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

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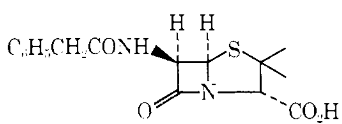
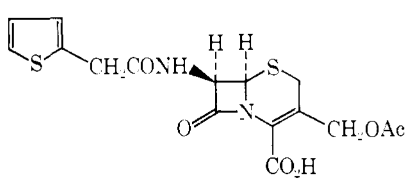
6-Tritylaminopenicillanyl *p*-toluenesulfonate (**6**) formed (6-tritylaminopenicillanyl)pyridinium *p*-toluenesulfonate (**9**) in hot pyridine. Acid-catalyzed removal of the trityl group afforded (6-aminopenicillanyl)pyridinium *p*-toluenesulfonate (**10**), hydrogenation of which yielded 6-amino-2,2-dimethyl-3-piperidinomethylpenam (**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)acrylate (**27**). The proof of structure of **27** consisted, in part, of desulfurization to methyl 2-(2-phenylacetamido)-3-(3-methyl-2-butenylamino)acrylate (**28**) which was hydrolyzed to methyl benzyl penaldate (**29**) and 3-methyl-2-butenylamine (**30**). The mechanism of the formation of the aziridines, **25** and **26**, and the structure of the *p*-toluenesulfonates are discussed. Compounds **18** and **24** exhibited antibacterial activity in mice against *Staphylococcus aureus*.

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



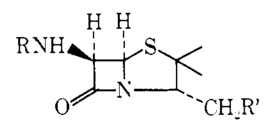
**1**

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]



**2**

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.



**3**, R = $C_6H_5CH_2CO$; R' = OH
**4**, R = $(C_6H_5)_3C$; R' = OH
**5**, R = $C_6H_5CH_2CO$; R' = OTs
**6**, R = $(C_6H_5)_3C$; R' = OTs
**7**, R = $C_6H_5CH_2CO$; R' = ONs
**8**, R = $(C_6H_5)_3C$; R' = ONs

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 participation[4] 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 $H_5$–$H_6$ splitting indicated that these protons were still *cis*. Wolfe,[5] Johnson,[6] and Bose[7] observed a coupling constant of 1.5–2.0 Hz for the $H_5$–$H_6$ 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.

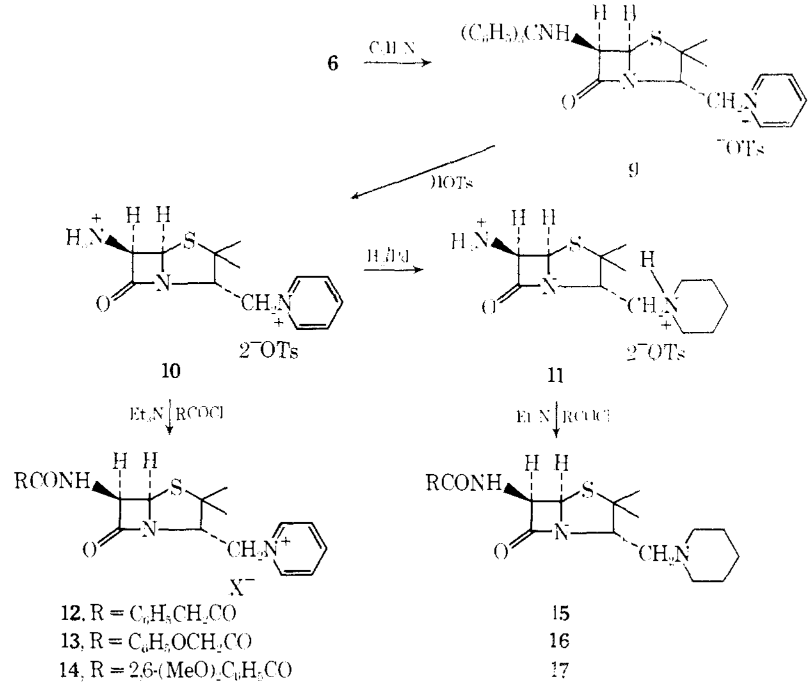
(5) S. Wolfe and W. S. Lee, *Chem. Commun.*, 242 (1968).

(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).

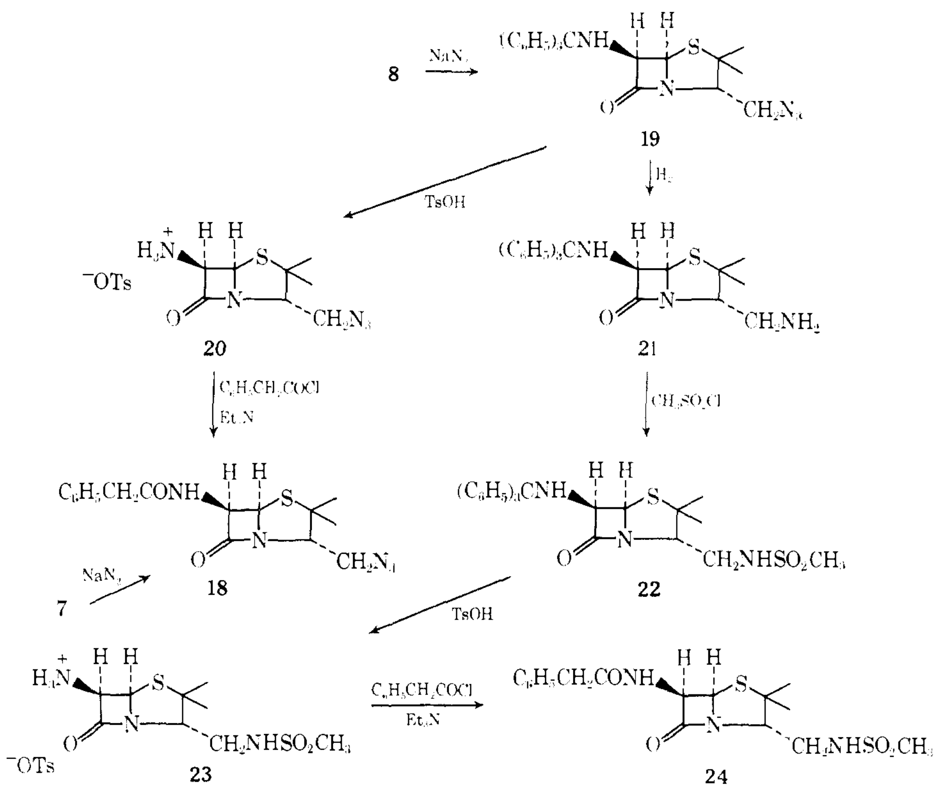
(7) A. K. Bose, G. Speigelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, **90**, 4506 (1968).

(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.

Scheme I



Scheme II



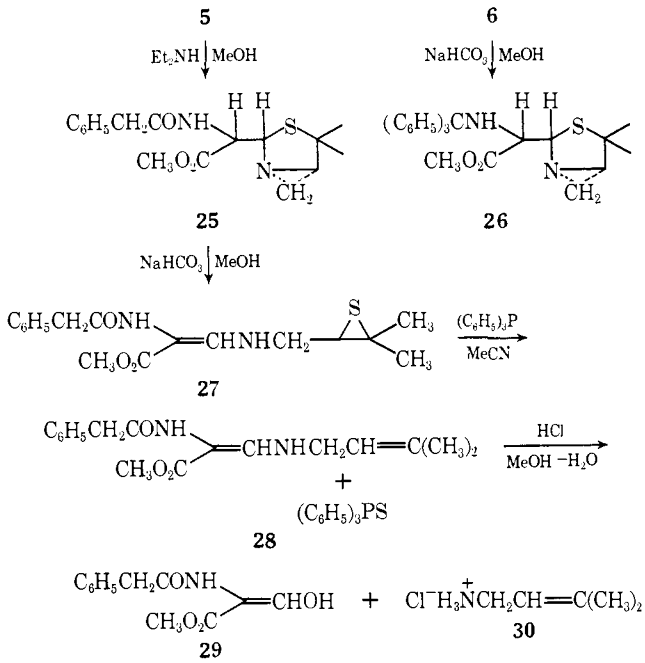
inactive 6-aminopenicillanic acid to potent antibacterial agents.

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 $NaN_3$ in aqueous acetone since the toluenesulfonates were unaffected under these conditions, and under more vigorous conditions yielded products which lacked $\beta$-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 **26**[9] (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).

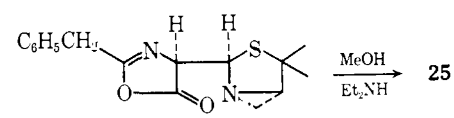
Scheme III



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]

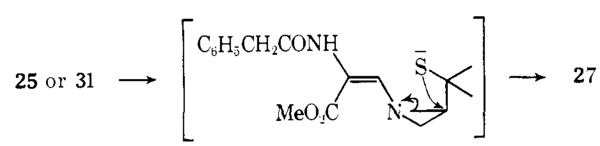
Employment of excess $NaHCO_3$ as the catalyst in the methanolysis of **5** led to a mixture of approximately equal parts of **25** and the episulfide enamine **27** in the period of time required for the consumption of **5**. The aziridine could be obtained in essentially quantitative yield by use of excess $Et_2NH$ in MeOH; it was transformed to the episulfide by $NaHCO_3$ in hot MeOH or NaOMe in MeOH at room temperature. In contrast, the aziridine **26** was unaffected by $NaHCO_3$ or NaOMe in hot MeOH. The structure of the episulfide enamine **27** followed from its strong uv absorption at 280 m$\mu$, characteristic of the $\beta$-aminoacrylic ester chromophore,[12] and its desulfurization by $PPh_3$[13] 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 reaction 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 $NaHCO_3$ 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 $HCO_3^-$ could participate directly by attack at the lactam CO followed by methanolysis of the carbonate–carboxylate mixed anhydride to give **26**. The failure to observe diethylamide in the methanolysis of **5** in the presence of twofold excess of $Et_2NH$ 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



**31**

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



**32**

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 $CH_2$ protons of a penicillin structure.

It is nevertheless conceivable that the sulfonate esters are ring-expanded products since the sequence **33** → **34** → **35** would regenerate the penicillin nucleus. The step **33** → **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 radical[18] gave only complex mixtures

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

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

(12) S. A. Glickman and A. C. Cope, *J. Amer. Chem. Soc.*, **67**, 1017 (1945).

(13) (a) R. E. Davis, *J. Org. Chem.*, **23**, 1767 (1958); (b) D. B. Denney and M. J. Boskin, *J. Amer. Chem. Soc.*, **82**, 4736 (1960).

(14) R. L. Peck and K. Folkers in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson Ed., Princeton University Press, Princeton, N. J., 1949, p 73.

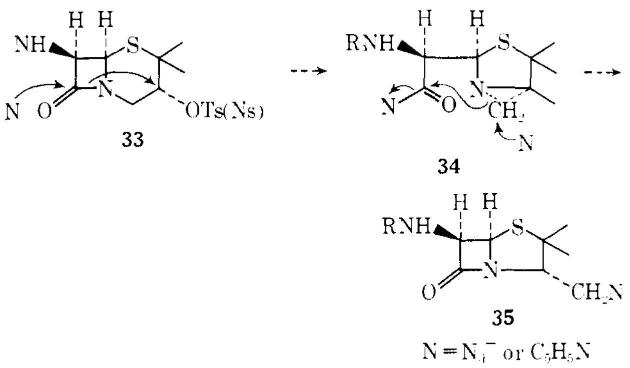
(15) D. Semenow, C. Shih and W. G. Young, *J. Amer Chem. Soc.*, **80**, 5472 (1958).

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

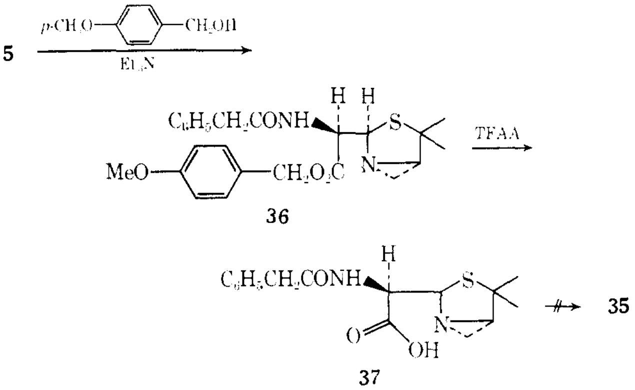
(17) (a) G. Buchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Amer. Chem. Soc.*, **88**, 3099 (1966); (b) J. W. Huffman, T. Kamiya, and C. B. S. Rao, *J. Org. Chem.*, **32**, 700 (1967); (c) B. Capon, *Quart. Rev.* (London), 71 (1964).

(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** → **35** is operative we should be able to generate a β-lactam corresponding to **35** from the acid azide **34** (N = $N_3^-$). 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 mμ 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** → **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 μg/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,[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. Kullnig. 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**[2] 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-$H_2O$. The product was extracted ($CH_2Cl_2$) and washed in the cold with 10% $H_3PO_4$ until acidic, then with $H_2O$ and saturated $NaHCO_3$. The dried ($Na_2SO_4$) filtrate 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 (amide > C=O); nmr ($CDCl_3$) δ 1.26 and 1.37 [s each, 3 each, C($CH_3$)$_2$], 2.42 (s, 3, aryl-$CH_3$), 3.58 (s, 2, aryl-$CH_2$), 3.75–4.3 (m, 3, > CH$CH_2$O), 5.05 (d, 1, *J* = 4.5 Hz, C-5**H**), 5.25–5.60 (m, 1, *J* = 4.5 and 9 Hz, C-6**H**), 6.4 (d, 1, *J* = 9 Hz, N**H**) and 7.2–8.0 ppm (m, 9, aryl **H**). *Anal.* ($C_{23}H_{26}N_2O_5S_2$) C, H, N, S.

**6-Tritylaminopenicillanyl *p*-toluenesulfonate (6)** was prepared in the same manner as **5**. It crystallized readily ($CHCl_3$) forming a solvate with 1 mol of $CHCl_3$. The analytical sample was purified by dry column chromatography[23] using alumina as absorbent and $Et_2O$ as solvent: mp 102–105° dec; ir (KBr) 5.65 μ (β-lactam > C=O); nmr ($CDCl_3$) δ 1.26 and 1.49 [s each, 3 each, C($CH_3$)$_2$], 2.35 (s, 3, aryl-$CH_3$), 3.08 (broad, 1, N**H**), 3.7–4.4 (m, 5, C-3**H**, C-5H, C-6**H**, $CH_2$O), and 7.0–7.9 ppm (m, 16, aryl **H**, $CHCl_3$). *Anal.* ($C_{34}H_{34}N_2O_3S_2 \cdot CHCl_3$) 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 ($CHCl_3$) 5.62 (lactam >C=O), 5.91 (amide >C=O), and 6.54, 7.45 μ ($NO_2$).

**6-Tritylaminopenicillanyl *p*-Nitrobenzenesulfonate (8).**—The ester was prepared in the same manner as **7** and isolated as a glass containing some residual $Et_2O$: ir ($CHCl_3$) 5.65 (lactam >C=O), 6.53 and 7.45 μ ($NO_2$); nmr ($CDCl_3$) δ 1.27 and 1.42 [s each, 6, C($CH_3$)$_2$], 3.17 (d, 1, *J* = 11.5 Hz, N**H**), 3.75–4.5 (m, 5, C-3**H**, C-5**H**, C-6**H**, $CH_2$), 7.0–7.67 (m, 15, aryl **H**), and 7.83–8.42 ppm (m, $A_2B_2$, 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 $N_2$. The solution was cooled and 300 ml of $Et_2O$ was slowly added to give 30 g (70%) of crystalline product. A 10-g portion of this product was twice recrystallized from MeCN to give 6 g (41%) of **9** as a monohydrate acetonitrile solvate, mp 130° dec. *Anal.* ($C_{39}H_{39}N_3O_3S_2 \cdot CH_3CN \cdot H_2O$) C, H, N.

**1-(6-Aminopenicillanyl)pyridinium Di-*p*-toluenesulfonate (10).** To 15 g (0.021 mol) of **9** in 450 ml of $CHCl_3$ 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 R. L. Basch, *ibid.*, 556 (1967).

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

from DMF–$CHCl_3$, 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 $H_2$. Compound **10** (12.2 g) was added and the hydrogenation was continued. Theoretical uptake of $H_2$ 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 $Et_2O$ to give 12 g (95%) of white crystals. The product was recrystallized from DMF–$Me_2CO$, mp 168–171° dec. *Anal.* ($C_{13}H_{23}N_3OS\cdot 2\ C_7H_8SO_3\cdot H_2O$) C, H, N.

The free base was liberated by treatment with cold 1 *N* NaOH followed by extraction with $Et_2O$: mp 77–79° (hexane); nmr ($CDCl_3$) δ 1.16–2.17 [m, 14, $C(CH_3)_2$, $(CH_2)_3$, $NH_2$], 2.25–2.83 [m, 6, $N(CH_2)_3$], 3.9 (t, 1, C-3**H**), 4.43 (d, 1, $J$ = 4 Hz, C-5**H**), 5.22 ppm (d, 1, $J$ = 4 Hz, C-6**H**). *Anal.* ($C_{13}H_{23}N_3OS$) 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 mole-equiv of triethylamine. The acylations of **11** (free base form) were performed in alcohol-free $CHCl_3$ at −78°. When acylations were performed at 0° the products displayed strong absorption at 320 mμ 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 $NaN_3$ in 1.2 l. of $Me_2CO$ and 120 ml of $H_2O$ 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 ($Na_2SO_4$), and evaporated *in vacuo* at 25°. The crude product (40 g) was chromatographed on 1200 g of Florisil and eluted with $Et_2O$ 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 ($CDCl_3$) δ 1.29, 1.4 [s each, 6, $C(CH_3)_2$], 3.32 (d, 2, $CH_2N_3$), 3.57 (s, 2, $CH_2CO$), 3.85 (t, 1, C-3**H**), 5.17–5.67 (m, 2, C-5**H**, C-6**H**), 6.08–6.5 (d, 1, $J$ = 9.5 Hz, N**H**), and 7.22 ppm (s, 5, aryl **H**). *Anal.* ($C_{16}H_{19}N_5O_2S$) 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.* ($C_{27}H_{27}N_5OS$) N, S.

**6-Aminopenicillanyl Azide** (20).—To a solution of 9.5 g (0.02 mol) of the azide **19** in 200 ml of $Me_2CO$ 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 $Et_2O$. 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.* ($C_8H_{13}N_5OS\cdot C_7H_8O_3S$) 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 $H_2$. 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 $Et_2O$–$C_6H_{12}$, 7.9 g (70%) of a white solid. It was recrystallized from $Et_2O$–$C_6H_{12}$, mp 108–112° dec. *Anal.* ($C_{27}H_{29}N_3OS\cdot C_6H_{12}$) 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 $MeSO_2Cl$ 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–$H_2O$, and extracted with EtOAc. The extract was washed with 10% $H_3PO_4$ (until acidic), $H_2O$, and brine. The solution was dried ($Na_2SO_4$), charcoaled, and evaporated *in vacuo*. The residue was crystallized from a minimum amount of hot $C_6H_6$ to afford 4.8 g (52%) of matted crystals, mp 182–184° dec. A sample was recrystallized from 1:1 EtOAc–$C_6H_{12}$, mp 181–183° dec. *Anal.* ($C_{28}H_{31}N_3O_3S_2$), C, H, N.

***N*-(6-Aminopenicillanyl)methanesulfonamide** (23).—A solution of 4.8 g (0.009 mol) of **22** in 45 ml of $Me_2CO$ was combined with a solution of 1.75 g (0.0092 mol) of TsOH in 45 ml of $Me_2CO$ and stirred at 25° for 1 hr. The crystalline product was filtered, dissolved in a minimum amount of MeOH, and precipitated with absolute $Et_2O$ to afford 2.55 g (62%) of the *p*-toluenesulfonate as a hemihydrate, mp 85–135° dec. *Anal.* ($C_9H_{17}N_3O_3S_2\cdot C_7H_8O_3S\cdot 0.5\ H_2O$) 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.* ($C_{12}H_{23}N_3O_4S_2$) 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 $CH_2Cl_2$ and washed ($H_2O$, brine). The dried ($Na_2SO_4$) filtrate was evaporated. The residual syrup was taken up in excess absolute $Et_2O$ and concentrated to 100 ml to afford 11.4 g (81%) of white crystals, mp 104–106°. An earlier sample was recrystallized from $C_6H_6$–hexane: mp 104–106.6°; $[\alpha]^{25}D$ + 68.2° (*c* 1, $CHCl_3$); uv max (95% EtOH) benzene envelope; ir ($CHCl_3$) 5.73 (ester >C=O) and 5.99 μ (amide >C=O); nmr ($CDCl_3$) δ 1.43, 1.53 [s each, 3 each, $C(CH_3)_2$], 1.58–1.83 (m, 2, $NCH_2$), 2.16–2.41 (m, 1, $CH_2CHC$), (s, 2, aryl-$CH_2$), 3.69 (s, 3, $OCH_3$), 4.41–4.83 (m, 2, C**H**C**H**), 6.49 (d, broad 1, N**H**), and 7.29 ppm (s, 5, aryl **H**). *Anal.* ($C_{17}H_{22}N_2O_3S$) C, H, N, S.

When the reaction was carried out with 3 mol-equiv of $Et_2NH$ 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 $NaHCO_3$, and 200 ml of MeOH was stirred at reflux for 2 hr. The solvent was removed *in vacuo* and the residue was dissolved in $CH_2Cl_2$ and washed ($H_2O$, brine). The dried ($Na_2SO_4$) 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 ($CDCl_3$) δ 1.20, 1.35 [s each, 3 each, $C(CH_3)_2$], 1.60–1.90 (m, 2, $NCH_2$), 2.0–2.25 (m, 1, $CH_2CHC$), 3.15 (s, 3, $OCH_3$), 3.0–3.6 (m, 2, COC**H**N**H**), 4.76 (d, 1, $J$ = 9 Hz, C**H**S), and 7.0–8.0 ppm (m, 15, aryl **H**); after $D_2O$ exchange at 3.38 ppm (d, 1, $J$ = 9 Hz, COCHN). *Anal.* ($C_{28}H_{30}N_2O_2S$) 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 $NaOCH_3$ in 480 ml of MeOH was stirred at 25° for 1.75 hr. (This conversion could also be accomplished with $NaHCO_3$ in hot MeOH.) The solvent was removed at 25° and the residue dissolved in $Et_2O$ and washed ($H_2O$, brine). The dried ($Na_2SO_4$) filtrate was concentrated to give 10.7 g (76%) of white crystals, mp 111.5–113°. A sample was recrystallized from $Et_2O$: mp 112.5–114°; $[\alpha]^{25}D$ + 18.6° (*c* 1, $CHCl_3$); uv max (95% EtOH) 279 mμ (ε 21,800); ir (KBr) 5.91 (ester >C=O), and 6.01 μ (amide >C=O); nmr ($CDCl_3$) δ 1.55 [s, 6, $C(CH_3)_2$], 2.66–3.00 (m, 1, > CHS), 3.38 (app t, 2, $NCH_2CH$), 3.61 (s, 5, aryl-$CH_2$, $OCH_3$), 5.82–6.58 (m, 1, >N**H**), and 6.91–7.66 ppm (m, 7, aryl **H**, =CHN, >CON**H**). *Anal.* ($C_{17}H_{22}N_2O_3S$) 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 $PPh_3$ in 75 ml of MeCN was refluxed for 20 hr. The solvent was evaporated and the residue treated with $Et_2O$. 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.* ($C_{18}H_{15}PS$) C, H.

The $Et_2O$ 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°; $[\alpha]^{25}D + 1.4 \pm 0.3°$ (*c* 1, $CHCl_3$); uv max (95% EtOH) 282 mμ (ε 22,000); ir (KBr) 5.88 (ester > C=O), 6.09 (amide > C=O), and 6.18 μ (>C=C<); nmr ($CDCl_3$) δ 1.62, 1.70 [s each, 3 each, $C(C\mathbf{H}_3)_2$], 3.58 (s, 3, $OC\mathbf{H}_3$), 3.33–4.0 (m, 4, $\mathbf{CH_2}N$ and aryl-$CH_2$), 5.15 [t, 1, *J* = 7 Hz, **CH** = $C(CH_3)_2$], 5.50–6.00 (m, 1, C=CN**H**), and 6.83–7.66 ppm (m, 7, aryl **H**, =**C**HN, CON**H**). *Anal.* ($C_{17}H_{22}N_2O_3$) 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 benzylpenaldate[14] showed no depression.

The MeOH filtrate was evaporated to dryness and the residue partitioned in $CHCl_3$–$H_2O$. The aqueous phase was separated, washed ($CHCl_3$), and then evaporated *in vacuo* to give a yellowish solid. It was recrystallized from EtOH–$Et_2O$ to afford 0.15 g of shiny leaflets, mp 194.5–198° dec, identical with authentic **30** (ir spectrum, mixture melting point).[15]

***p*-Methoxybenzyl 4,4-Dimethyl-α-(phenylacetamido)-3-thia-1-azabicyclo[3.1.0]hexane-2-acetate (36).**—Compound **5** (1 g, 0.0021 mol) was heated with 0.34 ml (0.0023 mol) of $Et_3N$ and 4 ml of *p*-anisyl alcohol on a steam bath for 3 hr. The yellow solution was diluted ($CHCl_3$) and washed ($H_2O$, 5% $H_3PO_4$, $H_2O$ until neutral pH, saturated brine). The dried ($Na_2SO_4$) 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 tlc (silica plates, benzene–$Et_2O$ 1:1). Isolation of the band next to the origin afforded 650 mg of a colorless gum: ir ($CHCl_3$) 5.73 (ester > C=O) and 5.97 μ (amide > C=O); nmr ($CDCl_3$) δ 1.4, 1.5 [s each, 3 each, $C(C\mathbf{H}_3)_2$], 1.57–1.83 (m, 2, $NC\mathbf{H}_2$), 2.13–2.38 (m, 1, $CH_2C\mathbf{H}C$), 3.58 (s, 2, aryl-$C\mathbf{H}_2$), 3.73 (s, 3, $OC\mathbf{H}_3$), 4.58–4.75 (m, 2, C**H**C**H**), 5.07 (s, 2, aryl-$C\mathbf{H}_2O$), 6.2–6.6 (broad, 1, N**H**), and 6.7–7.4 ppm (m, 9, aryl H).

**4,4-Dimethyl-α-(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 $CHCl_3$ and washed in the cold with saturated $NaHCO_3$. The basic extracts were combined and acidified in the cold with 10% aqueous $H_3PO_4$ to pH 3. The gum was extracted with cold $CHCl_3$ and the combined organic fractions washed ($H_2O$, brine). The dried ($Na_2SO_4$) filtrate was evaporated *in vacuo* at 25° to afford a colorless, amorphous solid: ir ($CHCl_3$) 3.8–4.1 (broad OH), 5.79 (acid > C=O), and 5.98 μ (amide > C=O); nmr ($CDCl_3$) δ 1.4, 1.5 [s each, 3 each, $C(C\mathbf{H}_3)_2$], 1.67–2.0 (m, 2, $NC\mathbf{H}_2$), 2.33–2.67 (m, 1, $CH_2C\mathbf{H}C$), 3.6 (s, 2, aryl-$C\mathbf{H}_2$), 4.42–5.08 (m, 2, C**H**C**H**), 7.0–7.42 (m, 6, aryl **H**, N**H**), and 10.6 ppm (s, 1, COO**H**). The carboxylic acid was unstable at room temperature in the amorphous state or in chloroform solution. The change was apparent from the nmr spectra which became diffuse and uninterpretable.

# 2-Tetrahydropyridylindoles as Histamine and Serotonin Antagonists

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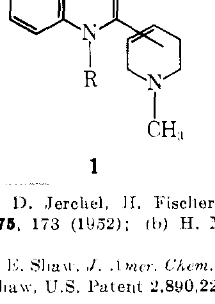
A series of 2-(1-methyl-1,2,5,6-tetrahydro-3(and 4)-pyridyl)indoles was synthesized by borohydride reduction of the corresponding pyridinium compounds. The compounds were tested for antihistaminic and antiserotonin activity.

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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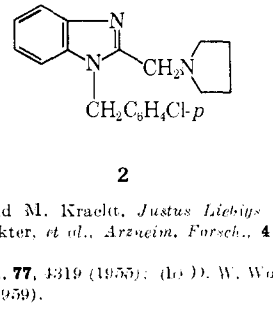

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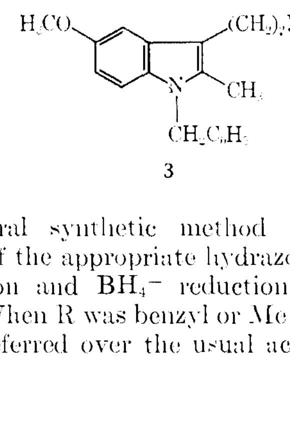

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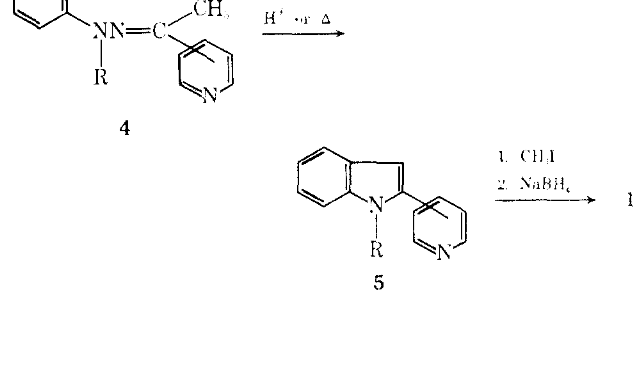
The general synthetic method involves Fischer cyclization of the appropriate hydrazone **4** followed by quaternization and $BH_4^-$ reduction of the pyridylindoles **5**. When R was benzyl or Me thermal indolization was preferred over the usual acid-catalyzed procedure.

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