[JOINT CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES, DIVISION OF MERCK AND CO., INC., AND THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Totally Synthetic Penicillins

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Nine new penicillin analogs have been synthesized totally in multigram quantities from *t*-butyl 4-carbobenzyloxy-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (I). Reaction of this amine with various chloroformates, sulfonyl chlorides, isocyanates, a carbamyl chloride, a sulfamyl chloride and dinitrofluorobenzene produced the corresponding substitution products. Most of these products then satisfactorily underwent successive hydrohalogenolysis of the *t*-butyl ester, β-lactam cyclization with thionyl chloride and catalytic hydrogenolysis of the benzyl ester to yield the new penicillin analogs which were isolated as crystalline N-ethylpiperidine salts. All of these analogs (prepared in the DL-form) represent types of substitution on 6-aminopenicillanic acid unobtainable directly by fermentation. Specifically, the following substituents occupy the position normally occupied by the phenylacetyl group in benzylpenicillin (penicillin G): methylsulfonyl, benzenesulfonyl, *p*-aminobenzenesulfonyl, *p*-chlorobenzylsulfonyl, methoxycarbonyl, phenoxycarbonyl, *p*-chlorophenoxycarbonyl, N,N-pentamethylenesulfamyl and 2,4-diaminophenyl. A study of the stability of several of the analogs in acid solution revealed that they were very much more resistant to acid inactivation than benzylpenicillin.

The discovery and proof of structure of a new therapeutically useful antibiotic is usually succeeded by investigations directed toward the preparation of structural modifications of the active compound. This is a natural sequence of events since even slight structural changes may exert profound effects on the antibacterial and physiological actions of an antibiotic. Structural modifications assume chemotherapeutic value when useful and desirable actions are enhanced, when undesirable actions are suppressed, or, when new qualities of activity are introduced.

Since their discovery, it has been apparent that the naturally produced penicillins are not beyond improvement and possess a number of major as well as minor shortcomings. Most serious are their rapid rate of excretion, their relatively low stability, their limited coverage of the bacterial spectrum and, of increasing clinical concern, their sensitivity to *Staphylococcal penicillinase*.

The methods available for producing structural variations in the penicillin molecule are: (1) By alteration of the naturally produced antibiotic or intermediate by chemical methods. (2) By incorporation of specific structural features present in partially or wholly utilized precursors added to the fermentation medium. (3) By total synthesis of the desired structure. Until very recently[2] it had not been possible to prepare by these methods "penicillins"[3] in which the entire acyl group had been replaced by substituents other than certain limited monosubstituted acetic acids. Total synthesis offered a solution to the problem and the development of the synthesis of 6-benzylsulfonamidopenicillanic acid by Sheehan, Cruikshank and Hoff[4,5] opened a way by which certain analogs could be synthesized. The present report describes work, completed in 1957, on the application of this synthesis to a number of new penicillin analogs (in the DL-form) in which the side chains are sulfonyl, sulfamyl, urethan and aryl hydrocarbon derivatives.

The α-isomer of *t*-butyl DL-4-benzyloxycarbonyl-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (I) served as the common intermediate for the preparation of all the analogs. Acylation of this amine was performed in methylene chloride essentially by the procedure described by Sheehan and Hoff.[5] A few acid chlorides which did not react under these conditions were treated with the amine in dioxane at room temperature or above. The dioxane method was also used in the condensation of phenyl and ethyl isocyanates with the amine. Reaction of 2,4-dinitrofluorobenzene with the amine was carried out in aqueous alcohol in the presence of sodium bicarbonate.

The *t*-butyl esters II were cleaved with anhydrous hydrogen chloride in benzene. Acid hydrochlorides III which separated in crystalline form were collected by filtration while those products which did not crystallize or which separated in a gelatinous condition were isolated by concentrating the reaction mixture *in vacuo*. Every product isolated by the latter method was a dry white powder. For characterization purposes, a few of the non-crystalline hydrochlorides were dissociated with water to obtain the crystalline bases.

The β-lactam cyclization was effected with thionyl chloride in methylene chloride solution. Yields and other pertinent data are summarized in Table III. Because of low yields or dominant side reactions, three of the acids failed to give crystalline β-lactam products. Cyclization attempts on 4-carbobenzyloxy-5,5-dimethyl-α-piperidinecarbonamido - 2 - thiazolidineacetic acid hydrochloride (III, R = $C_5H_{10}NCO$–) yielded a lyophilized product in which the presence of benzyl 6 - piperidinecarbonamidopenicillanate (IV) was

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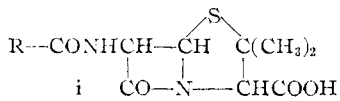
(2) F. R. Batchelor, F. P. Doyle, J. H. C. Nayler and G. N. Rolinson, *Nature*, **183**, 257 (1959); J. C. Sheehan and K. R. Henery-Logan, THIS JOURNAL, **81**, 5838 (1959).

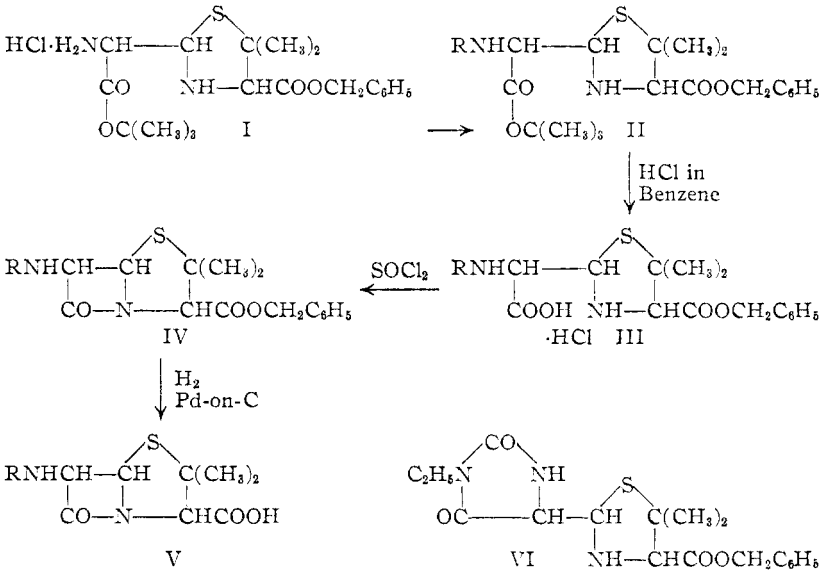
(3) The term penicillin refers to those compounds possessing the following general structure (i). A penicillin analog in which the entire



side chain (R–CO) has been replaced by a group lacking the carbonyl function can no longer be named by the usual penicillin nomenclature. A number of the analogs described in the present paper fall into this category. Therefore, the suggested penicillanic acid nomenclature [J. C. Sheehan, K. R. Henery-Logan and D. A. Johnson, THIS JOURNAL, **75**, 3292 (1953)] has been used throughout the paper for the synthetic analogs. Note however, that some of the analogs such as 6-ethoxycarbonamidopenicillanic acid (R = $C_3H_5O$) can be named correctly by the penicillin nomenclature, *e.g.*, ethoxypenicillin.

(4) J. C. Sheehan and P. A. Cruikshank, THIS JOURNAL, **78**, 3683 (1956).

(5) J. C. Sheehan and D. R. Hoff, *ibid.*, **79**, 237 (1957).




indicated by infrared data. However, the amount present was so small that chromatographic adsorption did not effect sufficient purification to yield a crystalline product. Both of the substituted carbamyl acids (III, R = $C_6H_5NHCO$– and R = $C_2H_5NHCO$–) yielded cyclization products in which only traces of the $\beta$-lactam function were indicated by infrared spectra. In the ethyl carbamyl series (R = $C_2H_5NHCO$–) the lyophilized material yielded a crystalline product which analyses showed to be isomeric with the expected lactam IV. Comparison of its infrared spectrum with the spectra of similarly substituted hydantoins proved beyond doubt that it has the hydantoin structure shown in formula VI.

An infrared spectrum was obtained for each of the pure, crystalline $\beta$-lactam esters IV. The spectral determinations were made on potassium bromide disks containing 0.35% by weight of compound. Every product exhibited a very strong absorption band at 5.58–5.62 $\mu$ which is characteristic of the $\beta$-lactam carbonyl function.

Cleavage of the benzyl esters by catalytic hydrogenolysis was carried out in purified dioxane. The presence of mineral acid was not necessary for satisfactory reduction. The conditions and relative quantities of reactants were the same for all the esters. Benzyl esters of a high degree of purity cleaved rapidly and in good yield. Lower quality esters reduced slowly due to catalyst poisoning which eventually caused the reduction to cease. Hydrogen consumption slowed to a negligible rate when hydrogenolysis was complete.

After removal of the catalyst, an equivalent amount of N-ethylpiperidine was added to the dioxane solution. The dioxane was then evaporated under reduced pressure and, when a small volume was reached, crystallization of the N-ethylpiperidine salt of the analog usually occurred. The two halogenated analogs (V, R = $p$-$ClC_6H_4CH_2SO_2$– and R = $p$-$ClC_6H_4OCO$–) suffered some dehalogenation under the hydrogenolysis conditions. However, proper choice of solvents for crystallization of the N-ethylpiperidine salts resulted in elimination of the undesired dehalogenated products. Nitro groups were reduced to amino groups during the catalytic debenzylation.

An N-ethylpiperidine salt of 6 - (2,4 - diaminophenylamino)-penicillanic acid (V, R = 2,4-$(NH_2)_2C_6H_3$–) was not prepared. Instead, after removal of the catalyst, the dioxane solution was shell-frozen and lyophilized. The product was obtained as a neutral yellow powder which resisted crystallization. However, analyses and infrared spectra were consistent with the assigned penicillanic acid structure.

All of the N-ethylpiperidine salts were fairly soluble in water. The infrared spectra of the pure salts were determined from a potassium bromide disk containing 0.35% of compound. Absorption due to the benzyl ester carbonyl function was absent. The spectra showed very strong absorption due to the carboxylate ion and very strong absorption at 5.62–5.66 $\mu$ characteristic of the $\beta$-lactam carbonyl group.

Four of the analogs were subjected to a stability study in acid solution at 25°. The N-ethylpiperidine salts (15–30 mg.) were dissolved in 30 ml. of 0.3 $N$ hydrochloric acid and clear solutions resulted. The amount of penicillanic acid remaining after various intervals of time was determined by microbiological assay of an aliquot. A plot of the log of concentration *vs.* time yielded a straight line from which the half-life was read. These values appear in Table IV. Since benzylpenicillin would have a rather fleeting existence in 0.3 $N$ acid it was not compared directly with the synthetic analogs. However, the half-life of 0.31 hr. at $p$H 2.0 and 24° reported by Benedict, Schmidt and Coghill[6] for benzyl penicillin is mentioned here to point out the striking increased resistance to acid shown by the analogs.

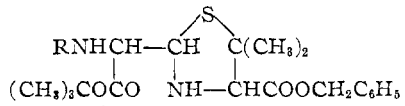
In general, the antibacterial spectrum paralleled that displayed by benzylpenicillin. All of the analogs showed some degree of antimicrobial activity but none were more active than benzylpenicillin in an *in vitro* serial dilution assay. However, the potency observed does compare favorably with other accepted antibiotics. Some of the analogs showed greater activity (adjusted for their racemic state[7]) than benzylpenicillin against various clinically isolated strains of resistant Staphylococci. In addition, *Staphylococcal penicillinase*, in a non-microbial test, inactivated the synthetic penicillins at a slower rate than benzylpenicillin.

**Acknowledgments.**—We are indebted to W. Riley McGaughran for the infrared spectrophotometric data, to Kermit B. Streeter, Yung C. Lee and

(6) R. G. Benedict, W. H. Schmidt and R. D. Coghill, *J. Bacteriol.*, **51**, 291 (1946).

(7) Microbiological testing results on DL and D-penicillin V, reported by J. C. Sheehan and K. R. Henery-Logan [THIS JOURNAL, **79**, 1262 (1957)], indicate that the L-penicillins have little, if any, antibiotic activity.

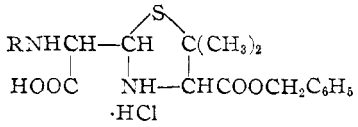
TABLE I



| R | Acylating agent | Method | Solvent for crystallization | Yield,[g] % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3SO_2-$ | $CH_3SO_2Cl$ | A | Methylene chloride | 42 | 130–131 | $C_{20}H_{30}N_2O_6S_2$ | 52.38 | 52.70 | 6.59 | 6.52 | 6.11 | 6.10 |
| $C_6H_5SO_2-$ | $C_6H_5SO_2Cl$ | A | Ethyl alcohol | 37 | 141–143 | $C_{25}H_{32}N_2O_6S_2$ | 57.67 | 57.76 | 6.20 | 6.16 | 5.38 | 5.37 |
| $p$-$O_2NC_6H_4SO_2-$ | $p$-$O_2NC_6H_4SO_2Cl$ | A | Methyl alcohol | 41 | 175–177 | $C_{25}H_{31}N_3O_8S_2$ | 53.08 | 53.23 | 5.52 | 5.73 | 7.43 | 7.31 |
| $p$-$ClC_6H_4CH_2SO_2-$ | $p$-$ClC_6H_4CH_2SO_2Cl$[b] | A | Methyl alcohol | 68 | 146–147 | $C_{26}H_{33}ClN_2O_6S_2$ | 54.87 | 54.92 | 5.84 | 5.75 | 4.92 | 4.91 |
| $CH_3OCO-$ | $CH_3OCOCl$ | A | Benzene–petr. ether | 43 | 97–98 | $C_{21}H_{30}N_2O_6S$ | 57.52 | 57.76 | 6.90 | 7.10 | 6.39 | 6.38 |
| $C_6H_5OCO-$ | $C_6H_5OCOCl$[c] | A | Methyl alcohol | 67 | 78–82 | $C_{26}H_{32}N_2O_6S$ | 62.38 | 61.85 | 6.44 | 6.73 | 5.60 | 5.40 |
| $p$-$ClC_6H_4OCO-$ | $p$-$ClC_6H_4OCOCl$[d] | A | Methyl alcohol | 38 | 115–116 | $C_{26}H_{31}ClN_2O_6S$ | 58.36 | 58.33 | 5.84 | 5.88 | 5.24 | 5.13 |
| $C_5H_{10}NSO_2-$[a] | $C_5H_{10}NSO_2Cl$[e] | B | Ethyl alcohol | 13 | 140–142 | $C_{24}H_{37}N_3O_6S_2$ | 54.64 | 54.90 | 7.07 | 6.91 | 7.97 | 7.89 |
| $C_6H_{10}NCO-$[a] | $C_5H_{10}NCOCl$[f] | B | Isopropyl ether | 57 | 117–119 | $C_{25}H_{37}N_3O_6S$ | 61.08 | 60.99 | 7.59 | 7.56 | 8.55 | 8.56 |
| $C_6H_5NHCO-$ | $C_6H_5NCO$ | C | Isopropyl alcohol | 65 | 165–168 | $C_{26}H_{33}N_3O_6S$ | 62.50 | 62.47 | 6.66 | 6.76 | 8.41 | 8.49 |
| $C_2H_5NHCO-$ | $C_2H_5NCO$ | C | Isopropyl alcohol | 42 | 144–146 | $C_{22}H_{33}N_3O_6S$ | 58.51 | 58.46 | 7.37 | 7.18 | 9.52 | 9.24 |
| 2,4-$(NO_2)_2C_6H_3-$ | 2,4-$(NO_2)_2C_6H_3F$ | D | Isopropyl alcohol | 79 | 161–162 | $C_{26}H_{30}N_4O_8S$ | 54.94 | 55.18 | 5.53 | 5.40 | 10.25 | 10.38 |

[a] $C_5H_{10}N$ = 1-piperidyl. [b] G. Dougherty and R. H. Barth, U. S. Patent 2,293,971 (1943). [c] Phenyl chloroformate was prepared from phenol and phosgene [F. Strain, *et al.*, THIS JOURNAL, **72**, 1254 (1950)]. [d] $p$-Chlorophenyl chloroformate was prepared from $p$-chlorophenol and phosgene by the method of F. Strain, *et al.* (see ref. *c*); b.p. 102–104° (15 mm.), $n^{25}D$ 1.5322. [e] 1-Piperidinesulfonyl chloride was prepared by an improved version of the method of Binkley and Degering [THIS JOURNAL, **61**, 3250 (1939)]. Piperidine (2 moles) in 250 ml. of carbon tetrachloride was added to sulfuryl chloride (1 mole) in 250 ml. of carbon tetrachloride at −20° over a 1.75-hour period. The mixture was allowed to warm to room temperature (2.5 hours), the piperidine hydrochloride was removed by filtration and the filtrate was distilled. The yield was 30% of product boiling at 131–135° at 15 mm. [f] 1-Piperidinecarbonyl chloride was prepared from piperidine and phosgene; b.p. 104–107° (12 mm.), $n^{25}D$ 1.4940 [A. Sekera, I. Jakubec, J. Kral and C. Vrba, *Chem. Listy*, **46**, 762 (1952); *C. A.*, **47**, 12302f (1953)]. [g] The yields given are for pure product.

TABLE II



| R | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| $CH_3SO_2-$ | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |
| $CH_3SO_2-$ | 143–144[b] | $C_{16}H_{22}N_2O_6S_2$ | 47.74 | 47.89 | 5.51 | 5.52 | 6.96 | 6.94 |
| $C_6H_5SO_2-$ | 117–118 | $C_{21}H_{24}N_2O_6S_2 \cdot HCl$ | 50.34 | 50.38 | 5.03 | 4.98 | 5.59 | 5.56 |
| $p$-$NO_2C_6H_4SO_2-$ | 135–137 | $C_{21}H_{23}N_3O_8S_2 \cdot HCl$ | 46.19 | 46.07 | 4.43 | 4.38 | 7.70 | 7.74 |
| $p$-$ClC_6H_4CH_2SO_2-$ | 117–118 | $C_{22}H_{25}ClN_2O_6S_2 \cdot HCl$ | 48.08 | 48.32 | 4.77 | 4.54 | 5.10 | 5.06 |
| $CH_3OCO-$ | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |
| $CH_3OCO-$ | 135–136[b] | $C_{17}H_{22}N_2O_6S$ | 53.39 | 53.68 | 5.80 | 6.07 | 7.33 | 7.32 |
| $C_6H_5OCO-$ | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |
| $p$-$ClC_6H_4OCO-$ | 116–117 | $C_{22}H_{23}ClN_2O_6S \cdot HCl$ | 51.27 | 51.83 | 4.69 | 4.92 | 5.44 | 5.08 |
| $C_5H_{10}NSO_2-$[a] | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |
| $C_5H_{10}NCO-$[a] | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |
| $C_5H_{10}NCO-$[a] | 136–137[c] | $C_{21}H_{29}N_3O_6S$ | 57.91 | 57.82 | 6.71 | 6.82 | 9.65 | 9.84 |
| $C_6H_5NHCO-$ | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |
| $C_2H_5NHCO-$ | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |
| 2,4-$(NO_2)_2C_6H_3-$ | Non-cryst. | Not analyzed | ... | ... | .. | .. | .. | .. |

[a] $C_5H_{10}N$ = 1-piperidyl. [b] HCl-free compound; crystallized from isopropyl alcohol. [c] HCl-free compound; crystallized from ethyl alcohol.

staff for the microanalyses, to Esther Bishop for the bioassays, to A. Katherine Miller and staff for microbiological data and to Elizabeth H. Thiele for the penicillinase resistance studies.

## Experimental[8]

**Acylation of *t*-Butyl-DL-4-Benzyloxycarbonyl-5,5-dimethyl-α-amino-2-thiazolidineacetate Hydrochloride. Method A.**—The acylation was carried out essentially as described by Sheehan and Hoff[5] using the same concentrations of reactants. However, after the reaction mixture had been allowed to stand for 20 hours, the triethylamine hydrochloride was removed by extraction of the reaction mixture with water. The methylene chloride solution was then dried with sodium sulfate and the solvent was removed under vacuum. Table I indicates the solvents used to crystallize the residues.

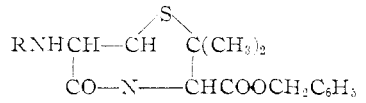
(8) All melting points are uncorrected. The infrared spectra were obtained with a Perkin-Elmer model 21 spectrophotometer.

**Method B.**—To a solution of 12.0 g. (0.12 mole) of triethylamine in 200 ml. of pure dioxane there was added 16.8 g. (0.04 mole) of *t*-butyl DL-4-benzyloxycarbonyl-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (I) and 0.08 mole of the acid chloride. A clear solution was obtained by warming the mixture to 50°; then it was allowed to stand at room temperature for 20 hours. The precipitated triethylamine hydrochloride was removed by filtration and the filtrate was concentrated *in vacuo* to a viscous sirup. Crystals were obtained by using the solvents indicated in Table I.

**Method C.**—The same procedure as method B except that 0.08 mole of an isocyanate was used instead of an acid chloride.

**Method D.**—A solution of 5.52 g. (0.066 mole) of sodium bicarbonate in 60 ml. of water was added to a solution of 12.51 g. (0.03 mole) of *t*-butyl DL-4-benzyloxycarbonyl-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (I) and 5.58 g. (0.03 mole) of 2,4-dinitrofluorobenzene in 180 ml. of methyl alcohol and 30 ml. of ether. A clear solution resulted which almost immediately began to effervesce and

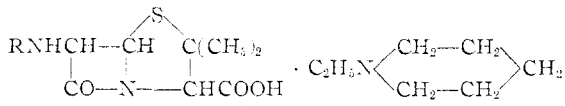
TABLE III



| R | Reflux time, min. | Crystallization solvent[a] | Recrystallization solvent[b] | Yield,[c] % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3SO_2$– | 45 | Benzene–isopropyl ether | Benzene–isopropyl ether | 35 | 110–112 | $C_{16}H_{20}N_2O_5S_2$ | 49.98 | 50.17 | 5.24 | 5.03 | 7.29 | 7.21 |
| $C_6H_5SO_2$– | 30 | [d] | Benzene–hexane | 40 | 125–126 | $C_{21}H_{22}N_2O_5S_2$ | 56.49 | 56.65 | 4.97 | 4.99 | 6.28 | 6.24 |
| *p*-$NO_2C_6H_4SO_2$– | 45 | [d] | Benzene | 65 | 159–161 | $C_{21}H_{21}N_3O_7S_2$ | 51.31 | 51.61 | 4.31 | 4.40 | 8.55 | 8.45 |
| *p*-$ClC_6H_4CH_2SO_2$– | 30 | Ethyl ether | Ethyl alcohol | 45 | 123–125 | $C_{22}H_{23}ClN_2O_5S_2$ | 53.38 | 53.37 | 4.68 | 4.82 | 5.66 | 5.70 |
| $CH_3OCO$– | 20 | *Isopropyl alcohol* | *Isopropyl alcohol* | 40 | 89–91 | $C_{17}H_{20}N_2O_5S$ | 56.04 | 56.36 | 5.53 | 5.58 | 7.69 | 7.68 |
| $C_6H_5OCO$– | 60 | Ethyl ether | Isopropyl alcohol | 45 | 103–104 | $C_{22}H_{22}N_2O_5S$ | 61.95 | 62.09 | 5.21 | 5.28 | 6.57 | 6.77 |
| *p*-$ClC_6H_4OCO$– | 30 | [d] | Benzene | 45 | 157–158 | $C_{22}H_{21}ClN_2O_5S$ | 57.32 | 57.47 | 4.58 | 4.48 | 6.09 | 6.24 |
| $C_5H_{10}NSO_2$–[e] | 30 | $CCl_4$ | Isopropyl alcohol | 20 | 92–93 | $C_{20}H_{27}N_3O_5S_2$ | 52.97 | 52.86 | 6.00 | 5.99 | 9.27 | 9.30 |
| $C_5H_{10}NCO$–[e] | 45 | [f] | ..... | .. | ..... | ..... | ... | ... | .. | .. | ... | ... |
| $C_6H_5NHCO$– | 30 | [g] | ..... | .. | ..... | ..... | ... | ... | .. | .. | ... | ... |
| $C_2H_5NHCO$– | 30 | [h] | ..... | .. | ..... | ..... | ... | ... | .. | .. | ... | ... |
| 2,4-$(NO_2)_2C_6H_3$– | 30 | [d,i] | Ethyl acetate | 35 | 167–169 | $C_{21}H_{20}N_4O_7S$ | 53.39 | 53.40 | 4.27 | 4.29 | 11.86 | 12.00 |

[a] For preparation of crystalline material from lyophilized products. [b] For preparation of samples for analysis. [c] The yields quoted represent an average of two or more successful cyclizations. [d] Product crystallized from benzene during reaction workup; no lyophilization necessary. [e] $C_5H_{10}N$ = 1-piperidyl. [f] Crystalline product not obtained. [g] *No* β-lactam was present in the reaction mixture. [h] No β-lactam was present in the reaction mixture. A crystalline product was isolated from benzene in 25% yield which appeared to be the isomeric hydantoin VI, m.p. 151–152°. *Anal.* Calcd. for $C_{18}H_{23}N_3O_4S$: C, 57.28; H, 6.14; N, 11.13. Found: C, 57.22; H, 6.07; N, 11.22. [i] The crystalline products from benzene solution contain benzene of crystallization. This product rapidly dissolved in a small amount of cold ethyl acetate from which a solvent-free product immediately crystallized.

TABLE IV



| R | Crystallization solvent[c] | M.p., °C. | Yield,[d] % | Half-life in 0.3 *N* acid, min. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3SO_2$– | Methyl alcohol (1)–ethyl ether (5) | 174–175 | 88 | 150 | $C_{16}H_{29}N_3O_5S_2$ | 47.15 | 47.46 | 7.17 | 7.39 | 10.31 | 10.13 |
| $C_6H_5SO_2$– | Ethyl alcohol (2.5)–isopropyl alcohol (7.5) | 153–155 | 61 | .. | $C_{21}H_{31}N_3O_5S_2$[e] | 53.71 | 54.02 | 6.66 | 6.72 | 8.95 | 8.78 |
| $C_6H_5CH_2SO_2$–[a] | Methyl alcohol (1)–ethyl ether (6) | 152–153 | 86 | 190 | $C_{22}H_{33}N_3O_5S_2$ | 54.64 | 54.69 | 6.89 | 6.92 | 8.69 | 8.58 |
| *p*-$H_2NC_6H_4SO_2$– | Methyl alcohol (1)–ethyl ether (3) | 205–207 | 76 | .. | $C_{21}H_{32}N_4O_5S_2$[e] | 52.04 | 51.73 | 6.66 | 6.73 | 11.56 | 11.38 |
| *p*-$ClC_6H_4CH_2SO_2$– | Methyl alcohol (2)–ethyl ether (1)[f] | 135–140 | 64 | .. | $C_{22}H_{32}ClN_3O_5S_2$[g] | 51.00 | 50.82 | 6.23 | 6.31 | 8.11 | 8.23 |
| $CH_3OCO$– | Acetone | 131–133 | 79 | 110 | $C_{17}H_{29}N_3O_5S$ | 52.69 | 52.70 | 7.54 | 7.55 | 10.84 | 10.78 |
| $C_6H_5OCO$– | Acetone | 140–142 | 76 | 175 | $C_{22}H_{31}N_3O_5S$ | 58.78 | 58.86 | 6.95 | 7.08 | 9.35 | 9.24 |
| *p*-$ClC_6H_4OCO$– | Methyl alcohol (1)–ethyl ether (8) | 141–143 | 50 | .. | $C_{22}H_{30}ClN_3O_5S\cdot(C_2H_5)_2O$[h] | 55.95 | 55.96 | 7.22 | 7.02 | 7.53 | 7.38 |
| *p*-$ClC_6H_4OCO$– | ..... | ..... | .. | .. | $C_{22}H_{30}ClN_3O_5S$[i,j] | 54.60 | 54.54 | 6.25 | 6.47 | 8.68 | 8.55 |
| $C_5H_{10}NSO_2$–[b] | Isopropyl alcohol | 150–152 | 47[k] | .. | $C_{25}H_{36}N_4O_5S_2\cdot(CH_3)_2CHOH$ | 51.46 | 51.06 | 8.26 | 8.03 | 10.44 | 10.33 |
| 2,4-$(NH_2)_2C_6H_3$– | Non-crystalline[l] | ..... | 95 | .. | ..... | ... | ... | .. | .. | ... | ... |

[a] J. C. Sheehan and D. R. Hoff[5] reported the N-(3,3-diphenylpropyl)-piperidine salt of this analog. [b] $C_5H_{10}N$ = 1-piperidyl. [c] For preparation of sample for analysis (figures in parentheses for mixtures show parts by volume). [d] Unless otherwise noted, yields are those obtained directly from dioxane after concentration to a small volume. [e] Sample for analysis dried at 80°. [f] Before recrystallization from this mixture, the product was washed with methylene chloride in which it is insoluble. The unhalogenated analog is soluble in methylene chloride. [g] Calcd.: Cl, 6.84. Found: Cl, 6.50. [h] This crystalline etherate was stable *in vacuo* at room temperature. [i] Etherate dried at 76° *in vacuo* for 2 hours. [j] Calcd.: Cl, 7.33. Found: Cl, 7.00. [k] After the dioxane was removed from the reduction filtrate, a sirup remained which was crystallized from a mixture of one volume of ethyl alcohol and fifteen volumes of ether. [l] This product was not isolated as the N-ethylpiperidine salt. A solid but non-crystalline free acid was obtained from the hydrogenolysis reaction by lyophilization of the dioxane. Due to retention of a small amount of this solvent the product was not analytically pure. However, its infrared spectrum indicated a high degree of purity.

deposit crystalline material. After 3 hours at 25°, the product was collected, washed with 100 ml. of 75% methyl alcohol, 500 ml. of water and then again with 100 ml. of 75% methyl alcohol. See Table I for yield and analyses.

**Hydrohalogenolysis of the *t*-Butyl Esters.**—The *t*-butyl esters (II) were cleaved with anhydrous hydrogen chloride in benzene under the conditions reported by Sheehan and Hoff.[5] Products which separated from the reaction in a crystalline state were obtained in better than 90% yield and were analyzed without further purification. These are reported in Table II as hydrochlorides.

When the products remained in solution or separated as an oil or a gel the entire reaction mixture was vacuum concentrated at a temperature below 35°. The products (in the form of hydrochlorides) were then obtained in essentially quantitative yield as dry, nonsticky powders. These were not analyzed.

For characterization purposes, some of these powders were converted to the crystalline, hydrogen chloride-free compounds by treatment with water. The powders became gummy when added to water, but with vigorous rubbing and repeated changes of the wash water, crystalline products resulted which were recrystallized from organic solvents. These compounds are included in Table II and attention is directed to them by footnotes.

**β-Lactam Formation.**—The β-lactam cyclization was carried out by the procedure of Sheehan and Hoff[5] using thionyl chloride in methylene chloride as the cyclizing agent. The thiazolidineacetates (III) were used for cyclization in the condition in which they were isolated from the hydrohalogenolysis reaction. Non-crystalline hydrochlorides cyclized just as well as their crystalline counterparts. The optimum reaction time at reflux temperature as set forth in Table III was determined from the yields of β-lactam after individual cyclization reactions had proceeded for varying periods of time. After working up the reactions by the Sheehan and Hoff[5] procedure, the products were obtained in benzene solution. This solution was shell-frozen and lyophilized to remove the solvent. A few products crystallized directly from the benzene and lyophilization was unnecessary. Such cases are noted by footnotes to Table III. All lyophilized products were obtained as fluffy yellow powders. The β-lactam content of these powders was always assessed by infrared analysis and the products showing little or no absorption at 5.5–5.6 μ were discarded. Chromatographic adsorption on alumina as described by Sheehan and Hoff was not necessary for preparative work. However, it was convenient to use chromatography to achieve the initial purification necessary to obtain seed crystals of new β-lactam preparations. Yield, crystallization solvents and analyses are reported in Table III.

**Catalytic Hydrogenolysis of the Benzyl Esters and Formation of N-Ethylpiperidine Salts of the Penicillanic Acids (V).** A suspension of 2 g. of 10% palladium-on-carbon (Norite) catalyst in 100 ml. of purified dioxane was saturated with hydrogen at atmospheric pressure and 25°. To this suspension was then added 0.0025 mole of the benzyl ester IV and the hydrogenation was continued under the same conditions. The theoretical quantity of hydrogen was absorbed in about 2 hours and the reduction ceased. After removal of the catalyst by filtration, 0.283 g. (0.0025 mole) of N-ethylpiperidine was added to the filtrate. Concentration of the solution was carried out under vacuum with a bath temperature not exceeding 25°. Crystallization commenced when the volume was reduced to 5–10 ml. The products were collected and washed with cold dioxane.

For the diaminophenyl analog (V, R = 2,4-$(H_2N)_2C_6H_3$) the hydrogenolysis and reduction of the nitro groups were carried out using the same conditions and relative quantities of reagents as described in the preceding paragraph. However, after removal of the catalyst, no N-ethylpiperidine was added. The dioxane solution was shell-frozen and lyophilized and the product was obtained as a yellow, neutral powder. Yields and analyses are shown in Table IV.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF FORDHAM UNIVERSITY]

# Ozonolysis of Polycyclic Aromatics. VII.[1] Dibenz[a,h]anthracene[2,3]

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Corrected oxidation–reduction potentials for dibenz[*a*,*h*]anthracene-7,14-dione and dibenz[*a*,*h*]anthracene-5,6-dione are, respectively, 0.418 v. and 0.381 v. As previously suggested by us, ozone should therefore predominantly attack the 5,6-bond in dibenz[*a*,*h*]anthracene (I). Compound I, on absorption of one and two molar equivalents of ozone, yields, respectively, unstable, probably monomeric 5,6-ozonide Ia and stable, dimeric 5,6,12,13-diozonide Ib in inert solvents, and, respectively, monomeric, dimethoxy peroxide II and probably polymeric, tetramethoxy peroxide VIII in methanol solvent. Oxidation of Ia and II, and Ib and VIII gave, respectively, 2-(*o*-carboxyphenyl)-3-phenanthrene carboxylic acid (IV) and *p*-terphenyl-2,2′,5′,2″-tetracarboxylic acid (X). Reduction of Ia and II, and VIII, gave, respectively, 2-(*o*-formylphenyl)-3-phenanthrenecarboxaldehyde, and *p*-terphenyl-2,2′,5′,2″-tetracarboxaldehyde. The dimethyl ester V of IV was converted to X *via* 2-(*o*-carbomethoxyphenyl)-3-carbomethoxy-9,10-phenanthrenequinone (VII).

In several recent publications,[1,4a,4b] we have noted that the positions of *predominant* ozone attack on polycyclic aromatic hydrocarbons correspond to those of the *o*- or *p*-quinone with the lowest corrected quinone–hydroquinone oxidation–reduction potential (*i.e.*, those positions yielding the most stable of all possible dihydro structures).[5] Thus, for example, corrected oxidation–reduction potentials for benz[*a*]anthracene-7,12- and -5,6-dione are, respectively, 0.353 and 0.380 v. Reaction of benz[*a*]anthracene with one molar equivalent of ozone in methylene chloride, carbon tetrachloride and methylene chloride–methanol afforded a 64% yield of the 7,12-dione based on the amount of benz[*a*]anthracene utilized.[1,4b] Thus *predominant* ozone attack on benz[*a*]anthracene occurred at those positions (7,12-) whose corresponding quinone had the lowest oxidation–reduction potential.

In dibenz[*a*,*h*]anthracene (DBA = I), molecular orbital calculations predict the 7- and 14-carbon atoms to have the lowest carbon localization energies[6a,9] (reactivity numbers),[6b] the 7,14-positions to have the lowest *p*-localization energy,[7,10] and the 5,6-bond to have the lowest bond localization energy[7] (*o*-localization energy).[6a] Chemical

(1) Part VI, E. J. Moriconi, W. F. O'Connor and F. T. Wallenberger, THIS JOURNAL, **81**, 6466 (1959).

(2) For a preliminary report on part of this work see E. J. Moriconi, G. W. Cogswell, W. J. Schmitt and W. F. O'Connor, *Chemistry & Industry*, 1591 (1958).

(3) Presented in part at The Meeting-in-Miniature of The Metropolitan Long Island Subsection, American Chemical Society, New York Section, March, 1959, and at The Symposium on Ozone Chemistry, 136th National Meeting of The American Chemical Society, Atlantic City, N. J., Sept., 1959.

(4) (a) E. J. Moriconi, W. F. O'Connor and L. B. Taranko, *Arch. Biochem. and Biophys.*, **83**, 283 (1959); (b) E. J. Moriconi, W. F. O'Connor and F. T. Wallenberger, *Chemistry & Industry*, 22 (1959).

(5) This correlation is especially pertinent to those polycyclics whose most reactive positions are not the termini of the most reactive bond. The most reactive carbon atoms theoretically have the lowest carbon localization energy[6] and, experimentally, are the positions at which electrophilic, nucleophilic and radical substitution occurs; the most reactive bond has the lowest bond localization energy[6a,7] and is the site of attack by bond reagents, osmium tetroxide and diazoacetic ester.[8] Relevant polycyclic aromatics which have been ozonized include anthracene, naphthacene, benz[*a*]anthracene, pyrene and dibenz[*a*,*h*]anthracene.

(6) (a) M. J. S. Dewar, THIS JOURNAL, **74**, 3357 (1952); (b) M. J. S. Dewar, *Record Chem. Progr. Kresge-Hooker Sci. Lib.*, **19**, 1 (1958).

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(8) G. M. Badger, *ibid.*, **5**, 147 (1951).

(9) G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).

(10) E. C. Kooyman and J. A. A. Ketelaar, *Rec. trav. chim.*, **65**, 859 (1946).