Transformations of 6-Phenylacetamido- and 6-Tritylaminopenicillanyl *p*-Toluenesulfonate and *p*-Nitrobenzenesulfonate

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Received September 2, 1969

6-Tritylaminopenicillanyl *p*-toluenesulfonate (6) formed (6-tritylaminopenicillanyl)pyridinium *p*-toluenesulfonate (9) in hot pyridine. Acid-catalyzed removal of the trityl group afforded (6-aminopenicillanyl)pyridinium *p*-toluenesulfonate (10), hydrogenation of which yielded 6-amino-2,2-dimethyl-3-piperidinomethylpenam (11). The amines 10 and 11 were each converted into the corresponding 6-phenylacetamido, 6-phenoxyacetamido, and 6-(2,6-dimethoxybenzamido) derivatives 12-14 and 15-17, respectively. From 6-phenylacetamido- and 6-tritylaminopenicillanyl *p*-nitrobenzenesulfonate (7 and 8) were prepared the corresponding azides, 18 and 19. The azide 19 was transformed in 4 steps to N-(6-phenylacetamidopenicillanyl)methanesulfonamide (24). Base-catalyzed methanolysis of 5 and 6 gave methyl 4,4-dimethyl- α -(phenylacetamido)-3-thia-1-azabicyclo[3.1.0]-hexane-2-acetate (25) and the corresponding α -tritylamino compound 26, respectively. Further treatment of 25 with base yielded methyl 3-[(3,3-dimethyl-2-thiiranyl)methyl]amino-2-(2-phenylacetamido)-3-(3-methyl-2-butenylamino)acrylate (28) which was hydrolyzed to methyl benzyl penaldate (29) and 3-methyl-2-butenylamino(30). The mechanism of the formation of the aziridines, 25 and 26, and the structure of the *p*-toluenesul-fonates are discussed. Compounds 18 and 24 exhibited antibacterial activity in mice against *Staphylococcus aurcus*.

Replacement of the phenylacetyl group of penicillin G (1) by other acyl groups has led to several valuable semisynthetic derivatives.¹ By comparison with the enormous number of reported variations of the side



chain acyl group relatively few modifications of the ring system have been recorded. No useful drugs have emerged from these changes with the exception of the cephalosporin C class of antibiotics represented by the semisynthetic derivative cephalothin (2).¹



The availability of the alcohols **3** and 4^2 suggested that their sulfonate esters could be versatile intermediates for the synthesis of a variety of novel derivatives which might include products with a ring-expanded structure related to the cephalosporin C ring system.³ With this motivation we prepared the *p*-toluenesulfonates **5** and **6** and *p*-nitrobenzenesulfonates **7** and **8**. We report their behavior with the nucleophiles pyridine, azide ion, and methanol and the results of the antibacterial testing of some of the new derivatives.



Boiling pyridine served to transform the toluenesulfonate **6** to the pyridinium quaternary salt **9** (Scheme I). In contrast, the toluenesulfonate **5** yielded intractable mixtures. A 6-acyl group, as in **5**, very likely contributes to the great reactivity of the β -lactam in penicillins through formation of oxazolone intermediates. Its replacement by the trityl group not only eliminates the possibility of side chain participation⁴ but also provides a degree of steric protection of the β -lactam function. These factors undoubtedly contributed to the survival of the ring system of **6** and **9** in boiling pyridine.

The nmr spectrum of **9** was broad and diffuse but the spectra of the detritylation and reduction products **10** and **11** were well defined. In the case of **11** the coupling constant of 4 Hz for the H₅-H₆ splitting indicated that these protons were still *cis*. Wolfe,⁵ Johnson,⁶ and Bose⁷ observed a coupling constant of 1.5-2.0 Hz for the H₅-H₆ protons in C-6 epimeric penicillins.⁸

Detritylation and hydrogenation gave 10 and 11 which were converted into the amides 12–17. The same acyl groups are known to transform the relatively

⁽¹⁾ F. P. Doyle and J. H. C. Nayler, Advan. Drug Res., 1, 1-69 (1964). This reference provides an excellent introduction to the development of the penicillin and cephalosporin C class of antibiotics.

⁽²⁾ Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, N. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, J. Med. Chem., 7, 483 (1964).

⁽³⁾ R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews [J. Amer. Chem. Soc., 91, 1401 (1969)] report ring expansion of a penicillin sulfoxide to a derivative possessing the cephalosporin C ring system.

⁽⁴⁾ J. C. Sheehan and K. R. Henery-Logan, *ibid.*, **84**, 2983 (1962). These workers used the trityl protecting group in place of an acyl group to prevent oxazolone ring formation from competing with β -lactam ring formation in the cyclization of penicilloic acids to penicillins.

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 ^{(6) (}a) D. A. Johnson, D. Mania, C. A. Panetta, and H. H. Silvestri, Tetrahedron Lett., 1903 (1968);
 (b) D. A. Johnson and D. Mania, *ibid.*, 267 (1969).

⁽⁷⁾ A. K. Bose, G. Speigelman, and M. S. Manhas, J. Amer. Chem. Soc. **90**, 4506 (1968).

⁽⁸⁾ We consider it unlikely in our system that both C-5 and C-6 are inverted to maintain the observed cis relationship of hydrogens at these positions.



inactive 6-aminopenicillanic acid to potent antibacterial agents.

The principal objective of the conversions outlined in Scheme II was the preparation of the sulfonamide 24 in the hope that the acidic sulfonamide group would resemble the carboxyl group in the natural penicillin antibiotics. The nitrobenzenesulfonates 7 and 8 were required for conversion into the azides 18 and 19 by NaN₃ in aqueous acetone since the toluenesulfonates were unaffected under these conditions, and under more vigorous conditions yielded products which lacked β -lactam absorption in the ir. The remaining conversions in Scheme II are routine and require no comment.

In the presence of excess Et_2NH in hot MeOH the toluenesulfonates 5 and 6 were rapidly transformed to the aziridines 25 and 26⁹ (Scheme III). There was no

(9) A report of the methanolysis of the tosylates has appeared in preliminary form: M. R. Bell and R. Oesterlin, *Tetrahedron Lett.*, 4975 (1968).



evidence for the formation of Me ethers. The spectra of the aziridines were in accord with the assigned structures. Resonance peaks occurred in the nmr spectra at 1.74 (2 protons) and 2.12 ppm (1 proton) in the case of 25 and 1.70 (2 protons) and 2.28 ppm (1 proton) in the case of 26. The 4 protons on C of ethylenimine appear as a singlet at 1.62 ppm.¹⁰ The disappearance of the signals assigned to the three-membered ring protons upon exposure to dilute aqueous HCl provided additional evidence for the aziridine ring since aziridines are known to undergo ring opening when treated with mineral acids.¹¹

Employment of excess NaHCO₃ as the catalyst in the methanolysis of 5 led to a mixture of approximately equal parts of 25 and the episulfide enamine 27 in the period of time required for the consumption of 5. The aziridine could be obtained in essentially quantitative yield by use of excess Et₂NH in MeOH; it was transformed to the episulfide by NaHCO₃ in hot MeOH or NaOMe in MeOH at room temperature. In contrast, the aziridine 26 was unaffected by NaHCO₃ or NaOMe in hot MeOH. The structure of the episulfide enamine 27 followed from its strong uv absorption at 280 m μ , characteristic of the β -aminoacrylic ester chromophore,¹² and its desulfurization by PPh₃¹³ in boiling MeCN to the optically inactive enamine 28 without change in the uv absorption. Mild acid hydrolysis of 28 led to penaldic acid Me ester $(29)^{14}$ and 3-methyl-2-butenylamine (30).¹⁵

Neither toluenesulfonate ester was affected by boiling MeOH alone, an observation which suggested the reac-

tion was not initiated by ionization of the sulfonate with participation of the electron pair on the lactam N. If it is assumed that -OMe is generated in a hot solution of NaHCO₃ in MeOH, a simple picture of the reaction course for conversion of 6 into 26 would be attack by -OMe at the lactam CO followed by or simultaneous with formation of the aziridine ring. Alternatively HCO₃⁻ could participate directly by attack at the lactam CO followed by methanolysis of the carbonatecarboxylate mixed anhydride to give 26. The failure to observe diethylamide in the methanolysis of 5 in the presence of twofold excess of Et₂NH supports the view that the transformation of 5 begins by removal of the proton from the side chain N followed by formation of the oxazolone-aziridine intermediate **31**. The expected high reactivity of this oxazolone might account for its



reaction with solvent rather than the more nucleophilic diethylamine. Whatever the explanation, there is precedent for *sec*-amine-catalyzed alcoholysis of oxazo-lones.¹⁶ The intermediate **32**, derived from **25** or **31** in a base-catalyzed elimination process, is a possible precursor to the episulfide enamine **27**.

25 or 31
$$\rightarrow$$
 $\begin{bmatrix} C_{6}H_{3}CH_{2}CONH \\ MeO_{2}C \\ 32 \end{bmatrix} \rightarrow$ 27

The possibility that the sulfonate esters 5–8 possess a ring-expanded tetrahydrothiazine structure 33 must be considered since there is precedent for the apparent participation of the N of an amide group at a cationic center in ring enlargements.¹⁷ The evidence that the products of the reaction with pyridine and N_3^- are indeed penicillin derivatives and not tetrahydrothiazine derivatives is based on their nmr spectra. For example, the spectra of 11 and 18 have a well-defined triplet at 3.88 and 3.85 ppm corresponding to one proton with J = 7 Hz. In the case of the azide 18 a two proton doublet with J = 7 Hz is discernible at 3.30 ppm. These signals are best assigned to the C-3 proton and adjacent CH₂ protons of a penicillin structure.

It is nevertheless conceivable that the sulfonate esters are ring-expanded products since the sequence $33 \rightarrow 34$ $\rightarrow 35$ would regenerate the penicillin nucleus. The step $33 \rightarrow 34$ is analogous to our proposed pathway for the formation of the aziridine 26. The nmr spectra of the sulfonate esters were unrevealing as the C-3 and the adjacent proton signals are clustered in an uninterpretable pattern. Efforts to regenerate the parent alcohol by treatment of the toluenesulfonate esters with sodium naphthalene anion radical¹⁸ gave only complex mixtures

⁽¹⁰⁾ Spectrum No. 372 of the Varian Nmr Spectra Catalog.

⁽¹¹⁾ P. E. Fanta in "Heterocyclic Compounds with Three- and Fourmembered Rings," A. Weissberger, Ed., Interscience, New York, N. Y. 1964, p 551.

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⁽¹⁶⁾ B. J. Nicolet, J. Biol. Chem., 100, 287 (1933).

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⁽¹⁸⁾ W. D. Closson, P. Wreide and S. Bank, J. Amer. Chem. Soc., 88, 1581 (1966).

which appeared to contain none of the parent or closely related carbinol.



If the sequence $33 \rightarrow 35$ is operative we should be able to generate a β -lactam corresponding to 35 from the acid azide 34 (N = N₃⁻). We were unable to prepare this azide but we were able to isolate the corresponding carboxylic acid 37 by cleavage of the *p*-methoxybenzyl ester 36 in trifluoroacetic acid.¹⁹ Efforts to convert 37



via activated ester intermediates into a β -lactam with concomitant cleavage of the aziridine ring resulted in mixtures which exhibited no ir β -lactam absorption. The products did display strong absorption at 320 m μ characteristic of the penicillenic acid chromophore.²⁰ Clearly oxazolone ring formation had occurred rather than acylation of the aziridine ring N. It thus appears unlikely that the process $34 \rightarrow 35$ would be operative and we favor, therefore, the unrearranged structures 5-8 for the sulfonate esters.

Biological Results.²¹—Compounds 18 and 24 were tested *in vitro* against a variety of Gram-positive and Gram-negative bacteria. A minimum inhibitory concentration of about 12 μ g/ml was observed for 18 when tested against *Staphylococcus aureus* 209 but the compound was inactive when tested against other bacteria. Compounds 12–17 and 24 were inactive *in vitro* when tested against *S. aureus*.

When tested *in vivo* in mice infected with *S. aureus* Smith, **18** provided 100% protection from lethality at a dose of 200 mg/kg orally but was less active at lower doses. The derivative **24** provided 100% protection at

50 mg/kg subcutaneously but was orally inactive. These compounds are much less active than penicillin G_{c}^{22} results which serve to emphasize the importance of a carboxyl group at C-3 in a penicillin for maximal antibacterial activity.

Experimental Section

Melting points were taken in capillary tubes in an oil bath. They are not corrected but are within 1° of the melting points of standards. Spectra were determined under the supervision of Dr. R. K. Kullaig. Nmr spectra were determined with a Varian Model A-60 nmr spectrometer (TMS). Ir spectra were determined with a Perkin-Elmer Model 21 spectrophotometer, uv spectra with a Carey Model 15 spectrophotometer. Spectra were determined on all compounds and are in accord with the indicated structures. Spectra are reported only for compounds of unusual structure, for key compounds which were not obtained in crystalline form, and for compounds where the spectra provided crucial evidence for their structure. Analyses were carried out under the supervision of Mr. K. D. Fleischer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

6-Phenylacetamidopenicillanyl p-Toluenesulfonate (5). To 40 g (0.125 mol) of crude 3° in 210 ml of pyridine was added with stirring at -20° 26 g (0.137 mol) of TsCl. After storage at 0.5° for 4 hr the clear, red solution was slowly treated with ice and then ice -H₂O. The product was extracted (CH₂Cl₂) and washed in the cold with 10° (H₃PO₄ until acidic, then with H₂O and saturated NaHCO₅. The dried (Na₂SO₄) fibrate was evaporated at 25° and the residual gummy solid (61 g) crystallized (MeOH) to afford 25 g (42°) of solid, mp 122–124° dec. It was recrystallized from MeOH: mp 120–122.5° dec; ir (KBr) 5.65 (β-lactam > C==O) and 5.99 μ (anide > C==O); mut (CDCl₃) δ 1.26 and 1.37 [s each, 3 each, C(CH₃)₃], 2.42 (s, 3. aryl-CH₃), 3.58 (s, 2, aryl-CH₂), 3.75-4.3 (m, 3, > CHCH₂O), 5.05 (d, 1, J = 4.5 Hz, C-5H), 5.25–5.60 (m, 1, J = 4.5 and 9 Hz, NH) and 7.2–8.0 ppm (m, 9. aryl H). Anal. (C₂₃H₂₆N₂O₅S₂) C, H, N, S.

6-Tritylaminopenicillaryl *p*-toluenesulfonate (6) was prepared in the same manner as **5**. It crystallized readily (CHCl₈) forming a solvate with 1 mol of CHCl₈. The analytical sample was purified by dry column chromatography²³ using alumina as absorbent and Et₂O as solvent: mp 102-105° dec; ir (KBr $5.65 \ \mu \ (\beta\text{-lactam} > C = O); \text{ mmr} \ (\text{CDCl}_3) \ \delta \ 1.26 \text{ and} \ 1.40 \text{ Is}$ each, 3 each, $\text{C}(\text{CH}_3)_2$, 2.35 (s, 3, aryl-CH₈), 3.08 (broad, 1, NH), 3.7-4.4 (m, 5, C-3H, C-5H, C-6H, CH₂O), and 7.0-7.9 ppm (m, 16, aryl H, CHCl₈). Anal. (C₃₄H₃₄N₂O₄S₂·CHCl₈) C, H, Cl, N.

6-Phenylacetamidopenicillanyl *p*-nitrobenzenesulfonate (7) was prepared in the same manner as **5** using *p*-nitrobenzenesulfonyl chloride and isolated as a foam: ir (CHCl₄) 5.62 (lactam >C=0), 5.91 (amide >C=0), and 6.54, 7.45 μ (NO₂).

6-Tritylaminopenicillanyl p-Nitrobenzenesulfonate (8). The ester was prepared in the same manner as 7 and isolated as a glass containing some residual Et₂O: ir (CHCl_z) 5.65 (lactam >C₂=O), 6.53 and 7.45 μ (NO₂): nmr (CDCl₃) δ 1.27 and 1.42 [s each, 6, C(CH₃)₂], 3.17 (d, 1, J = 11.5 Hz, NH), 3.75 4.5 (m, 5, C-3H, C-5H, C-6H, CH₂), 7.0-7.67 (m, 15, aryl H), and 7.83-8.42 ppm (m, A₂B₂, 4, aryl H).

1-(6-Tritylaminopenicillanyl)pyridinium p-Toluenesulfonate (9). A solution of 43 g (0.06 mol) of 6 in 300 ml of pyridine was refluxed for 8 hr under N₂. The solution was cooled and 300 ml of Et₂O was slowly added to give 30 g ($70C_{\ell}$) of crystalline product. A 10-g portion of this product was twice recrystallized from MeCN to give 6 g ($41C_{\ell}$) of 9 as a monohydrate acetonitrile solvate, mp 130° dec. Anal. ($C_{39}H_{39}N_3O_4S_2 \cdot CH_3CN \cdot H_2O$) C H N.

1-(6-Aminopenicillanyl)pyridinium Di-p-toluenesulfonate (10).

To 15 g (0.021 mol) of **9** in 450 ml of CHCl₈ was added 4 g (0.021 mol) of TsOH. The solution was stirred at 25° for 0.5 hr. The product precipitated from the reaction solution, 12.5 g (97%). The analytical sample was prepared by recrystallization

⁽¹⁹⁾ The stability of the aziridine ring of **36** and **25** in trifluoroacetic acid contrasts with the lability of this ring system in **25** in aqueous mineral acid.

⁽²⁰⁾ Reference 14, p 162.

⁽²¹⁾ We are indebted to Dr. William A. Goss and Dr. John R. O'Connor for biological test results. In vitro test methodology may be found in W. A. Goss and E. B. Cimijotti, Appl. Microbiol., **16**, 1414 (1968). In vivo test methodology was essentially the same as that described in ref 22.

⁽²²⁾ G. J. Miraglia and H. L. Basch, *ibid.*, 556 (1967).

⁽²³⁾ B. Loev and M. M. Goodman, Chem. Ind. (London), 2026 (1967).

from DMF-CHCl₃, mp 121-123° dec. Anal. $(C_{27}H_{33}N_3O_7S_3 \cdot 2H_2O)$ C, H, N.

6-Amino-2,2-dimethyl-3-piperidinomethylpenam (11).—A suspension of 10 g of 10% Pd–C in 250 ml of DMF was prereduced at 3.5 kg cm⁻² of H₂. Compound 10 (12.2 g) was added and the hydrogenation was continued. Theoretical uptake of H₂ was achieved in 2 hr at 3.1 kg cm⁻². The filtered solution was diluted with 3 l. of ether. A gum separated which gradually crystallized. The product was filtered and washed with E_{20} to give 12 g (95%) of white crystals. The product was recrystallized from DMF-Me₃CO, mp 168–171° dec. Anal. (C₁₃H₂₃N₃OS·2 C₇H₈-SO₃·H₂O) C, H, N.

The free base was liberated by treatment with cold 1 N NaOH followed by extraction with Et₂O: mp 77-79° (hexane); nmr (CDCl₃) δ 1.16-2.17 [m, 14, C(CH₃)₂, (CH₂)₃, NH₂], 2.25-2.83 [m, 6, N(CH₂)₃], 3.9 (t, 1, C-3H), 4.43 (d, 1, J = 4 Hz, C-5H), 5.22 ppm (d, 1, J = 4 Hz, C-6H). Anal. (C₁₃H₂₃N₃OS) C, H, N, S.

Preparation of 12-17.—None of these derivatives was obtained in crystalline form. In the case of the pyridinium salts 12-14 the ir was checked for the presence of strong β -lactam and amide bands. The tlc, ir, and nmr of 15-17 showed them to be quite pure preparations. The acylations of the quaternary salt 10 were carried out in DMF at -78° in the presence of 2 moleequiv of triethylamine. The acylations of 11 (free base form) were performed in alcohol-free CHCl₃ at -78° . When acylations were performed at 0° the products displayed strong absorption at 320 m μ characteristic of the penicillenic acid chromophore.²⁰ This absorption was absent in the products isolated from acylations at -78° .

6-Phenylacetamidopenicillanyl Azide (18).---A solution of 55 g (0.109 mol) of the *p*-nitrobenzenesulfonate ester 7 and 7.1 g (0.109 mol) of NaN₃ in 1.2 l. of Me₂CO and 120 ml of H₂O was refluxed for 25 hr. The reaction mixture was evaporated in vacuo at 25° and the residue was partitioned between EtOAc and H_2O . The organic layer was separated, washed with H_2O and brine, dried (Na₂SO₄), and evaporated in vacuo at 25°. The crude product (40 g) was chromatographed on 1200 g of Florisil and eluted with Et₂O containing 5% EtOAc. Fractions which were shown by tlc to contain the desired product only were combined and evaporated yielding 15.5 g (40%) of a pale yellow viscous oil. Upon long standing a sample of this product crystallized. It was recrystallized from 1:3 EtOAc-hexane to afford white crystals: mp 91–93°; nmr (CDCl₃) δ 1.29, 1.4 [s each, 6, C(CH₃)₂], 3.32 (d, 2, CH₂N₃), 3.57 (s, 2, CH₂CO), 3.85 (t, 1, C-3H), 5.17–5.67 (m, 2, C-5H, C-6H), 6.08–6.5 (d, 1, J =9.5 Hz, NH), and 7.22 ppm (s, 5, aryl H). Anal. (C₁₆H₁₉N₅O₂S) C, H, N, S.

The azide 18 was also prepared by phenylacetylation of the amine 20.

6-Tritylaminopenicillanyl Azide (19).—This preparation was carried out in the same manner as the azidolysis of 7. The product crystallized from hexane to afford a white solid (57% yield), mp 138–140°. It was recrystallized from hexane, mp 139–140.5°. Anal. ($C_{27}H_{27}N_{3}OS$) N, S.

6-Aminopenicillaryl Azide (20).—To a solution of 9.5 g (0.02 mol) of the azide 19 in 200 ml of Me₂CO was added 3.85 g (0.02 mol) of TsOH. The solution was stirred at 25° in the dark for 0.5 hr and evaporated *in vacuo* at 25°. The gummy residue solidified when triturated with Et₂O. The solid was filtered and washed to give 5.85 g (74%) of off-white product. A sample was recrystallized from EtOAc to afford off-white crystals of the *p*-toluenesulfonate, mp 115–116° dec. Anal. (C₃H₁₃N₅OS. C₇H₈O₃S) C, H, S; N: calcd, 17.53; found, 16.72.

3-Aminomethyl-2,2-dimethyl-6-tritylaminopenam (21).—A suspension of 10 g of 10% Pd-C in 200 ml of EtOAc was prereduced at 3.5 kg/cm⁻² of H₂. A solution of 10 g (0.0214 mol) of **19** in 50 ml of EtOAc was added and the hydrogenation was continued for 20 min. The product crystallized as a cyclohexane solvate from $\text{Et}_2\text{O}-\text{C}_6\text{H}_{12}$, 7.9 g (70%) of a white solid. It was recrystallized from $\text{Et}_2\text{O}-\text{C}_6\text{H}_{12}$, mp 108–112° dec. Anal. (C₂₇H₂₉N₈OS·C₆H₁₂) C, H, N, S.

N-(6-Tritylaminopenicillanyl)methanesulfonamide (22).—To a solution of 9.3 g (0.0176 mol) of the amine 21 in 72 ml of pyridine at -40° was added dropwise a solution of 2.01 g (0.0176 mol) of MeSO₂Cl in 18 ml of pyridine. The reaction mixture was stirred at -40° for 10 min and was allowed to warm to 25° over 1.5 hr. The yellow solution was treated with ice, poured into ice-H₂O, and extracted with EtOAc. The extract was washed with 10% H₂PO₄ (until acidic), H₂O, and brine. The solution was dried (Na₂SO₄), charcoaled, and evaporated *in* vacuo. The residue was crystallized from a minimum amount of hot C₆H₆ to afford 4.8 g (52%) of matted crystals, mp 182–184° dec. A sample was recrystallized from 1:1 EtOAc-C₆H₁₂, mp 181–183° dec. Anal. (C₂₈H₈₁N₃O₃S₂), C, H, N.

N-(6-Aminopenicillanyl)methanesulfonamide (23).—A solution of 4.8 g (0.009 mol) of 22 in 45 ml of Me₂CO was combined with a solution of 1.75 g (0.0092 mol) of TsOH in 45 ml of Me₂CO and stirred at 25° for 1 hr. The crystalline product was filtered, dissolved in a minimum amount of MeOH, and precipitated with absolute Et₂O to afford 2.55 g (62%) of the *p*-toluenesulfonate as a hemihydrate, mp 85–135° dec. *Anal.* (C₉H₁₇N₃O₃-S₂·C₁H₃O₃S·0.5 H₂O) C, H; N: calcd, 9.12; found, 8.53; S: calcd, 20.88; found, 20.45.

N-(6-Phenylacetamidopenicillanyl)methanesulfonamide (24). —This compound was obtained from 20 g (0.058 mol) of 23 in 18% yield in a manner analogous to the preparation of 18. It was recrystallized from EtOAc to afford 4.2 g of white crystals, mp 184–185°. Anal. (C₁₂H₂₃N₃O₄S₂) C, H, N.

Methyl 4,4-Dimethyl- α -(phenylacetamido)-3-thia-1-azabicyclo[3.1.0] hexane-2-acetate (25).—A solution of 20 g (0.042 mol) of 5 and 4.8 ml (0.046 mol) of Et_2NH in 500 ml of absolute MeOH was refluxed for 3 hr. The solvent was removed in vacuo, and the residue was dissolved in CH₂Cl₂ and washed (H₂O, brine). The dried (Na_2SO_4) filtrate was evaporated. The residual syrup was taken up in excess absolute $\mathrm{Et}_2\mathrm{O}$ and concentrated to 100ml to afford 11.4 g (81%) of white crystals, mp 104-106°. An earlier sample was recrystallized from C6H6-hexane: mp 104-106.6°; $[\alpha]^{25}D + 68.2^{\circ}$ (c 1, CHCl₃); uv max (95% EtOH) benzene envelope; ir (CHCl₃) 5.73 (ester >C=O) and 5.99 μ (amide >C=0); nmr (CDCl₃) δ 1.43, 1.53 [s each, 3 each, C(CH₃)₂], 1.58–1.83 (m, 2, NCH₂), 2.16–2.41 (m, 1, CH₂CHC), (s, 2, aryl-CH₂), 3.69 (s, 3, OCH₃), 4.41-4.83 (m, 2, CHCH), 6.49 (d, broad 1, NH), and 7.29 ppm (s, 5, aryl H). Anal. (C₁₇H₂₂-N₂O₃S) C, H, N, S.

When the reaction was carried out with 3 mol-equiv of Et₂NH no sign of diethylamide could be discerned in the nmr spectrum of the total crude product.

Methyl 4,4-Dimethyl- α -(tritylamino)-3-thia-1-azabicyclo-[3.1.0]hexane-2-acetate (26).—A suspension of 10 g (0.0139 mol) of 6, 3.4 g (0.0404 mol) of NaHCO₃, and 200 ml of MeOH was stirred at reflux for 2 hr. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ and washed (H₂O, brine). The dried (Na₂SO₄) filtrate was evaporated and the residual gum was crystallized from hexane to give 6.0 g (94%) of white product. It was recrystallized from hexane: mp 130–131.5°; uv max (95% EtOH) benzene envelope; ir (KBr) 5.7 μ (ester >C=O); nmr (CDCl₃) δ 1.20, 1.35 [s each, 3 each, C(CH₃)₂], 1.60–1.90 (m, 2, NCH₂), 2.0–2.25 (m, 1, CH₂CHC), 3.15 (s, 3, OCH₃), 3.0–3.6 (m, 2, COCHNH), 4.76 (d, 1, J = 9 Hz, COCHN). Anal. (C₂₈H₃₀N₂O₂S) N, S.

Methyl 3-[(3,3-Dimethyl-2-thiiranyl)methylamino]-2-(2-phenylactamido)acrylate (27).—A solution of 14 g (0.042 mol) of 25 and 2.5 g (0.0465 mol) of NaOCH₃ in 480 ml of MeOH was stirred at 25° for 1.75 hr. (This conversion could also be accomplished with NaHCO₃ in hot MeOH.) The solvent was removed at 25° and the residue dissolved in Et₂O and washed (H₂O, brine). The dried (Na₂SO₄) filtrate was concentrated to give 10.7 g (76%) of white crystals, mp 111.5-113°. A sample was recrystallized from Et₂O: mp 112.5-114°; [α]²⁵D + 18.6° (c 1, CHCl₃); uv max (95% EtOH) 279 m μ (ϵ 21,800): ir (KBr) 5.91 (ester >C=O), and 6.01 μ (amide >C=O); nmr (CDCl₃) δ 1.55 [s, 6, C(CH₃)₂], 2.66-3.00 (m, 1, > CHS), 3.38 (app t, 2, NCH₂CH), 3.61 (s, 5, aryl-CH₂, OCH₃), 5.82-6.58 (m, 1, >NH), and 6.91-7.66 ppm (m, 7, aryl H, = CHN, >CONH). Anal. (C₁₇H₂₂N₂O₃S) C, H, N.

Methyl 2-(2-Phenylacetamido)-3-(3-methyl-2-butenylamino)acrylate (28).—A solution of 2 g (0.006 mol) of 27 and 1.6 g (0.0061 mol) of PPh₃ in 75 ml of MeCN was refluxed for 20 hr. The solvent was evaporated and the residue treated with Et₂O. The white crystals were filtered and recrystallized (EtOH) to give 1.3 g (74%) of triphenylphospine sulfide, mp 161–163° lit.^{13b} mp 158°). Anal. (C₁₅H₁₅PS) C, H.

The $\dot{E}t_2O$ filtrate and washings were combined and evaporated to afford 2.25 g of a light yellow oil. It was chromatographed on 60 g of alumina. Elution with Et_2O and then EtOAc furnished 1.9 g of a pale yellow gum which crystallized when triturated with Et_2O . It was recrystallized from hexane to give 1.4 g (78%) of white crystals: mp 80–84°; $[\alpha]^{25}D + 1.4 \pm 0.3^{\circ}$ (c 1, CHCl₃); uv max (95% EtOH) 282 m μ (ϵ 22,000); ir (KBr) 5.88 (ester > C=O), 6.09 (amide > C=O), and 6.18 μ (>C=C<): mur (CDCl₃) δ 1.62, 1.70 [s each, 3 each, C(CH₃)₂], 3.58 (s, 3, OCH₃), 3.33–4.0 (m, 4, CH₂N and aryl-CH₂), 5.15 [t, 1, J = 7 Hz, CH = C(CH₃)₂], 5.50–6.00 (m, 1, C=CNH), and 6.83–7.66 ppm (m, 7, aryl H, =CHN, CONH). Anal. (C₁₇H₂₂N₂O₃) C, H, N.

Hydrolysis of 28 to Methyl Benzylpenaldate (29) and 3-Methyl-2-butenylamine (30).—To 0.5 g (0.00165 mol) of 28 in 25 ml of warm MeOH was added 0.33 g (0.00165 mol) of 2,4-dinitrophenylhydrazine in 60 ml of warm MeOH and 4 drops of concentrated HCl. The solution was left at 25° overnight. The mixture was cooled to 0°, filtered, and washed with cold MeOH to give 0.5 g (73%) of yellow, matted needles, mp 180–181°: mixture melting point with authentic 2,4-dinitrophenylhydrazone of methyl benzylpenaldate¹⁴ showed no depression.

The MeOH filtrate was evaporated to dryness and the residue partitioned in CHCl₃-H₂O. The aqueous phase was separated, washed (CHCl₃), and then evaporated *in vacuo* to give a yellowish solid. It was recrystallized from EtOH-Et₂O to afford 0.15 g of shiny leaflets, mp 194.5-198° dec, identical with authentic **30** (ir spectrum, nixture melting point).¹⁵

p-Methoxybenzyl 4,4-Dimethyl- α -(phenylacetamido)-3-thia-1azabicyclo[3.1.0] hexane-2-acetate (36).—Compound 5 (1 g, 0.0021 mol) was heated with 0.34 ml (0.0023 mol) of Et₃N and 4 ml of *p*-anisyl alcohol on a steam bath for 3 hr. The yellow solution was diluted (CHCl₃) and washed (H₂O, 5^C_C H₃PO₄, H₂O until neutral pH, saturated brine). The dried (Na₂SO₄) filtrate was evaporated and some of the excess *p*-anisyl alcohol distilled at 65–80° and 0.07 mm (oil bath temperature 95°). The residual viscous oil was purified by preparative the (silica plates, benzene Et₂O 1;1). Isolation of the band next to the origin afforded 650 mg of a colorless gum: ir (CHCl₃) 5.73 (ester > C==O) and 5.97 μ (anide > C==O); nmr (CDCl₃) δ 1.4, 1.5 [s each, 3 each, C(CH₃)₂], 1.57–1.83 (m, 2, NCH₂), 2.13 - 2.38 (m, 1, CH₂CHC), 3.58 (s, 2, aryl-CH₂), 3.73 (s, 3, OCH₃), 4.58–4.75 (m, 2, CHCH), 5.07 (s, 2, aryl-CH₂O), 6.2–6.6 (broad, 1, NH), and 6.7–7.4 ppm (m, 9, aryl H).

4,4-Dimethyl-\alpha-(phenylacetamido)-3-thia-1-azabicyclo[3.1.0]-hexane-2-acetic Acid (37).—A sample of **36** was treated in the cold with TFAA to give a deep red solution. After 5 min the excess acid was evaporated *in vacuo* at 25°. The residual red mush was dissolved in CHCl₃ and washed in the cold with saturated NaHCO₃. The basic extracts were combined and acidified in the cold with 10⁺/₄ aqueous H₃PO₄ to pH 3. The gum was extracted with cold CHCl₃ and the combined organic fractions washed (H₂O, brine). The dried (Na₂SO₄) filtrate was evaporated *in vacuo* at 25° to afford a colorless, amorphous solid; ir (CHCl₃) 3.8–4.1 (broad OH), 5.79 (acid > C=O), and 5.98 μ (anide > C=O); nmr (CDCl₄) § 1.4, 1.5 [s each, 3 each, C(CH₃)₂], 1.67–2.0 (m, 2, NCH₂), 2.33–2.67 (m, 1, CH₂CHC), 3.6 (s, 2, ary]-CH₂), 4.42–5.08 (m, 2, CHCH), 7.0–7.42 (m, 6, ary] H, NH), and 10.6 ppm (s, 1, COOH). The carboxylic acid was unstable at room temperature in the anorphous state or in chloroform solution. The change was apparent from the innur spectra which became diffuse and uninterpretable.

2-Tetrahydropyridylindoles as Histamine and Serotonin Antagonists

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Received July 9, 1969

A series of 2-(1-methyl-1,2,5,6-tetrahydro-3(and 4)-pyridyl)indoles was synthesized by borohydride reduction of the corresponding pyridinium compounds. The compounds were tested for antihistaminic and antiserotonin activity.

During an investigation of 2-tetrahydropyridylindoles 1 as intermediates in the synthesis of certain model indole alkaloid systems, it was found that a few of these compounds exhibited antihistaminic and antiserotonon activity. We noticed that those compounds with an indole-*N*-benzyl moiety bore structural resemblance to clemizole (2);¹ structural features of the serotonin antagonist benanserin $(3)^2$ are also present.

This paper describes the synthesis and pharmacological action of a small series of such compounds (Table I). Our objective was to obtain a compound which possessed both good antihistaminic and antiserotonin activity.



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The general synthetic method involves Fischer cyclization of the appropriate hydrazone 4 followed by quaternization and BH_4^- reduction of the pyridylindoles 5. When R was benzyl or Me thermal indolization was preferred over the usual acid-catalyzed procedure.

