part by Krukoff and Letouzey,[4] the remainder will be published later.

(4) B. A. Krukoff and R. Letouzey, *Rev. de Bot. Appl.* 329-350, Mars-Avril, 1950.

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ABSORPTION SPECTRA OF SULFURIC ACID CHROMOGENS OBTAINED FROM ADRENAL STEROIDS AND RELATED COMPOUNDS

Sir:

The observation that certain adrenocortical steroids when treated with concentrated sulfuric acid furnish colored solutions, has been recorded by several authors.[1,2] However, no data have been published concerning the absorption spectra of these chromogens. In order to establish the possible analytical value of such spectral data, the absorption curves of the chromogens obtained from the six active adrenal steroids and 8 other related compounds have been determined. The procedure used was as follows: 3 ml. of concentrated sulfuric acid (reagent grade) was added to 70 to 90 micrograms of the dry steroid in a test-tube. The tube was stoppered and allowed to stand at room temperature for two hours. The optical density of the solution, from 220 to 600 mμ, was then read in a Beckman spectrophotometer, using concentrated sulfuric acid as a blank.

Table I summarizes the results obtained with the fourteen steroids studied. The curves obtained were all different with respect to shape and position of the absorption maxima. Acetates and free compounds gave identical curves. One of the important features of the procedure is the small amount of material required for analysis. The absorption spectra of these chromogens have already proven of great value when used in conjunction with the paper chromatographic method of analysis for adrenal steroids,[4] in establishing the identity of compounds isolated from biological sources.

TABLE I

Compounds[3]	Absorption maxima, mμ
17-Hydroxycorticosterone	280, 395, 475
17-Hydroxy-11-dehydrocorticosterone	280, 343, 415
Corticosterone	285, 330, 373, 455
11-Dehydrocorticosterone	280, 355, 415
17-Hydroxy-11-desoxycorticosterone	285, 535
11-Desoxycorticosterone	285, 370, 440
allo-Pregnane-3(β),11(β),17(α)-21-tetrol-20-one	330, 415, 510
allo-Pregnane-3(β),17(α),21-triol-11,20, dione	333, 410
allo-Pregnane-3(β),17(α),21-triol-20-one	315, 410
Pregnane-17(α);21-diol-3,11,20-trione	270, 340, 415
3-Hydroxy-11-keto-etiocholanic acid	320, 405
3,9-Epoxy-11-keto-etiocholanic acid	290, 405
Δ⁴-Androstene-3,11,17-trione	280
Androstane-3,11,17-trione	No maxima

(1) Wintersteiner and Pfiffner, *J. Biol. Chem.*, **116**, 291 (1936).

(2) Reichstein and Shoppee, "Vitamins and Hormones," **1**, 345 (1943).

(3) Generously donated by Drs. T. F. Gallagher, P. L. Julian, E. C. Kendall, C. D. Kochakian, M. H. Kuizenga, H. L. Mason, E. Oppenheimer, G. Pincus, T. Reichstein and C. R. Scholz.

(4) Zaffaroni, Burton and Keutmann, *Science*, **111**, 6 (1950).

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THE TOTAL SYNTHESIS OF A 5-PHENYL PENICILLIN: METHYL 5-PHENYL-(2-CARBOMETHOXYETHYL)-PENICILLINATE

Sir:

By the use of a new method we have synthesized a 5-phenyl penicillin which has the complete structure of the natural penicillins, including the fused thiazolidine-β-lactam ring system with all of the correctly situated substituents, and in addition possesses a 5-phenyl group.

Interaction of methyl 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylate[1] (II), succinimidoacetyl chloride (I) and triethylamine yielded 4-carbomethoxy-5,5-dimethyl-2-phenyl-α-succinimido-2-thiazolidineacetic acid β-lactam (III) in 13% yield, m. p. 186.8–187.4° (cor.), obtained as the cyclohexane solvate. *Anal.* Calcd. for $C_{19}H_{20}N_2O_5S \cdot {}^1/_2C_6H_{12}$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.17; H, 6.12; N, 6.42. In tetrachloroethane solution the infrared absorption spectrum showed bands at 5.65, 5.72 and 5.84 μ, assignable to the β-lactam carbonyl, the ester carbonyl and the succinimido ring, respectively. Oxidation of III with potassium permanganate in acetic acid–dioxane–water mixture by a procedure identical with that used in preparing penicillin methyl ester sulfone[2] afforded an 82% yield of the sulfone (IV), m. p. 230.0° (cor.) with decomposition. *Anal.* Calcd. for $C_{19}H_{20}N_2O_7S$: C, 54.32; H, 4.79; N, 6.67. Found: C, 54.10; H, 4.90; N, 6.73. After alkaline hydrolysis of III, N-phenacylsuccinamic acid was isolated as the 2,4-dinitrophenylhydrazone, m. p. 186.4–187.2°, undepressed upon admixture with an authentic sample (m. p. 186.4–187.3°) prepared in a similar manner from N-phenacylsuccinimide.[3] *Anal.* Calcd. for $C_{18}H_{17}N_5O_7$: C, 52.05; H, 4.13; N, 16.86. Found: C, 51.69; H, 4.24; N, 16.72.

Selective basic hydrolysis of III followed by esterification with diazomethane yielded methyl 5-

(1) This thiazoline is readily obtained through the reaction of ethyl benzimidate hydrochloride with penicillamine methyl ester Sheehan and Buhle, THIS JOURNAL, in preparation.

(2) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 177. This book also provides a good review of previous attempts to synthesize penicillin and related β-lactams.

(3) Scheiber and Reckleben, *Ber.*, **46**, 2413 (1913).

phenyl-(2-carbomethoxyethyl)-penicillinate (V), m. p. 131.0–132.2° (cor.). *Anal.* Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.02; H, 5.68; N, 6.60. The infrared absorption spectrum showed bands at 5.65, 5.72, 5.79 and 5.93 μ, assignable respectively to a β-lactam carbonyl, two ester carbonyls and the amide carbonyl. Both V and methyl benzylpenicillinate have the characteristic monosubstituted amide N–H stretching band at 2.94 μ and N–H bending band at 6.63 μ. Compounds III, IV and V are biologically inactive when tested by conventional penicillin assay methods.[4]

This work is part of a substantial program directed toward the total synthesis of the penicillins and simpler analogs with similar structural features. We have obtained adducts in yields ranging from 13 to 56% from phthalimidoacetyl chloride and other acid chlorides with a variety of imines and thiazolines, including benzalaniline, 2-phenyl-2-thiazoline, 5,5-dimethyl-2-phenyl-2-thiazoline and methyl 5,5-dimethyl-2-thiazoline-4-carboxylate. In every case in which the constitution of the adduct has been definitely established, the structure has proved to be entirely analogous to III. Fused thiazolidine-β-lactams with the α-phenylacetylamino substituent characteristic of benzylpenicillin (penicillin G) have also been synthesized in practical yields, and these results will be reported in a forthcoming series of communications from this laboratory.

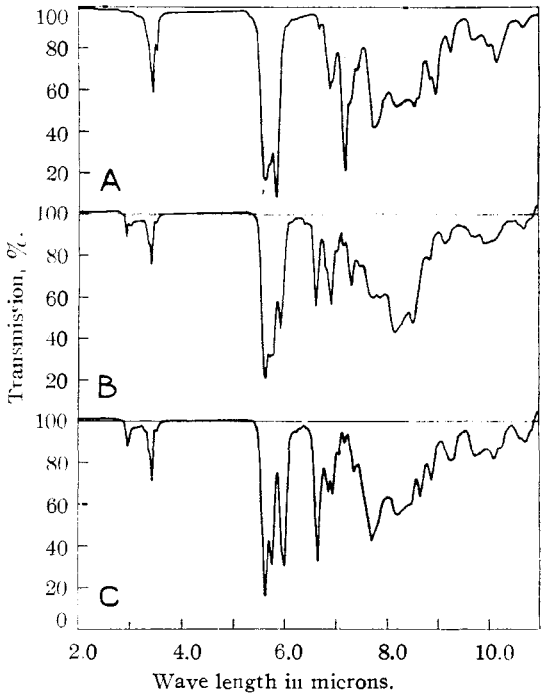
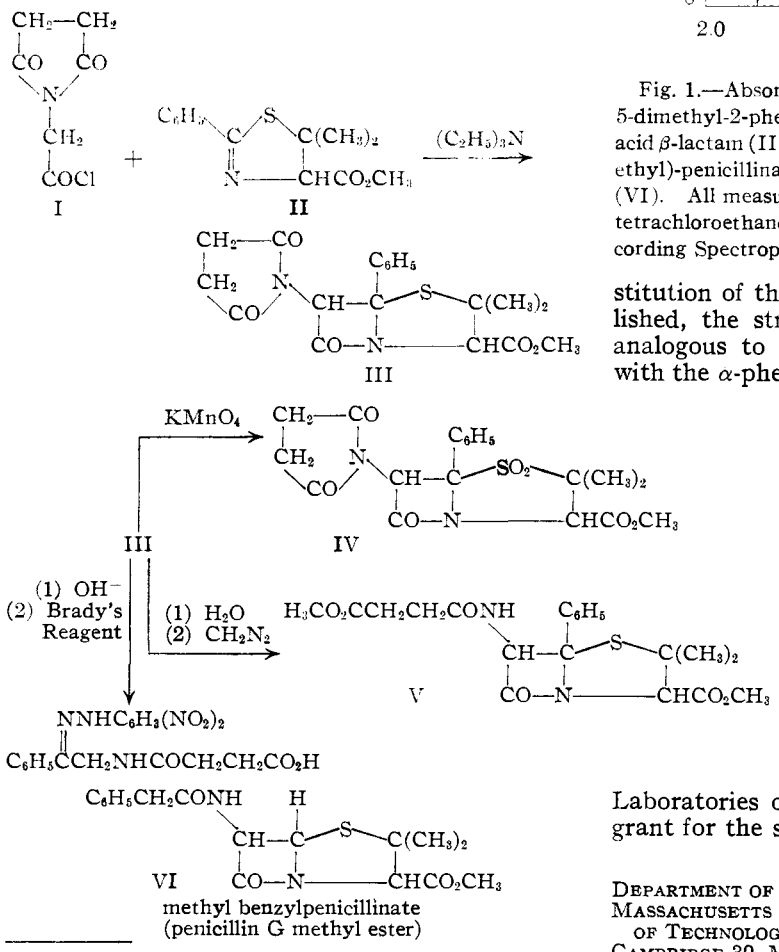


Fig. 1.—Absorption spectra of: A, 4-carbomethoxy-5,5-dimethyl-2-phenyl-α-succinimido-2-thiazolidineacetic acid β-lactam (III); B, methyl 5-phenyl-(2-carbomethoxyethyl)-penicillinate (V); C, methyl benzylpenicillinate (VI). All measurements were made on 5% solutions in tetrachloroethane, determined with a Baird Infrared Recording Spectrophotometer, Model B.



These products have many physical and chemical properties typical of the natural penicillins, and the reactions provide convincing evidence from the synthetic side for the correctness of the β-lactam formulation for the penicillins.

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(4) The bioassays were carried out at Bristol Laboratories, Syracuse, N. Y.