. Maslen, *ibid.*, **79**, 393 (1961).

(5) R. R. Chauvette, E. H. Flynn, B. G. Jackson, E. R. Lavagnino, R. B. Morin, R. A. Mueller, R. P. Pioch, R. W. Roeske, C. W. Ryan, J. L. Spencer, and E. Van Heyningen, *J. Am. Chem. Soc.*, **84**, 3402 (1962).

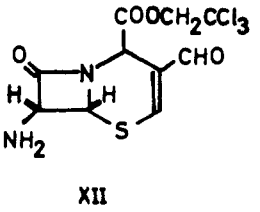
(6) G. E. Woodward and E. F. Schroeder, *ibid.*, **59**, 1690 (1937).

(7) Elemental analytical data in excellent accord with theory were obtained for this substance.

(8) The structure of this ester was most convincingly demonstrated by its preparation from the action of diazomethane upon the corresponding *acid*,[7] mp 187.5°, $[\alpha]^{20}D$ +123° [*c* 1.02 (1 *N* NaOH)], obtained by an alternative method; the structure of the acid was rigorously established by a complete X-ray crystallographic study. This and the other crystal structure determinations mentioned in the sequel were brilliantly executed by Dr. J. Zanos Gougoutas (Harvard), to whom we are glad to express our warm appreciation.



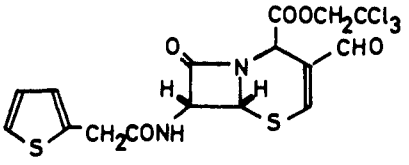
XI



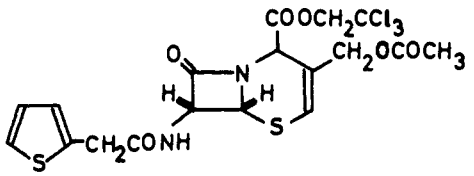
XII

XI, $[\alpha]^{20}D$ −122° (*c* 0.46, $CHCl_3$), which in trifluoroacetic acid solution at room temperature during 2.5 hr was transformed to the aminoaldehyde XII, $\lambda_{max}$ 292 mμ (13,600, EtOH); this sensitive intermediate was used in subsequent reactions without extensive purification.

Condensation of the aminoaldehyde XII in benzene with thiophene-2-acetyl chloride in the presence of pyridine led to the amide[7] XIII, mp 135–135.5°, $[\alpha]^{20}D$ +485° (*c* 1.14, $CHCl_3$), which was treated in tetrahydrofuran solution with diborane, followed by pyridine–acetic anhydride, to give isocephalothin β,β,β-trichloroethyl ester[7] (XIV), mp 102°, $[\alpha]^{20}D$ +320° (*c* 1.01,

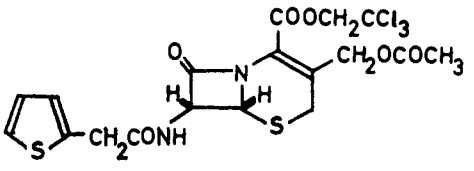


XIII



XIV

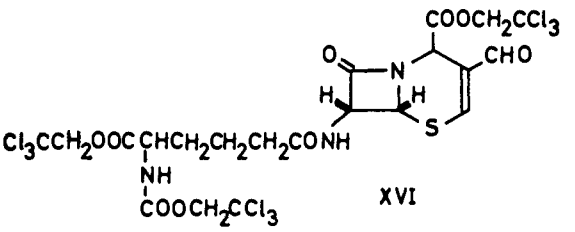
$CHCl_3$). When the iso ester was allowed to stand in anhydrous pyridine solution at room temperature during 3 days it was smoothly equilibrated ($K_{normal/iso}$ = 1/3) with the normal ester[7] XV, mp 120–123°,



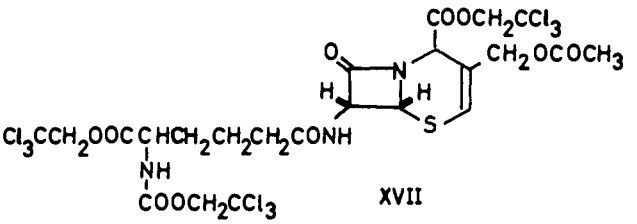
XV

$[\alpha]^{20}D$ +14° (*c* 0.95, $CHCl_3$), which was easily separated by chromatography on silica gel, and reduced by zinc dust in 90% aqueous acetic acid at room temperature to cephalothin (II), mp 160–160.5°, $[\alpha]^{20}D$ +50° (*c* 1.03, $CH_3CN$), whose properties were identical in all respects with those of material prepared from natural cephalosporin C.[5]

In another series of reactions the aminoaldehyde XII was condensed in tetrahydrofuran with N-β,β,β-trichloroethyloxycarbonyl-D-(−)-α-aminoadipic acid,[7] mp 137.5°, $[\alpha]^{20}D$ −8° (*c* 1.03, 1 *N* NaOH), in the presence of dicyclohexylcarbodiimide. The crude reaction mixture was esterified, using β,β,β-trichloroethanol in methylene chloride in the presence of dicyclohexylcarbodiimide and pyridine. Elution of the resulting material from silica gel by benzene–ethyl acetate (3:1) gave two products, of which XVI was the more polar, since it was converted by reduction in

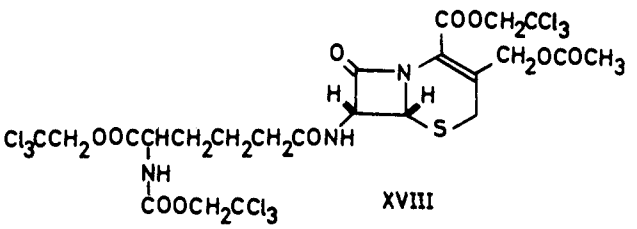


XVI



XVII

tetrahydrofuran with diborane, followed by acetylation with acetic anhydride–pyridine to the iso ester[7] XVII, mp 111–114°, $[\alpha]^{20}D$ +220° (*c* 1.01, $CHCl_3$). When the latter was allowed to stand in pyridine at room temperature for 3 days, it was equilibrated ($K_{normal/iso}$ = 1/4) with the normal ester[7] XVIII, mp 157–159°, $[\alpha]^{20}D$



XVIII

+40° (*c* 0.76, $CHCl_3$), which was easily separated by chromatography on silica gel and reduced by zinc dust and 90% aqueous acetic acid at 0° during 2.5 hr to cephalosporin C (I), identical with natural material in paper chromatographic behavior, and in antibacterial activity against *Neisseria catarrhalis*, *Alcaligenes faecalis*, *Staphylococcus aureus*, and *Bacillus subtilis;* further, the synthetic crystalline barium salt, $[\alpha]^{20}D$ +80° (*c* 0.57, $H_2O$), was identical in optical rotation and spectroscopic properties with the salt of natural cephalosporin C.

**Acknowledgment.** We are pleased to acknowledge the very generous support we have received from CIBA, Ltd., and especially the never-failing confidence and encouragement of Dr. Albert Wettstein.

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## Pyracyloquinone

*Sir:*

Although Hückel's 4*n* + 2 rule strictly applies only to monocyclic hydrocarbons, polycyclic aromatics possessing this number of π electrons are frequently misnamed Hückel aromatics. Nevertheless, the simple LCAO calculations do predict these compounds to have a high resonance energy. Brown[1] predicted that pyracylene (I), a 4*n* + 2 aromatic hydrocarbon, should

(1) R. D. Brown, *J. Chem. Soc.*, 2391 (1951).