trostatic potentials, one must abandon the rigourous topographical equivalence between the aromatic ring of dopamine and the virtual cycle in orthopramides and allow a slight and lateral displacement of the two rings relative to each other. This is illustrated in Figure 5B where the aromatic ring of dopamine is made to coincide with the amide group of a model orthopramide, allowing the best possible fit between the regions of maximum positive potential, as well as between the regions of maximum negative potential.

Such distinct modes of binding as postulated here for orthopramides and dopamine are not a novel proposal. Indeed, McDermed et al.[32] and Wikström et al.[33] have concluded from their studies that agonists of various chemical and stereochemical classes have different modes of binding to a hypothetical dopamine receptor model. While the nitrogen binding site is well defined, the aromatic ring can occupy a variety of positions, a situation also postulated here (see Figure 5B). These models should be challenged with MEP and other structural data of various D-2 receptor agonists and antagonists.

Figure 5 also suggests that orthopramides may interact with elements of the D-2 receptor not involved in dopamine binding. This is in particular the case of the aromatic substituents of orthopramides, which as mentioned earlier play a critical role in the D-2 receptor affinity of these compounds.[18] Understanding the role played by these substituents, as well as by other structural features of orthopramides, should help rationalize differences in therapeutic activities (see introduction). Indeed, these differences may be due to contrasting distribution of orthopramides and/or to selectivity for different subpopulations of D-2 receptors. More detailed studies of the electronic structure of substituted benzamides belonging to different therapeutic classes may reveal crucial differences. Additional pharmacological and physicochemical investigations have to verify or falsify hypotheses deduced from the results of quantum mechanical calculations. For example, it has been shown that the closely related benzamides sulpiride and sultopride (see Chart I) differ markedly in terms of crossing of the blood–brain barrier and intracerebral regional distribution.[34] Additionally, it may or may not be relevant that the receptor binding of orthopramides, in contrast to other dopamine antagonists, is strongly Na^+ dependent,[8] suggesting distinct D-2 binding sites or a distinct mode of binding. Work in progress (collaborative study with the Department of Neurology, Institute of Psychiatry, University of London) involves assessment of lipophilicity–activity relationships and thermodynamics of D-2 receptor binding.

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(32) Freeman, H. S.; McDermed, J. D. "The Chemical Regulation of Biological Mechanisms"; Creighton, A. M., Turner, S., Eds.; The Royal Society of Chemistry: London, 1982; pp 154–166.
(33) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L. E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.
(34) Mizuchi, A.; Kitagawa, N.; Miyachi, Y. *Psychopharmacology* **1983**, *81*, 195.

Analogues of Poison Ivy Urushiol. Synthesis and Biological Activity of Disubstituted *n*-Alkylbenzenes

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The total synthesis of different isomers and analogues of poison ivy urushiol is described. These include the positional isomers **1**–**5** and the nitrogen-containing analogues **6** and **8** and their mesylamino derivatives **7** and **9**. 3,4-Dimethoxybenzaldehyde, *m*-dimethoxybenzene, resorcinol, and *p*-dimethoxybenzene were used as starting materials for compounds **1**, **2**, **3**, and **4**, respectively. Compound **5** is prepared by catalytic hydrogenation of bilobol isolated from *Ginkgo biloba*. Compounds **6** and **7** were prepared from anacardic acid as the starting material while compounds **8** and **9** were prepared from phenol as the starting material. Compounds **1**–**9** were tested for their ability to cross-react with poison ivy urushiol in sensitized guinea pigs. Compounds **6** and **8** were reactive at the 10-μg dose level when applied topically, while compound **1** was a skin irritant at that dose. On the other hand, compounds **2**–**5**, **7**, and **9** showed no cross-reactivity up to the 30-μg dose level. Structural requirements for cross allergenicity are discussed.

Contact dermatitis, a widespread problem in the United States, is caused by many members of the family Anacardiaceae of which poison ivy (*Toxicodendron radicans*) is the most common. The chemicals responsible for this allergenic reaction are commonly referred to as urushiols. These are mixtures of 3-*n*-pentadec(en)yl- or 3-*n*-heptadec(en)ylcatechols.[1,2]

Studies from our laboratory showed that intravenous administration of the product urushiol acetate was effective in producing immune tolerance in naive guinea pigs and desensitization or hyposensitization in already sensitized animals.[3] However, these compounds were less effective by the oral route.[4] As part of our continuing efforts to

(1) Corbett, M. D.; Billets, S. *J. Pharm. Sci.* **1975**, *64*, 1715.
(2) Billets, S.; Craig, J. C.; Corbett, M. D.; Vickery, J. F. *Phytochemistry* **1976**, *15*, 533.
(3) Watson, E. S.; Murphy, J. C.; Wirth, P. W.; Waller, C. W.; ElSohly, M. A. *J. Invest. Dermatol.* **1981**, *76*, 164.
(4) Watson, E. S.; Murphy, J. C.; ElSohly, M. A. *J. Invest. Dermatol.* **1983**, *80*, 149.

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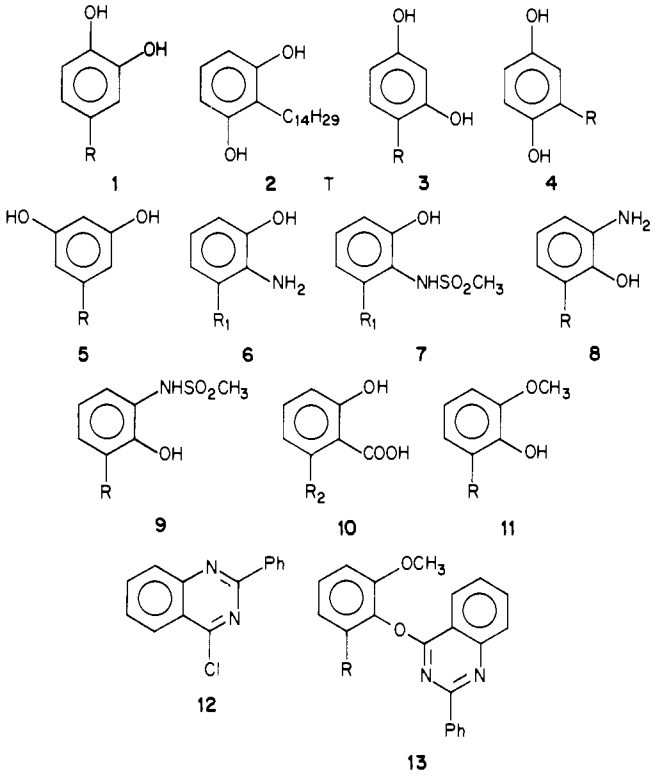
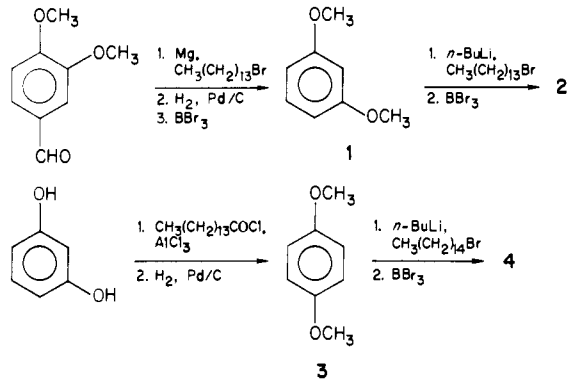
Chart I



R = $C_{15}H_{31}$; R_1 = $C_{13}H_{27}$, $C_{15}H_{31}$, $C_{17}H_{35}$; R_2 = $C_{13}H_{25}$, $C_{15}H_{29}$, $C_{17}H_{33}$

Scheme I



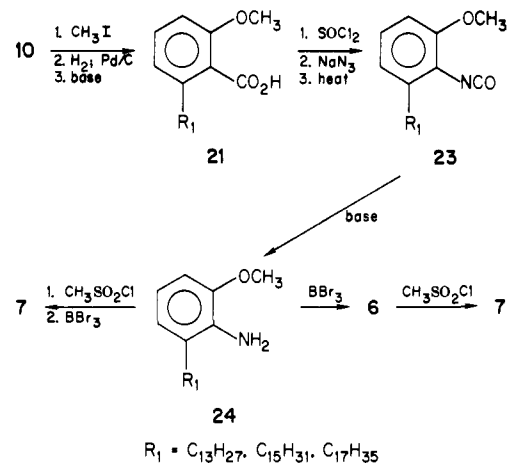
develop better desensitizing agents, various isomers and analogues (**1–9**, Chart I) of 3-*n*-pentadecylcatechol (PDC) were synthesized. This paper describes the total synthesis of these compounds and their cross reactivity with PDC in sensitized guinea pigs. The ability of these products to desensitize or produce tolerance against poison ivy allergy will be reported in a forthcoming publication.

Chemistry

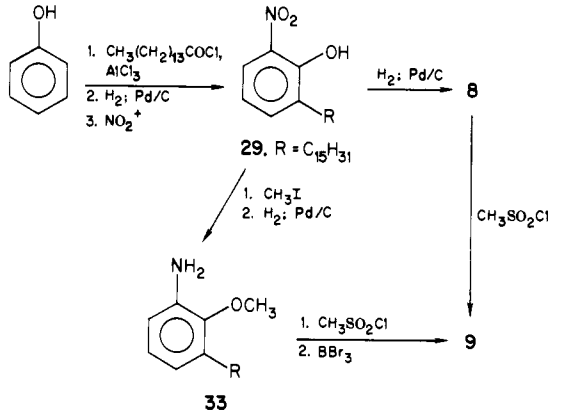
Various isomers of PDC, where the positions of the hydroxy groups and the alkyl side chain are interchanged, were synthesized by the procedures outlined in Scheme I for compounds **1–4**. Compound **5** was prepared by catalytic hydrogenation of its unsaturated congeners previously isolated in our laboratories from the fruits of the *Ginkgo biloba*.[5]

In compounds **6** and **7** the hydroxy group at position 2 of the PDC moiety was replaced by an amino and mesylamino function, respectively. Attempts to replace the hydroxyl group of 3-*n*-pentadecylcatechol 1-monomethyl ether (**11**) with an amino group by using 4-chloro-2-phenylquinazoline (**12**, AM-ex-ol)[6] were unsuccessful. Although the condensation of **11** and **12** with NaH resulted in a good yield of **13** (77%), subsequent pyrolytic rearrangement gave a very low yield.

Scheme II



Scheme III



The syntheses of compounds **6** and **7** were achieved through the pathways outlined in Scheme II, starting with anacardic acid (**10**) isolated from *Ginkgo biloba* fruits.[5] The conversion of the carboxylic group to the amino function was carried out through a Curtius rearrangement via the isocyanate intermediate **23** (Scheme II). Attempts to convert the carboxylic group into the amino group by using the Lossen rearrangement and Schmidt reaction were unsuccessful. Compound **7** could be prepared directly from the aminophenol **6** or from **24** as shown in Scheme II. The latter route provides compound **7** in better yield and proves the position of the mesyl group unequivocally.

Compounds **8** and **9** were synthesized from phenol as starting material (Scheme III). Friedel–Crafts acylation of phenol with *n*-pentadecanoyl chloride yielded a mixture of ortho and para isomers. The para isomer was removed from the reaction mixture by washing with aqueous NaOH solution. The acidity of the phenolic group of the para isomer was enhanced by the *p*-carbonyl group while the OH of the ortho isomer was weakly acidic because of the hydrogen bonding with the *o*-carboxyl group. Catalytic hydrogenation of the ortha isomer gave an *o*-alkylphenol, which then was nitrated with acetyl nitrate[7] to give a mixture of mono(dinitroalkyl)phenols. These were separated by using column chromatography (see Experimental

(5) Adawadkar, P. D.; ElSohly, M. A. *Fitoterapia* **1981**, *L11*, 129.

(6) Sherrer, R. A.; Beatty, H. R. *J. Org. Chem.* **1972**, *37*, 1681.

(7) Bordwell, F. G.; Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 3588.

Table I. Allergenic Cross-Reactivity of Compounds 1–9 in Guinea Pigs Sensitized to Poison Ivy Urushiol[a]

eliciting compound	no. reactive[b]/no. tested		av skin reaction[c]		eliciting dose, μg	
	test	control	test	control	test	control
1	2/9	9/9	0.1	2.2	1	2
2	0/8	7/8	0	2.3	10	3
3	0/15	15/15	0	1.9	30	2
4	0/15	15/15	0	3.5	1	2
5	5/9	9/9	0.6	2.2	30	2
6	7/7	7/7	2.9	2.9	10	2
7	0/7	7/7	0	2.9	10	2
8	7/7	7/7	2.4	2.9	10	2
9	0/7	7/7	0.0	2.9	10	2

[a] Guinea pigs were sensitized by epicutaneous application of an acetone solution of purified poison ivy urushiol to the dorsal skin of the neck. One-milligram sensitizing doses were applied in 0.15 mL of acetone over an area of about 10 cm^2. After a 2-week rest period, eliciting doses of poison ivy urushiol and compounds 1–9 in acetone solution were applied to the abdominal skin in 5-mL aliquots. [b] Number of animals with a positive skin reaction vs. number tested. [c] Skin test reactivity (intensity of erytherma and edema) was scored by using a rating scale of 0–4 according to the method of Draize.[14] Sites of application of eliciting doses were scored 24, 48, and 72 h after application of these substances. An average of the three readings for erytherma and for edema were computed separately and then combined to provide the average skin reaction of the animal to each test substance. The mean skin reactivity of each group of animals was then computed.

Section for regioassignments and purity). Catalytic hydrogenation of **29** gave the required aminophenol (**8**). The mesylamino)phenol **9** was prepared from the nitrophenol **29** by either of the two methods shown in Scheme III. The procedure involving methylation and demethylation of the phenolic group gave a better yield.

Attempts to prepare compounds **8** and **9** starting from 2-methoxy-3-nitrobenzaldehyde were unsuccessful.

Biological Activity

Compounds **1–9** were tested for their ability to produce an allergenic reaction to animals sensitized to poison ivy urushiol. Doses of 10 and 30 μg of each of these compounds were topically applied to sensitized guinea pigs, and their reactivity was recorded at 24, 48, and 72 h following previously outlined procedures.[3]

Compounds **6** and **8** were found to cross-react with poison ivy urushiol at the 10-μg dose level. This reaction was found to be specific since these compounds did not have any irritant activity when tested on naive (nonsensitized) guinea pigs. The only compound in this group that showed such irritant activity at this low dose of 10 μg was compound **1**. Compounds **2–5**, **7**, and **9** did not cross-react with urushiol (or PDC) at doses up to 30 μg (see Table I).

The finding that compounds **6** and **8** are allergenically cross-reactive with PDC suggests that two oxidizable functional groups, rather than two free hydroxy groups, suffice for cross-reactivity. The requirement for oxidation to quinone prior to covalent bonding to ε-amino groups and thiol groups on proteins has been shown to be crucial for allergenicity[7-13] and are likely to be important for cross-reactivity as well. Furthermore, the oxidizable functional groups must be ortho to each other since compounds **2–5** were not allergenically cross-reactive with PDC while compound **1** was. This positional requirement appears to be more important than the position of the alkyl side chain for cross-reactivity. The cross-reactivity of **6** and **8** with PDC could be explained on the basis of their capacity to be oxidized to a quinone type structure with susceptibility to neucleophilic attack at positions 5 and 6 on the ring by amino and thiol nucleophiles, respectively.

The lack of cross-reactivity of compounds **7** and **9** with PDC was surprising since the proton of a mesylamino group is an acidic proton, and thus the two compounds were expected to act like catechols. However, the lack of cross-reactivity could be explained on the basis of inability of compounds **7** and **9** to form quinone type intermediate.

Within the dihydroxyalkylbenzenes, it seems that the most important structure requirement is for the two hydroxy groups to be ortho to each other. The relative position of the alkyl side chain is not important for cross-reactivity.

In a forthcoming publication(s) we will report on the activity of these compounds as contact sensitizers and on their ability (or lack of) to produce immune tolerance or desensitization against poison ivy dermatitis.

Conclusion

The dihydroxyalkylbenzene derivatives **2–5**, which are positional isomers of 3-*n*-pentadecylcatechol (the saturated congener of poison ivy urushiol), showed no skin irritancy properties at doses up to 30 μg when applied topically. Doses higher than 3 μg of 3-*n*-pentadecylcatechol caused skin irritation. On the other hand, the isomer **1** was a skin irritant at the 10 μg dose level. This indicates that only alkylcatechols and not alkylresorcinols or -hydroquinones should be considered as strong skin irritants. While those compounds (**2–5**) might be skin sensitizers in themselves, they showed no cross-reactivity with poison ivy urushiol in sensitized guinea pigs. When either the hydroxy group of the catechol structure of 3-*n*-pentadecylcatechol was replaced with an amino function, the resulting compounds **6** and **8** showed cross-reactivity with urushiol at the 10-μg dose level. However, mesylation of the amino groups results in loss of the cross-reactivity even at higher doses (30 μg).

The data indicate that the most important structure requirement for cross-reactivity with poison ivy urushiol is the presence of two oxidizable functional groups (OH or NH_2) ortho to each other.

Experimental Section

Melting points were determined in open glass capillary tubes with a Thomas-Hoover Unimelt and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 MHz instrument. Chemical shifts were measured relative to Me_4Si as internal standard. ^{13}C NMR spectra were obtained on JEOL-FX60 Fourier transform instrument. Chemical shifts were reported in ppm, with Me_4Si as the internal standard. Deuterated chloroform was used as the solvent unless otherwise indicated. For GC/MS, a Finnigan 3200 GC/MS/DS instrument was used at 70 eV. The Me_3Si derivatives were prepared with BSTFA/pyridine and chromatographed on a 3% OV-225 column at 210 °C on a

(8) Byck, J. S.; Dawson, C. R. *Anal. Biochem.* **1968**, *25*, 123.
(9) Liberato, D. J.; Byers, V. S.; Dennick, R. G.; Castagnoli, N. *J. Med. Chem.* **1981**, *24*, 28.
(10) Mason, H. S.; Lada, A. *J. Invest. Dermatol.* **1954**, *22*, 457.
(11) Dunn, I. S.; Liberato, D. J.; Dastagnoli, N.; Byers, V. S. *Cell. Immunol.* **1982**, *74*, 220.
(12) Stauffer, J. Doctoral Dissertation, Columbia University, 1971.
(13) Baer, H.; Watkins, R. C.; Bowser, R. T. *Immunochemistry* **1966**, *3*, 479.

Beckman GC/65 instrument. IR spectra were recorded on a Perkin-Elmer 281 B instrument; samples were placed in sodium chloride cells as neat liquids. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements (performed by Galbraith Laboratories, Inc., Knoxville, TN) were within 0.4% of theoretical values.

Methyl Anacardate Methyl Ether (19). To a 100-mL, round-bottom flask was added 1.1 g (3.16 mmol) of anacardic acid (**10**),[5] 0.5 mL (7.9 mmol) of methyl iodide, 1.0 g of anhydrous K_2CO_3, and 40 mL of dry acetone, and the mixture was heated under reflux for 10 h. The reaction mixture then was cooled to room temperature and filtered through Celite, and the solvent was removed to obtain an oily product. This product was chromatographed over a silica gel column (2 × 22 cm) using 5% ether in petroleum ether to yield 1.0 g (91%) of the methyl ether methyl ester **19**; ^{1}H NMR δ 7.28 (t, J = 8 Hz, 1 H, Ar), 6.80 (m, 2 H, Ar), 5.40 (t, J = 5 Hz, 2 H, vinyl), 3.90 and 3.80 (s, 6 H, 2 × OCH_3), 2.60 (t, J = 8 Hz, 2 H, benzylic CH_2), 2.07 (br d, 4 H, allylic methylenes).

Methyl Dihydroanacardate Methyl Ether (20). To a Parr hydrogenation bottle were added 1.0 g (2.67 mmol) of **19** in 25 mL of MeOH and 200 mg of 10% Pd/C catalyst. The mixture was reacted at 35 psi of hydrogen for 5 h and then filtered through Celite. Removal of the solvent resulted in an oily product (933 mg, 95%), which solidified at low temperatures; ^{1}H NMR δ 7.20 (t, J = 8 Hz, 1 H, Ar), 6.85 (m, 2 H, Ar), 3.90 and 3.80 (s, 6 H, 2 × OCH_3), 2.60 (t, J = 8 Hz, 2 H, benzylic CH_2). Since the naturally occurring anacardic acid used as the starting material is a mixture of C_{13} (10%), C_{15} (67%), and C_{17} (22%) side chain isomers,[5] MS analysis shows molecular ions at m/z 404, 376, and 348. The base peak for all isomers was observed at m/z 161.

Dihydroanacardic Acid Methyl Ether (21). Into a 100-mL flask equipped with a reflux condenser was placed 600 mg (1.6 mmol) of **20** in 30 mL of 1,4-dioxane. To this solution 70 mg of LiOH and 100 mg of NaOH in 6 mL of H_2O–MeOH (1:5) were added, and the mixture was heated under reflux for 65 h. The oily residue obtained after removal of the solvent was dissolved in $CHCl_3$ and washed with dilute HCl (2 × 15 mL), H_2O (1 × 15 mL), and saturated NaCl (2 × 15 mL); the chloroform layer was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a light yellow oil, which was chromatographed on a silica gel 60 column (2 × 10 cm) using 10% ether in petroleum ether to obtain 403 mg (74%) of the acid **21**; ^{1}H NMR δ 11.20 (br s, 1 H, CO_2H), 7.31 (t, J = 8 Hz, 1 H, Ar), 6.80 (m, 2 H, Ar), 3.90 (s, 3 H, OCH_3), 2.75 (t, J = 8 Hz, 2 H, benzylic CH_2); MS, m/z 390, 363, and 334 for M^+ of the C_{17}, C_{15}, and C_{13} side chain isomers. The base peak for all isomers was observed at m/z 161.

3-*n*-Alkyl-2-isocyanatoanisole 23. Into a 25-mL, round-bottom flask equipped with a reflux condenser were placed 440 mg (1.21 mmol) of **21** and 2 mL of thionyl chloride. The mixture then was heated under reflux for 4 h and the excess thionyl chloride removed under vacuum to yield the acid chloride **22**: IR (neat) 1795 cm^{-1}. The acid chloride was dissolved in 10 mL of toluene, 200 mg (3.1 mmol) of NaN_3 was added, and the mixture was heated under reflux overnight. After cooling, the solution was filtered and the solvent evaporated to yield a light yellow oil. Chromatography of the residue on silica gel 60 using ether in petroleum ether mixtures (10–20% ether) gave 400 mg (92%) of the isocyanate **23**; mp 42–43 °C; IR (KBr) 2250 (N=C=O) cm^{-1}; ^{1}H NMR δ 7.08 (t, J = 8 Hz, 1 H, Ar), 6.80 (m, 2 H, Ar), 3.93 (s, 3 H, OCH_3), 2.67 (t, J = 8 Hz, 2 H, benzylic CH_2); MS, m/z 387, 359, and 331 for C_{17}, C_{15}, and C_{13} side chain isomers with the base peak at m/z 163.

2-Amino-3-*n*-alkylanisole 24. To a 50-mL, round-bottom flask were added 400 mg (1.1 mmol) of **23** in 10 mL of 1,4-dioxane and 300 mg (7.5 mmol) NaOH in 2 mL of H_2O, and the mixture was heated with hot air for 10 min. Evaporation of the solvent resulted in an oily residue, which was extracted in $CHCl_3$, and the solution washed with H_2O (10 mL) and dried over Na_2SO_4. Removal of the solvent afforded 360 mg (97%) of an oily residue of **24**; MS, m/z at 361, 333, and 305 for M^+ of the C_{17}, C_{15}, and C_{13} isomers with the base peak at m/z 136.

2-Amino-3-*n*-alkylphenol 6. To an ice-cooled solution of **24** (150 mg, 0.45 mmol) in CH_2Cl_2 (7 mL) was slowly added 0.6 mL (1.0 mmol) of a 1.7 mmol/mL solution of BBr_3 in CH_2Cl_2. After addition was complete, the solution was stirred at 0 °C for 1.0 h followed by 1.5 h at room temperature. The solution was then washed with H_2O (2 × 10 mL) and saturated NaCl (2 × 10 mL) and dried over Na_2SO_4. The solvent was then removed to give 68 mg (47%) of **6**; mp 165–166 °C; ^{1}H NMR (CD_3OD) δ 6.65 (m, 3 H, Ar), 2.50 (t, J = 8 Hz, 2 H, benzylic CH_2); MS, m/z at 347, 319, and 291 for M^+· of the C_{17}, C_{15}, and C_{13} isomers with base peak at m/z 122. Anal. ($C_{21}H_{37}NO$) C, H, N.

2-(Mesylamino)-3-*n*-alkylanisole 25. To an ice-cooled solution of **24** (128 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) were added 62 μL (0.76 mmol) of mesyl chloride and 62 μL (0.76 mmol) of pyridine. The solution was allowed to warm to room temperature and stirred overnight under N_2. The reaction mixture then was transferred to a separatory funnel and washed with 2 × 10 mL portions of dilute HCl, H_2O, and saturated NaCl and then dried over anhydrous Na_2SO_4. Removal of solvent afforded 100 mg (64%) of **25**; IR (KBr) 3240 (NH) and 1330 (SO_2CH_3) cm^{-1}; ^{1}H NMR δ 7.33–6.73 (m, 3 H, Ar), 3.90 (s, 3 H, OCH_3), 3.00 (s, 3 H, SO_2CH_3), 2.80 (t, J = 8 Hz, 2 H, benzylic CH_2); MS, m/z M^+· at 439, 411, and 383 for the C_{17},C_{15}, and C_{13} side chain isomers. Peaks corresponding to M^+· – 79 were observed for all isomers (loss of CH_3SO_2), and the base peak was observed at m/z 136.

2-(Mesylamino)-3-*n*-alkylphenol 7. Demethylation of **25** (85 mg) was achieved with use of BBr_3 as reported for compound **6** to yield 70 mg (83%) of **7** as a brown solid; mp 119–120 °C; IR (KBr) 3460 (OH), 3240 (NH), 1300 (SO_2CH_3) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 7.06–6.86 (m, 3 H, Ar), 3.03 (s, 3 H, SO_2CH_3), 2.66 (t, 2 H, benzylic CH_2); MS, m/z M^+· at 425, 397, and 369 for C_{17}, C_{15}, and C_{13} side chain isomers with the corresponding M^+· – 79 ions (loss of CH_3SO_2) and a base peak at m/z 122.

2-Hydroxy-*n*-pentadecanophenone (26). To a 500-mL, three-necked, round-bottom flask equipped with mechanical stirrer, reflux condenser, and additional funnel were added 38.4 g (408 mmol) of phenol, 140 mL of ethylene chloride, and 54.4 g (408 mmol) of aluminum chloride, and the mixture was heated at 85 °C for 6 h. Pentadecanoyl chloride (prepared from 49.4 g of pentadecanoic acid with use of thionyl chloride) was added dropwise with use of 20 mL of ethylene chloride, and heating was continued at 85 °C for 16 h. The reaction then was cooled, poured over 250 g of ice, and extracted with 500 mL of ether and 100 mL of ethyl acetate. The combined organic layers were washed with H_2O (3 × 200 mL) followed by 3% aqueous NaOH (3 × 100 mL) to remove the para isomer **27**. The solvent was dried over anhydrous Na_2SO_4 and evaporated, and the residue was crystallized twice from hexane to yield 28.7 g (44%) of **26**; mp 51–51.5 °C; IR (KBr) 3420, 2910, 2810, 1640 cm^{-1}; ^{1}H NMR δ 12.38 (s, 1 H, D_2O exchangeable OH), 6.67–7.80 (m, 4 H, aromatic), 2.98 (t, J = 7 Hz, 2 H, $COCH_2$), 1.27 (br s, 24 H, 12 CH_2), 0.89 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 318 M^+·, 1), 121 (100).

2-*n*-Pentadecylphenol (28). Compound **26** (16.0 g, 50.3 mmol) was catalytically hydrogenated in a ethyl acetate–acetic acid mixture over 10% Pd/C. Recrystallization of the product from isooctane yielded 15.25 g of colorless crystals (99.7%) of **28**; mp 45–47 °C; IR (KBr) 3310, 2910, 2840 cm^{-1}; ^{1}H NMR δ 6.67–7.20 (m, 4 H, aromatic), 4.82 (br s, 1 H, D_2O exchangeable, OH), 2.62 (t, J = 7 Hz, 2 H, benzylic CH_2), 1.26 (br s, 26 H, 13 CH_2), 0.89 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 304 (M^+· 29), 107 (100).

2-Nitro-6-*n*-pentadecylphenol (29). The alkylphenol **28** (2.2 g, 7.24 mmol) was dissolved in 125 mL of hexane and chilled to 0 °C. The nitrating solution (prepared by mixing 4 mL of ice-cold acetic anhydride and 0.4 mL of 70% HNO_3) was added slowly over a period of 6 h while the temperature was maintained between 10 and 30 °C. The reaction mixture was then poured over 10 g of ice and extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with H_2O (3 × 20 mL) and dried over Na_2SO_4, and the solvent evaporated to yield 2.2 g of yellow oil. Chromatography of the product over a silica gel 60 column using 20% ether in hexane afforded 1.2 g (47%) of compound **29**; mp 50–51 °C; IR (KBr) 3120, 2910, 2840 cm^{-1}; ^{1}H NMR δ 10.86 (s, 1 H, D_2O exchangeable, OH), 7.90 (dd, J = 8 and 2 Hz, 1 H), 7.38 (dd, J = 7 and 2 Hz, 1 H), 6.80 (dd, J = 7 and 8 Hz, 1 H), 2.70 (t, J = 7 Hz, 2 H, benzylic CH_2), 1.28 (br s, 26 H, 13 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 349 (M^+·, 4), 152 (100).

2-Amino-6-*n*-pentadecylphenol (8). Catalytic hydrogenation of **29** (1.0 g, 2.86 mmol) was achieved in hexane with 10% Pd/C. Removal of the solvent gave 560 mg (61%) of **8** as pale yellow solid; mp 70–71 °C; ^{1}H NMR δ 6.66 (br s, 3 H, Ar), 4.17 (br s, OH

and NH_2), 2.53 (t, J = 8 Hz, 2 H, benzylic CH_2), 1.26 (br s, 26 H, 13 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 319 (M^+·, 1), 122 (100). Anal. ($C_{21}H_{37}NO$) C, H, N.

2-Nitro-6-*n*-pentadecylanisole (32). Methylation of **29** (700 mg, 2.01 mmol) using methyl iodide/K_2CO_3 in dry acetone yielded 636 mg (88%) of **32**; ^1H NMR δ 7.63 (dd, J = 8 and 2 Hz, 1 H, Ar), 7.43 (dd, J = 8 and 2 Hz, 1 H, Ar), 7.15 (dd, J = 8 and 8 Hz, 1 H, Ar), 3.90 (s, 3 H, OCH_3), 2.72 (t, J = 8 Hz, 2 H, benzylic CH_2), 1.27 (br s, 26 H, 13 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z (M^+·, 2), 136 (100).

2-Amino-6-*n*-pentadecylanisole (33). Compound **32** (566 mg) was catalytically hydrogenated to yield 500 mg (96%) of a light brown residue of **33**; ^1H NMR δ 7.00–6.55 (m, 3 H, Ar), 3.77 (s, 3 H, OCH_3), 2.65 (t, J = 8 Hz, 2 H, benzylic CH_2), 1.29 (br, s, 26 H, 13 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3). MS of the Me_3Si derivative showed peaks at m/z 105 (M^+·, 51) and 178 (100).

2-(Mesylamino)-6-*n*-pentadecylanisole (34). To 300 mg (0.90 mmol) of **33** in $CHCl_3$ was added 117 mL (1.50 mmol) of mesyl chloride and 122 L (1.5 mmol) of pyridines as described for compound **25**. After workup and removal of the solvent, 310 mg (84%) of **34** was isolated; ^1H NMR δ 7.23 (m, 2 H, Ar), 6.97 (m, 1 H, Ar), 3.73 (s, 3 H, OCH_3), 3.02 (s, 3 H, SO_2CH_3), 2.67 (t, J = 8 Hz, 2 H, benzylic CH_2), 1.30 (br s, 26 H, 13 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 411 (M^+·, 9), 136 (100).

2-(Mesylamino)-6-*n*-pentadecylphenol (9). To 310 mg (0.75 mmol) of **34** was added 142 mL (1.5 mmol) of BBr_3 in CH_2Cl_2 as reported for the preparation of **6**. After workup, 280 mg (93.6%) of **9** was isolated as a white powder; mp 100–101 °C; IR (KBr) 3460 (OH), 3250 (NH), 1310 (SO_2CH_3) cm^{-1}; ^1H NMR δ 7.25–6.75 (m, 3 H, Ar), 3.00 (s, 3 H, SO_2CH_3), 2.63 (5, J = 8 Hz, 2 H, benzylic CH_2), 1.27 (br s, 26 H, 13 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 397 (M^+·, 0.8), 122 (100). Anal. ($C_{22}H_{39}NO_3S$) C, H, N, S.

1-(3,4-Dimethoxyphenyl)pentadecan-1-ol (14). The Grignard reagent prepared from 1-bromotetradecane (5.5 g, 20 mmol) and Mg (0.48 g, 20 mmol) was reacted overnight with 3.32 g (20 mmol) of veratraldehyde in dry THF under reflux. After removal of the solvent, the reaction mixture was dissolved in 250 mL of ether and extracted with 200 mL of 1.0 N HCl followed by 100 mL of H_2O. The organic layer was dried over Na_2SO_4 and evaporated to yield 7.0 g of a gummy product, which was purified by flash chromatography using hexane with increments of ethyl acetate as solvents, to yield 2.29 g of **14**; mp 74–75 °C; ^1H NMR δ 7.00 (s, 1 H, Ar), 6.93 (s, 2 H, Ar), 4.63 (t, J = 6 Hz, 1 H), 3.92 (s, 3 H, OCH_3), 390 (s, 3 H, OCH_3), 1.80 (m, 2 H), 1.27 (s, 24 H, 12 CH_2), 0.90 (t, J = 5 Hz, 3 H); MS, m/z 364 (M^+·, 3.0), 346 (M^+·, –18, 1), 167 (100).

4-*n*-Pentadecylveratrole (15). Catalytic reduction of **14** (1.0 g, 3.0 mmol) followed by chromatography of the product over silica gel afforded 748 mg (78%) of **15**; ^1H NMR δ 6.72 (m, 3 H, Ar), 3.83 and 3.86 (s, 6 H, 2 OCH_3), 2.57 (t, J = 8 Hz, 2 H, benzylic CH_2), 1.23 (s, 26 H, 13 CH_2), 0.88 (t, J = 5 Hz, 3 H, CH_3).

4-*n*-Pentadecylcatechol (1). Demethylation of **15** (644 mg, 1.85 mmol) using BBr_3 as reported for compound **6** yielded 420 mg of **1** as a white solid; mp 91–92 °C; ^1H NMR δ 6.73 (m, 3 H, Ar), 5.17 (br s, 2 H, exchange with D_2O, OH), 2.50 (t, J = 8 Hz, 2 H, benzylic CH_2), 1.26 (s, 26 H, 13 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 320 (M^+·), 123 (100). Anal. ($C_{21}H_{36}O_2$) C, H.

2-*n*-Tetradecyl-3-methoxyanisole (16). In a 100-mL, three-neck, round-bottom flask equipped with a reflux condenser and magnetic stirrer was added 1.7 g (12.3 mmol) of 1,3-dimethoxybenzene in 150 mL of dry THF. To this solution was added 12 mL of 1.2 M (14 mmol) n-butyllithium dropwise at room temperature. The yellow solution was heated under reflux for 90 min and allowed to come to room temperature before the addition of 3.4 g (12.3 mmol) of 1-bromotetradecane in 10 mL of THF. After refluxing overnight, the reaction was worked up by evaporating the solvent and extracting the residue with 125 mL of ethyl acetate. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to yield 4.9 g of a yellow oil. Chromatography of the oil on a silica gel 60 column using 10% ether in hexane gave 2.6 g (63%) of **16** as a colorless solid; mp 33–35 °C; IR (neat) 2920, 2845, 1590, 1646 cm^{-1}; ^1H NMR δ 7.08 (t, J = 8 Hz, 1 H), 6.45 (d, J = 8 Hz, 2 H), 3.75 (s, 6 H, 2 OCH_3), 2.75 (t, J = 7 Hz, 2 H, benzylic CH_2), 1.34 (br s, 24 H, 12 CH_2), 0.90 (t, J = 6 Hz, 3 H, CH_3); MS, m/z 334 (M^+·, 2), 151 (100).

2-*n*-Tetradecylresorcinol (2). Demethylation of **16** (380 mg, 1.14 mmol) using BBr_3 as reported for compound **6** resulted in 330 mg (95%) of **2** as a colorless solid; mp 77–78 °C; IR (KBr) 3480, 2910, 2840, 1580, 1460 cm^{-1}; ^1H NMR δ 6.90 (t, J = 8 Hz, 1 H), 6.35 (d, J = 8 Hz, 2 H), 4.93 (s, 2 H, exchangeable with D_2O, OH), 2.63 (t, J = 7 Hz, 2 H, benzylic CH_2), 1.25 (br s, 24 H, 12 CH_2), 0.90 (t, J = 6 Hz, 3 H, CH_3). Anal. ($C_{20}H_{34}O_2$) C, H.

2,4-Dihydroxy-*n*-pentadecanophenone (17). Resorcinol (3.3 g, 30 mmol) and pentadecanoyl chloride were reacted in the same way as previously outlined for compound **26** to yield after workup and chromatography on silica gel 2.8 g (56%) of **17**; ^1H NMR δ 12.90 (s, exchangeable with D_2O, 2 H, OH), 7.60 (d, J = 6 Hz, 1 H), 6.25–6.45 (m, 2 H, Ar), 2.85 (t, J = 5 Hz, 2 H, $COCH_2$), 2.15 (m, 2 H), 1.30 (s, 22 H, 11 CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 334 (M^+·, 1), 137 (100).

4-*n*-Pentadecylresorcinol (3). Catalytic hydrogenation of **17** (200 mg, 0.6 mmol) in EtOH–acetic acid yielded after purification on a silica gel column 175 mg (90%) of **3** as a light brown solid; mp 77–79 °C; IR (KBr) 3480, 2910, 2840, 1690, 1600 cm^{-1}; ^1H NMR δ 6.97 (d, J = 8 Hz, 1 H), 6.37 (d, J = 8 Hz, 1 H), 6.33 (s, 1 H), 4.67 (br s, exchangeable with D_2O, 2 H, OH), 2.54 (t, J = 7 Hz, 2 H, benzylic CH_2), 0.90 (t, J = 5 Hz, 3 H, CH_3); MS, m/z 320 (M^+·, 1), 123 (100). Anal. ($C_{21}H_{36}O_2$) C, H.

2-*n*-Pentadecylhydroquinone Dimethyl Ether (18). In a 250-mL, three-necked, round-bottom flask equipped with a septum, magnetic stirrer, reflux condenser, and dropping funnel was added 7.0 g (50.7 mmol) *p*-dimethoxybenzene in 125 mL of dry THF. To this solution was slowly added 24 mL of 1.6 M (38.4 mmol) *n*-butyllithium at 0 °C under an N_2 atmosphere. The yellow solution was stirred at 0 °C for 30 min and then heated under reflux for an additional 1.5 h. A solution of 7.4 g (25.4 mmol) of 1-bromopentadecane in 20 mL of THF was then added over a 30-min period and the reaction mixture heated under reflux for 1.5 h. The reaction was worked up by evaporating the solvent and extracting the residue with ether. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated, leaving a pale yellow oil, which was dissolved in 40 mL of 95% ethanol and cooled in a freezer. The white crystalline product was filtered and recrystallized from ethanol, yielding 5.1 g (58%) of 2-*n*-pentadecylhydroquinone dimethyl ether; mp 40–41 °C; ^1H NMR δ 6.64–6.78 (m, 4 H, Ar), 3.73 (s, 6 H, 2 OCH_3), 2.56 (2, 2 H, benzylic CH_2), 1.25 (br s, 26 H, 13 CH_2), and 0.88 (t, 3 H, CH_3); MS, m/z 348 (M^+·, 27), 120 (100).

2-*n*-Pentadecylhydroquinone (4). To an ice-cooled solution of **18** (5.0 g, 14.4 mmol) in 100 mL of CH_2Cl_2 was slowly added 30.0 mmol of a 1 mmol/mL solution of BBr_3 in CH_2Cl_2. After the addition was complete, the solution was stirred at 0 °C for 1 h followed by 2.0 h at room temperature. The solution was washed with H_2O (3 × 100 mL) and 10% $NaHCO_3$ (100 mL) and dried over Na_2SO_4. After evaporation of the solvent, the light brown residue was recrystallized from EtOAc–hexane, yielding 4.1 g (89%) of a white crystalline product; mp 104–105 °C; IR (KBr) 3270 (OH), 1456, 1193 cm^{-1}; ^1H NMR (pyridine-d_5) δ 7.00–7.28 (m, 3 H, aromatic), 4.81 (br s, 2 H, exchange with D_2O, 2 OH), 2.96 (t, 2 H, benzylic CH_2), 1.27 (br s, 26 H, 13 CH_2) 1.89 (t, 3 H, CH_3); MS, m/z 320 (M^+·, 59), 123 (100). Anal. ($C_{21}H_{36}O_2$) C, H.

Biological Testing. Biological testing was carried out in the same manner as previously reported.[3,4] Hartley guinea pigs weighing 300–400 g were purchased from Dutchland Laboratory Animals, Inc., and acclimated for 1 week prior to use. The animals were sensitized by a 1-mg dose of poison ivy urushiol in 0.15 mL of acetone applied topically to the dorsal neck skin. After i weeks, the sensitivity of the animals was determined by applying a 2-μg dose of PDC in 5 μL of acetone to the shaven abdominal skin. The skin test sites were observed at 24, 48, and 72 h for erythema and edema.

Allergenic cross-reactivity of compounds **1-9** with PDC was then determined in these sensitive animals by use of doses of 10 and 30 μg of **1-9** in 5 μL of acetone to abdominal test sites. Chemical irritancy was determined by applying similar doses of compounds **1-9** to the skin of nonsensitized guinea pigs.

Registry No. 1 (R = $C^{15}H^{31}$), 5394-77-4; **2**, 100486-25-7; **3** (R = $C_{15}H_{31}$), 16825-54-0; **4** (R = $C_{15}H_{31}$), 53918-51-7; **5** (R = $C_{15}H_{31}$), 3158-56-3; **6** (R_1 = $C_{13}H_{27}$), 100486-09-7; **6** (R_1 = $C_{15}H_{31}$),

100513-66-4; **6** (R_1 = $C_{17}H_{35}$), 100486-10-0; **7** (R_1 = $C_{13}H_{27}$), 100486-14-4; **7** (R_1 = $C_{15}H_{31}$), 100486-15-5; **7** (R_1 = $C_{17}H_{35}$), 100486-16-6; **8** (R = $C_{15}H_{31}$), 100486-19-9; **9** (R = $C_{15}H_{31}$), 100513-67-5; **10** (R_2 = $C_{13}H_{25}$), 28758-96-5; **10** (R_2 = $C_{15}H_{29}$), 28758-98-7; **10** (R_2 = $C_{17}H_{33}$), 28759-01-5; **14**, 100486-23-5; **15**, 50423-29-5; **16**, 100486-24-6; **17**, 100486-26-8; **19** (R_2 = $C_{13}H_{25}$), 100486-28-0; **19** (R_2 = $C_{15}H_{29}$), 100513-68-6; **19** (R_2 = $C_{17}H_{33}$), 100486-29-1; **20** (R_1 = $C_{13}H_{27}$), 100485-96-9; **20** (R_1 = $C_{15}H_{31}$), 65446-29-9; **20** (R_1 = $C_{17}H_{35}$), 100485-97-0; **21** (R_1 = $C_{13}H_{27}$), 100485-98-1; **21** (R_1 = $C_{15}H_{31}$), 38449-25-1; **21** (R_1 = $C_{17}H_{35}$), 100485-99-2; **22** (R_1 = $C_{13}H_{27}$), 100486-00-8; **22** (R_1 = $C_{15}H_{31}$), 100486-01-9; **22** (R_1 = $C_{17}H_{35}$), 100486-02-0; **23** (R_1 = $C_{13}H_{27}$), 100486-03-1; **23** (R_1 = $C_{15}H_{31}$), 100486-04-2; **23** (R_1 = $C_{17}H_{35}$), 100486-05-3; **24** (R_1 = $C_{13}H_{27}$), 100486-06-4; **24** (R_1 = $C_{15}H_{31}$), 100486-07-5; **24** (R_1 = $C_{17}H_{35}$), 100486-08-6; **25** (R_1 = $C_{13}H_{27}$), 100486-11-1; **25** (R_1 = $C_{15}H_{31}$), 100486-12-2; **25** (R_1 = $C_{17}H_{35}$), 100486-13-3; **26**, 100486-17-7; **28**, 68593-72-6; **29**, 100486-18-8; **32**, 100486-20-2; **33**, 100486-21-3; **34**, 100486-22-4; PDC, 492-89-7; PhOH, 108-95-2; $CH_3(CH_2)_{13}C(O)Cl$, 17746-08-6; $CH_3(CH_2)_{13}Br$, 112-71-0; *m*-$(MeO)_2C_6H_4$, 151-10-0; $CH_3(CH_2)_{14}Br$, 629-72-1; veratraldehyde, 120-14-9; resorcinol, 108-46-3; 2-*n*-pentadecylhydroquinone dimethyl ether, 100486-27-9.

Aminoglycoside Antibiotics. 6. Chemical Reactions of Aminoglycosides with Disodium Carbenicillin

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Aminoglycoside antibiotics including kanamycin A, tobramycin, and the gentamicin C complex reacted with 1 mol of disodium carbenicillin to give products derived from acylation of their amino groups by the β-lactam function of the carbenicillin. Amikacin was acylated by two carbenicillin units. Chromatographic analysis of fragments from the acid hydrolysis of these derivatives showed that the preferred site of acylation was in the 2-deoxystreptamine unit of the aminoglycosides. The two sites of acylation in amikacin were the 6′-amino group and the amino group in the aminohydroxybutyryl substituent. The derivatives had almost no antibacterial activity, and they were not toxic.

Combinations of aminoglycoside antibiotics with penicillins or cephalosporins have been shown to exert synergistic effects in killing bacteria. Such combinations are used clinically in the treatment of infections by Gram-negative rods, especially those caused by *Pseudomonas aeruginosa*.[1-4] However, in vitro studies have shown that high concentrations of penicillins such as carbenicillin and ticarcillin inactivate the aminoglycosides. This inactivation does not usually cause clinical problems, but it can be a serious consideration in patients with renal failure.[5-8]

A number of studies have been addressed to the relative reactivity of various β-lactams and aminoglycosides with each other.[9-11] From them, it appears that penicillins are more reactive than cephalosporins.[12] Carbenicillin most readily produced inactivation, followed in decreasing order by ticarcillin, benzylpenicillin, and ampicillin.[10,13] Among the aminoglycosides, tobramycin was the most readily inactivated, followed by gentamicin and kanamycin.[14,15] Netilmicin and amikacin were relatively resistant.[16,17] Most of these studies were made with blood serum as the vehicle.

Despite the high interest in the biological consequences of the penicillin–aminoglycoside interactions and the development of assay methods to detect the extent to which they have occurred in mixtures of these two types of antibiotics, little is known about the chemistry of the interaction. Weinstein and co-workers suggested that it involves a nucleophilic opening of the β-lactam ring by an amino group of the aminoglycoside with formation of an inactive amide (Figure 1).[18] This is a most reasonable explanation, but it has not been verified. Furthermore, it does not address the question of which amino group or groups are acylated. Aminoglycosides can have four or five amino groups, and it would be valuable to know if there is selectivity in their acylation. One study has been directed toward elucidation of the chemistry.[19] It involved the reaction of benzylpenicillin with kanamycin A and reported that they formed *O*-(benzylpenicilloyl)kanamycin, which was converted into *N*-(benzylpenicilloyl)kanamycin and benzylpenicilloic acid. We felt that this rather complex process merited further study with emphasis on stoichiometry and selectivity of the reaction.

On the basis of the foregoing considerations, we decided to examine the chemical interactions between disodium

(1) Klastersky, J.; Meunier-Carpenter, F.; Prevost, J. M. *Am. J. Med. Sci.* **1977**, *273*, 157.
(2) White, G. W.; Malow, J. B.; Zimelis, V. M.; Pahlavanzadeh, H.; Panwalker, A. P.; Jackson, G. G. *Antimicrob. Agents Chemother.* **1979**, *15*, 540.
(3) Kurtz, T. O.; Winston, D. J.; Bruckner, D. A.; Martin, W. J. *Am. J. Med. Sci.* **1981**, *20*, 239.
(4) Brown, A. E.; Quesada, O.; Armstrong, D. *Antimicrob. Agents Chemother.* **1982**, *21*, 592.
(5) Riff, L. G.; Jackson, G. G. *Arch. Intern. Med.* **1972**, *130*, 887.
(6) Davies, M.; Morgan, J. R.; Anand, C. *Antimicrob. Agents Chemother.* **1975**, *7*, 431.
(7) Ervin, F. R.; Bullock, W. E., Jr.; Nuhall, C. C. *Antimicrob. Agents Chemother.* **1976**, *9*, 1004.
(8) Pieper, J. A.; Vidal, R. A.; Schentag, J. J. *Curr. Chemother. Infect. Dis. Proc. Int. Cong. Chemother. 11th* **1979**, *1*, 519.
(9) Pickering, L. K.; Gearhart, P. *Antimicrob. Agents Chemother.* **1979**, *15*, 592.
(10) Hale, D. C.; Jenkins, R.; Matsen, J. M. *Am. J. Clin. Pathol.* **1980**, *74*, 316.
(11) Pfaller, M. A.; Granich, G. G.; Valdes, R.; Murray, P. R. *Diagn. Microbiol. Infect. Dis.* **1984**, *2*, 93.
(12) Glew, R. H.; Pavuk, R. A. *Antimicrob. Agents Chemother.* **1983**, *24*, 474.
(13) Riff, L. J.; Thomason, J. L. *J. Antibiot.* **1982**, *35*, 850.
(14) Fluornoy, D. J. *Infection* **1978**, *6*, 241.
(15) Henderson, L. J.; Polk, R. E.; Kline, B. J. *Am. J. Hosp. Pharm.* **1981**, *38*, 1167.
(16) Farchione, L. A. *Antimicrob. Agents Chemother.* **1981**, *8*, 27.
(17) Pickering, L. K.; Rutherford, I. *J. Pharmacol. Exp. Ther.* **1981**, *217*, 345.
(18) Waitz, J. A.; Drube, C. G.; Moss, E. L., Jr.; Oden, E. M.; Bailey, J. V.; Wagman, G. H.; Weinstein, M. J. *J. Antibiot.* **1972**, *25*, 219.
(19) Yamana, T.; Mizukami, V.; Ichimura, F.; Yokogawa, K. *Yakuzaigaku* **1978**, *38*, 74.

0022-2623/86/1829-0611$01.50/0