additional 49.1 mg of III was added. When solution was complete the mixture was evaporated to dryness and the residue was recrystallized once from EtAc–hexane and three times from acetonitrile to constant specific activity (14,606 dpm/mg). From this the amount of III was calculated to be 861,750 dpm or 82% of this fraction.

Synthesis. 2,6-Dimethyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylic Acid *N*-Oxide (VII). A solution of 1.02 g (0.003 mol) of IV and 0.65 g (0.00375 mol) of *m*-chloroperbenzoic acid in 10 ml of EtOH was refluxed for 2 hr. The reaction mixture was taken to dryness and water was added. Sufficient 5% NaOH was added to dissolve all the solids. Then the pH was lowered slowly with dilute HCl until the *m*-chlorobenzoic acid crystallized out. It was collected by filtration. On further lowering to pH 1, 1.1 g of product was obtained. Recrystallization from aqueous NH_4OH–HCl gave white crystals, mp 184° dec. *Anal.* ($C_{16}H_{12}NO_5F_3 \cdot H_2O$).

6-Hydroxymethyl-2-methyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylic Acid γ Lactone (V). A sample of 0.5 g (0.0014 mol) of VII was treated with 0.18 ml (0.0017 mol) of acetic anhydride at 140° for 5 min, at which time most of the bubbling had stopped. The reaction mixture was evaporated to dryness and partitioned between 5% $NaHCO_3$ (with some concentrated NH_4OH added to keep it basic) and ether. After the aqueous layer had been washed with ether it was brought to pH 1 with HCl. The product was extracted into ether, the ether evaporated to dryness, and the residue dissolved in EtOH and warmed with 0.09 g of KOH (0.0016 mol) and some NH_4OH for a few minutes. This was evaporated to dryness and the residue heated on the steam bath for 2 hr in 10 ml of 6 *N* HCl. Cooling gave a white solid (0.21 g, 45%) which after recrystallization from CH_3CN–H_2O had mp 221.5–224°; uv λ_{max}^{EtOH} 275 mμ (ε 5900). *Anal.* ($C_{16}H_{10}NO_4F_3$).

2,6-Dimethyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylic Acid Bis(2-hydroxyethyl) Ester (XI). A sample of IV (6.0 g, 0.018 mol) was refluxed for 18 hr with 15 ml (24.6 g, 0.209 mol) of $SOCl_2$ and 100 ml of $CHCl_3$. The mixture was evaporated to dryness and 20 ml of ethylene glycol and 2.5 g of Na_2CO_3 (0.04 mol) were added. This was heated for 1 hr on a steam bath, diluted to 200 ml with water, and extracted three times with 100 ml of diethyl ether. The ether solution was washed three times with 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated. Recrystallization from toluene gave 3 g (39%) of white crystals, mp 86.0–87.5°. *Anal.* ($C_{20}H_{20}NO_6F_3$).

2,6-Dimethyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylic Acid Mono-2-hydroxyethyl Ester (VI). A mixture of 0.83 g (1.95 mmol) of XI was heated with 160 mg of 52% NaH in mineral oil (83 mg of NaH, 3.5 mmol) and 20 ml of ethylene glycol at 100° for 36 hr. It was diluted to 100 ml with water and extracted at this pH (pH ≥8) twice with 100 ml of ether. The pH of the aqueous layer was adjusted to 3.5–4.0 and extracted three times with 100 ml of EtOAc. This was washed twice with 100 ml of water containing 2 drops of 12 *N* HCl. Then it was dried over $MgSO_4$ and evaporated to dryness. This gave 0.41 g (57%) of product which after recrystallization from (1:2) EtOAc–hexane had mp 181–182°; uv λ_{max}^{EtOH} 272 mμ (ε 5040). *Anal.* ($C_{18}H_{16}NO_5F_3$).

Acknowledgments. We wish to thank the staff of our Analytical and Physical Chemistry Section for analytical and spectral analyses, our Biochemistry staff for providing biological samples, and Dr. Sidney Walkenstein for helpful suggestions.

References

(1) B. Loev and R. E. Tedeschi, U. S. Patent 3,511,847 (1970).
(2) B. R. Walker, S. G. Meister, and R. G. Familiar, *Clin. Pharmacol. Ther.*, 13, 155 (1972).
(3) S. S. Walkenstein, A. P. Intoccia, T. L. Flanagan, B. Hwang, D. Flint, J. Weinstock, A. J. Villani, D. Blackburn, and H. Green, *J. Pharm. Sci.*, in press.
(4) R. T. Williams, "Detoxication Mechanisms," Chapman and Hall, London, 1959, p 117.
(5) S. Oae, T. Kitao, and Y. Kitaoka, *J. Amer. Chem. Soc.*, 84, 3359 (1962).

An Acyclic Puromycin Analog. 6-Dimethylamino-9-[2-hydroxy-3-(*p*-methoxyphenyl-L-alanylamino)propyl]purine†

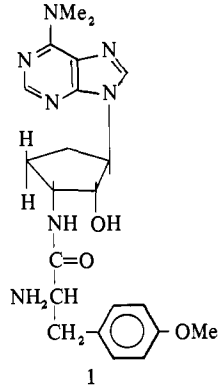
Robert Vince*,‡ and Raymond G. Isakson

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455. *Received May 4, 1972*

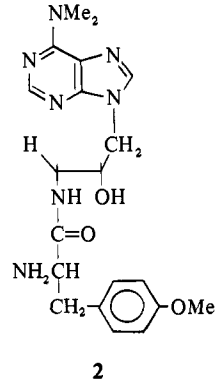
In a continuation of our studies on nonglycosyl puromycin analogs, 6-dimethylamino-9-[2-hydroxy-3-(*p*-methoxyphenyl-L-alanylamino)propyl]purine was synthesized and separated into its two diastereoisomers. The lack of antimicrobial activity of this acyclic puromycin analog when compared with the previously prepared carbocyclic analog is discussed in terms of possible conformational requirements for ribosomal binding.

In a previous report relating to our studies on puromycin analogs, the synthesis and antimicrobial activity of a carbocyclic puromycin analog **1** were described.[1] The antimicrobial activity[1] and the inhibition of *in vitro* protein biosynthesis[2] exhibited by the carbocyclic analog suggest a minimal contribution by the furanosyl oxygen and the hydroxymethyl moiety in the activity of puromycin.

Previous studies with isosteric nucleosides have revealed that rather large changes in the substituent at the 9 position of the purine nucleus can be made without markedly altering the capacity of the compound to bind to a given enzyme.[3] In fact, the replacement of the cyclic moiety at the 9 position of the purine by an acyclic moiety may result in enhanced binding to some enzymes.[4,5] In order to evaluate the antimicrobial activity of a compound with greater conformational freedom than **1**, we decided to prepared the acyclic derivative **2**.



1



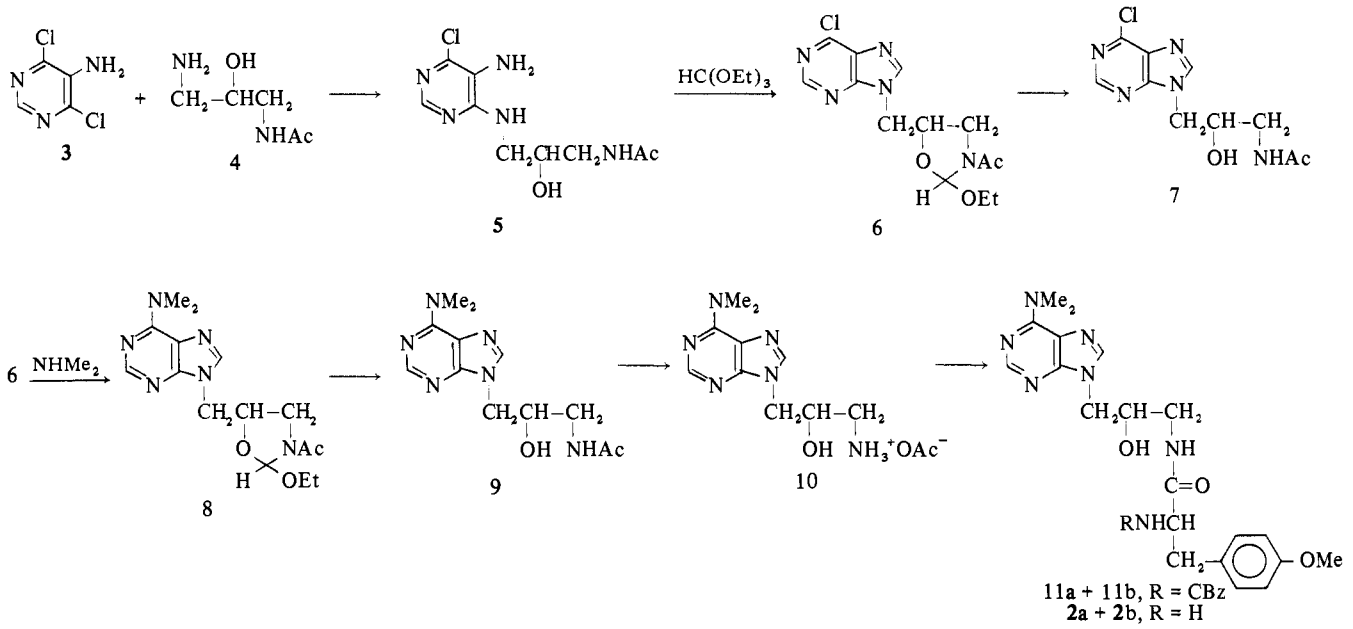
2

The acyclic puromycin analog **2** was synthesized by the route outlined in Scheme I. The condensation of 5-amino-4,6-dichloropyrimidine (**3**) with 2-hydroxy-3-acetamido-

†This work was generously supported by Grant AI 08142 from the U. S. Public Health Service.

‡Recipient of the Career Development Award, CA25258, U. S. Public Health Service.

Scheme I



propylamine (**4**) gave the corresponding pyrimidine **5**. Cyclization of **5** with triethyl orthoformate in the presence of ethanesulfonic acid gave the unexpected oxazolidine **6** which precipitated from the reaction mixture. The two isomers of **6** were not separated but were shown by nmr spectroscopy to be present in a 1:4 ratio. This was evidenced by the absorption of the C-2′ proton as a singlet at τ 3.8 (0.2 proton) and 4.0 (0.8 proton). Selective hydrolysis of the ethoxyoxazolidine ring to give **7** was accomplished with dilute acid. However, it was more convenient to prepare the 6-dimethylamino derivative **8** directly from **6**. Mild acid hydrolysis of **8** resulted in selective removal of the ethoxyoxazolidine ring and gave **9** in good yield. Hydrolysis of **9** with barium hydroxide gave the amine **10**, characterized as its acetate salt.

The amino alcohol **10** was coupled to *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine[6] by two methods: A, the nitrophenyl ester method,[7,8] and B, the dicyclohexylcarbodiimide-*N*-hydroxysuccinimide method.[9,10] The resulting carbobenzoxy blocked diastereomers **11a** and **11b** were separated by exhaustive recrystallization. Each diastereomer was converted to its unblocked amine, **2a** and **2b**, by hydrogenolysis of the carbobenzoxy group. Both methods of coupling gave products of the same optical purity. No attempt was made to determine the absolute stereochemistry of isomers **2a** and **2b** since neither compound exhibited significant biological activity.

Results and Discussion

Both diastereomers **2a** and **2b** were inactive against four different microbial systems at 2 m*M* concentrations. The carbocyclic analog **1** exhibited complete inhibition of growth in the same systems at the following concentrations (m*M*): *Staphylococcus aureus* (NRRL B-313), 0.244; *Bacillus subtilis* (NRRL B-545), 0.060; *Klebsiella pneumoniae* (NRRL B-117), 0.485; *Escherichia coli* (NRRL B-210), 0.120. Only isomer **2b** gave slight inhibition of *in vitro* poly-U- or poly-UC-directed polyphenylalanine synthesis in an *E. coli* system at 1000 times the concentration required for the same degree of inhibition by the carbocyclic analog **1**. For example, $10^{-3}M$ **2b** gave 21% inhibition of the poly-UC-directed polyphenylalanine synthesis while $10^{-6}M$ **1** gave 37% inhibition.[2]

Recently, Sundaralingam and Arora have determined the conformation of puromycin by single-crystal X-ray diffraction patterns.[11] They suggested a U-shaped conformation in which the benzene ring is stacked under the purine moiety of the nucleoside. An interesting mechanism of action of puromycin based on this conformation has been postulated by Raake[12] in which it was suggested that the antibiotic can "hug" the terminal adenine of peptidyl-tRNA. Thus, the dimethyladenine of puromycin, the terminal adenine, the methoxyphenyl of the antibiotic, and the penultimate cytosine of tRNA form one continuous stack of hydrophobic rings.[12] Based on a comparison of results from X-ray, molecular polarizability, and proton magnetic resonance studies of nucleosides and other compounds which show similar bond lengths and angles in tetrahydrofuran and cyclopentane ring systems,[13] it is not unreasonable to suggest similar conformations in puromycin and the carbocyclic analog **1**. However, it is very likely that the freely rotating acyclic puromycin analog would not favor such a U-shaped conformation. Alternatively, inspection of molecular models indicates that when **2** assumes the U-shaped conformation the amino acid moiety and the 2-hydroxyl group prefer a trans orientation. The requirement for a cis orientation of these two moieties is demonstrated by the fact that the corresponding analog of 1 in which the amino acid moiety is trans to the hydroxyl group exhibits the same inhibitory activity as **2b**.§ A study of conformation *vs.* activity of these and other related compounds will be the subject of a future paper.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured at ambient temperatures with a Perkin-Elmer 141 automatic polarimeter, nmr with a Varian A-60D spectrometer, ir with a Perkin-Elmer 237B spectrophotometer, and uv with a Cary 14 recording spectrophotometer. Analytical results are within ±0.4% of the calculated values. Biological testing methods have been described previously (ref 1 and 2).

§ R. Vince and S. Daluge, unpublished results.

4-(3-Acetamido-2-hydroxypropylamino)-5-amino-6-chloropyrimidine (5). A solution of **3** (3.67 g, 19.0 mmol), **4**[14] (3.39 g, 25.7 mmol), Et_3N (9 ml, 64 mmol), and 1-butanol (90 ml) was refluxed for 24 hr. The solution was evaporated to an amber oil which was diluted with water (30 ml). The product slowly crystallized and was removed by filtration. Recrystallization of the dried crystals from MeCN gave 3.17 g (64%) of the desired product. An analytical sample of **5** was obtained by recrystallization from acetone (mp 156–158°): uv max in mμ (ε × 10^{-4}) pH 1, 302 (1.54); pH 7, 290 (1.22) and 262 (1.16); pH 13, 290 (1.22) and 262 (1.16). *Anal.* ($C_9H_{14}ClN_5O_2$) C, H, N.

9-[(3-Acetyl-2-ethoxyoxazoladin-5-yl)methyl]-6-chloropurine (6). To a solution of ethanesulfonic acid (159 mg, 0.710 mmol) in triethyl orthoformate (60 ml) was added **5** (3.55 g, 13.7 mmol). The reaction mixture was stirred overnight at room temperature and hexane (50 ml) was added. The precipitate was removed by filtration and the filter cake was washed with hexane. The filtrate was chilled and a second crop of solid was obtained: total yield, 2.83 g (64%); mp 154–155°. The product was free of impurities as indicated by tlc. A small sample was recrystallized from EtOAc (mp 154–155°): uv max in mμ (ε × 10^{-3}) pH 1, 265 (9.39); pH 7, 265 (9.50); pH 13, 265 (9.63). *Anal.* ($C_{13}H_{16}ClN_5O_3$) C, H, N.

9-(3-Acetamido-2-hydroxypropyl)-6-chloropurine (7). The ethoxyoxazolidine 6 was converted to 7 by treatment with 0.1 *N* HCl for 10 min at room temperature. The reaction mixture was neutralized with $NaHCO_3$ and evaporated to dryness. The crude mixture was extracted with EtOH and the solvent was removed *in vacuo*. The crude product was purified by preparative tlc (silica gel PF 254, 5% MeOH in $CHCl_3$), followed by recrystallization from EtOAc, and gave the pure product (mp 162–163°): uv max in mμ (ε × 10^{-3}) pH 1, 265 (9.49); pH 7, 265 (9.49); pH 13,265 (9.63). *Anal.* ($C_{10}H_{12}ClN_5O_2$) C, H, N.

9-[(3-Acetyl-2-ethoxyoxazoladin-5-yl)methyl]-6-dimethylaminopurine (8). Crude 6 (4.27 g, 13.1 mmol) was washed into a stainless steel bomb with 25% dimethylamine (60 ml). The bomb was maintained at 90° overnight and the volatile materials were removed *in vacuo*. The amber oil product was diluted with EtOAc and filtered to remove the salts. The filtrate was evaporated to an amber oil, 2.2 g. Purification of 1.0 g of crude product by preparative tlc (silica gel PF 254, 10% MeOH in $CHCl_3$) gave 0.756 g of pure 6 as a colorless glass: uv max in mμ (ε × 10^{-4}) pH 1, 269 (1.76); pH 7, 277 (1.75); pH 13, 277 (1.76). *Anal.* ($C_{15}H_{22}N_6O_3$) C, H, N.

9-(3-Acetamido-2-hydroxypropyl)-6-dimethylaminopurine (9). To 3.49 g (10.7 mmol) of 6 in a stainless steel bomb was added dimethylamine (70 ml). The reaction mixture was maintained at 85–95° for 20 hr. The contents of the bomb were diluted with EtOH (200 ml) and evaporated to a light yellow solid. The crude material was dissolved in 10 ml of 10% HCl and heated for 5 min on a steam bath. The cooled solution was adjusted to pH 8 with $NaHCO_3$, diluted with EtOH, and evaporated *in vacuo*. An EtOH slurry of the dried mixture product was filtered and the filtrate was evaporated to a crude product. Recrystallization from MeCN gave 9 as the pure product (yield 2.83 g (93%), mp 182–184°): uv max in mμ (ε × 10^{-4}) pH 1, 269 (1.69); pH 7, 276 (1.72); pH 13, 278 (1.74). *Anal.* ($C_{12}H_{18}N_6O_2$) C, H, N.

9-(3-Amino-2-hydroxypropyl)-6-dimethylaminopurine Acetate Salt (10). A solution of 9 (496 mg, 1.78 mmol) in 0.5 *N* $Ba(OH)_2$ solution (25 ml) was heated under reflux for 5 hr. The reaction mixture was diluted with EtOH (25 ml) and treated with excess Dry Ice. The salts were removed by filtration and the filtrate was evaporated *in vacuo* to a gummy solid. The crude product was dissolved in absolute EtOH and the remaining barium salts were removed by filtration. Removal of the EtOH at reduced pressure left a light yellow gum. The gum was dissolved in CH_2Cl_2 (20 ml), and HOAc (0.1 ml) and water (0.1 ml) were added while the solution was stirred vigorously. The pure product, **10**, precipitated as the monohydrated acetate salt (yield 518 mg (92%), mp 109–116°): uv max in mμ (ε × 10^{-4}) pH 1, 268 (1.73); pH 7, 277 (1.73); pH 13, 277 (1.73). *Anal.* ($C_{12}H_{22}N_6O_4$) C, H, N.

***N*-Benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine *p*-Nitrophenyl Ester.** A procedure similar to that of Bodansky was used.[7] To an ice-cold solution of benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine (10.8 g, 32.9 mmol) and *p*-nitrophenol (5.11 g, 36.7 mmol) in EtOAc (75 ml) was added *N,N*-dicyclohexylcarbodiimide (7.55 g, 36.6 mmol) in EtOAc (75 ml). The reaction mixture was stirred at 0° for 15 min and at room temperature for 90 min. The mixture was charged with acetic acid (4 ml) and stirred for 15 min before removing the dicyclohexylurea by filtration. The filtrate was evaporated *in vacuo* and the solid residue was dissolved in acetone (50 ml). A small amount of dicyclohexylurea was removed by filtration and the filtrate was evaporated to a white solid. The crude product was dissolved in 200 ml of $CHCl_3$ and extracted with 5% NaOH (3 × 50 ml) and water (3 × 50 ml). The organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was recrystallized from EtOH and gave 11.7 g (79%) of the analytical material: mp 120–121°; ir (KBr) 1760 and 1700 (C=O), 1525 and 1350 cm^{-1} (NO_2); $[\alpha]^{23}D$ −9.2° (*c* 0.62, $CHCl_3$). *Anal.* ($C_{24}H_{22}N_2O_3$) C, H, N.

9-[2-Hydroxy-3-(benzyloxycarbony-*p*-methoxyphenyl-L-alanylamino)propyl]-6-dimethylaminopurine Diastereomers (11a and 11b). Method A. To a solution of **10** (733 mg, 2.63 mmol) in EtOH (60 ml) was added *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine *p*-nitrophenyl ester (1.19 g, 2.64 mmol). The solution was heated under reflux for 1 hr and the EtOH was removed *in vacuo*. The crude product was dissolved in $CHCl_3$ (75 ml) and washed with 5% NaOH (3 × 10 ml) and water (3 × 10 ml). The organic layer was dried *in vacuo* to a white solid, yield 2.23 g (85%). The two diastereoisomers were separated by exhaustive recrystallization from ethanol. Diastereomer 11a gave mp 217–218°; $[\alpha]^{23}D$ −8.3° (*c* 0.54, $CHCl_3$). Diastereoisomer 11b showed mp 168–170°; $[\alpha]^{23}D$ +13.5° (*c* 0.49, $CHCl_3$). The nmr spectra of both isomers were identical. The uv max in mμ (ε × 10^{-4}), 270 (1.97), in 0.1 *N* HCl for the mixture and for 11a and 11b were identical. *Anal.* ($C_{28}H_{33}N_7O_5$) C, H, N.

Method B. To a solution of **10** (1.36 g, 5.74 mmol), *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine[6] (2.01 g, 6.10 mmol), and *N*-hydroxysuccinimide (704 mg, 6.12 mmol) in DMF (35 ml) at −5° was added dicyclohexylcarbodiimide (1.26 g, 6.11 mmol) in 5 ml of DMF. After 45 min the mixture was allowed to warm to room temperature and stirred for 48 hr. The dicyclohexylurea was removed by filtration and the filtrate was evaporated *in vacuo* to a waxy solid. A $CHCl_3$ solution of the crude product was washed with water (30 ml) and half-saturated $NaHCO_3$ (2 × 30 ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. Exhaustive recrystallization from ethanol gave the diastereoisomers 11a and 11b identical in all respects with the samples described above.

9-[2-Hydroxy-3-(*p*-methoxyphenyl-L-alanylamino)propyl]-6-dimethylaminopurine (2a). A mixture of the diastereoisomer 11a (1.56 g, 2.91 mmol) and 10% Pd/C (720 mg) in HOAc (150 ml) was hydrogenated at atmospheric pressure for 30 min during which time 74 ml (3.3 mmoles) of H_2 was taken up. The reaction mixture was filtered through Celite and the filtrate was evaporated at reduced pressure. The oily residue was mixed with an excess of 5% $NaHCO_3$ and evaporated to a gummy solid. The product was extracted with hot $CHCl_3$ and the $CHCl_3$ was removed *in vacuo*. Recrystallization from benzene gave 1.01 g (84%) (mp 104–107°): uv max in mμ (ε × 10^{-4}) pH 1, 269 (1.87); pH 7, 276 (1.93); pH 13, 276 (1.93); $[\alpha]^{23}D$ −63.3° (*c* 0.70, $CHCl_3$). *Anal.* ($C_{20}H_{27}N_7O_3$) C, H, N.

9-[2-Hydroxy-3-(*p*-methoxyphenyl-L-alanylamino)propyl]-6-dimethylaminopurine (2b). The procedure used for the reduction of 11b was identical with the procedure described for 11a and gave an 85% yield of **2b** (mp 145–146°): uv max in mμ (ε × 10^{-4}) pH 1, 269 (1.92); pH 7, 276 (1.96); pH 13, 275 (1.98); $[\alpha]^{23}D$ −16.8° (*c* 0.56, $CHCl_3$). *Anal.* ($C_{20}H_{27}N_7O_3$) C, H, N.

Acknowledgments. The authors wish to thank Maxine Palm and Clare Ritter for their assistance in the biological testing.

References

(1) S. Daluge and R. Vince, *J. Med. Chem.*, **15**, 171 (1972).
(2) R. Vince, S. Daluge, and M. Palm, *Biochem. Biophys. Res. Commun.*, 46, 866 (1972).
(3) H. J. Schaeffer, S. Marathe, and V. Alks, *J. Pharm. Sci.*, **53**, 1368 (1964).
(4) H. J. Schaeffer and P. S. Bhargava, *Biochemistry*, 4, 71 (1965).
(5) H. J. Schaeffer, D. Vogel, and R. Vince, *J. Med. Chem.*, 8, 502 (1965).
(6) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, 77, 1 (1955).
(7) M. Bodansky, J. Meienhofer, and V. DuVigneaud, *ibid.*, **82**, 3195 (1960).
(8) B. R. Baker, D. V. Santi, J. K. Coward, H. S. Shapiro, and J. H. Jordan, *J. Heterocycl. Chem.*, **3**, 425 (1966).
(9) J. E. Zimmerman and G. W. Anderson, *J. Amer. Chem. Soc.*, 89, 7151 (1967).
(10) W. W. Lee, G. L. Tong, R. W. Blackford, and L. Goodman, *J. Org. Chem.*, **35**, 3808 (1970).
(11) M. Sundaralingam and S. K. Arora, *Proc. Nat. Acad. Sci. U. S.*,

64, 1021 (1969).
(12) I. D. Raacke, *Biochem. Biophys. Res. Commun.*, 43, 168 (1971).
(13) K. C. Murdock and R. B. Angier, *J. Amer. Chem. Soc.*, 84, 3758 (1962), and references cited therein.
(14) D. O. Spry and H. S. Aaron, *J. Org. Chem.*, 31, 3838 (1966).

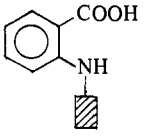
Acridan-4-carboxylic Acids and *N*-Aryl-2-amino-3-toluic Acids as Planar and Antiplanar Analogs of Antiinflammatory *N*-Arylanthranilic Acids

Tim R. Westby† and Charles F. Barfknecht*

Department of Medicinal Chemistry, College of Pharmacy, University of Iowa, Iowa City, Iowa 52240. *Received June 15, 1972*

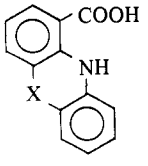
In an attempt to assess the importance of the relative conformation of the aryl rings of *N*-arylanthranilic acid and antiinflammatory agents, the title compounds were synthesized and tested for antiinflammatory activity. In the anti-uv erythema screen, antiplanar *N*-(2,3-xylyl)-2-amino-3-toluic acid had the same order of activity as planar 5,6-dimethylacridan-4-carboxylic acid while another antiplanar analog, *N*-(2,3,6-trimethylphenyl)anthranilic acid, was much more active than either. These results suggest that other factors are more important than relative conformation of the aryl rings in controlling antiinflammatory activity.

In 1964 Scherrer, Winder, and Short[1] proposed a hypothetical anti-uv-erythema and antibradykinin receptor designed to accommodate a number of classes of antiinflammatory agents including *N*-arylanthranilic acids. In order to fit this receptor, the two phenyl rings of *N*-arylanthranilic acids must assume an antiplanar conformation relative to each other as depicted in **1**.

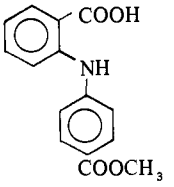


1

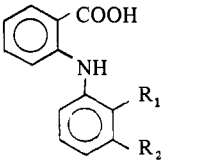
Several compounds which are closely related to *N*-arylanthranilic acids but which cannot exist in an antiplanar conformation have been shown to possess antiinflammatory activity. These include a phenothiazinecarboxylic acid **2**[2] and a phenoxazinecarboxylic acid **3**.[3] Also, many flexible *N*-arylanthranilic acids which are not restricted to an antiplanar conformation have antiinflammatory activity. Examples include *N*-(*p*-carbomethoxyphenyl)anthranilic acid (**4**),[4] mefenamic acid (**5a**),[5] and flufenamic acid (**5b**).[6]



2, X = S
3, X = O



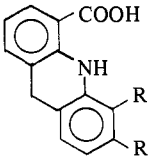
4



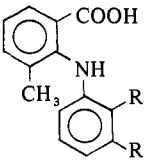
5a, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CF_3$

In an attempt to further assess the importance of the relative conformation of the aryl rings of *N*-arylanthranilic acids for antiinflammatory activity, compounds **6–11** with aryl rings either coplanar or antiplanar were synthesized and tested for antiinflammatory activity.

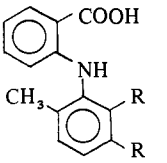
Chemistry. All compounds were prepared using a synthetic sequence which included the Chapman rearrangement.[7] The synthetic scheme to compounds **8**, **9**, and **11** is shown



6, R = CH_3
7, R = H



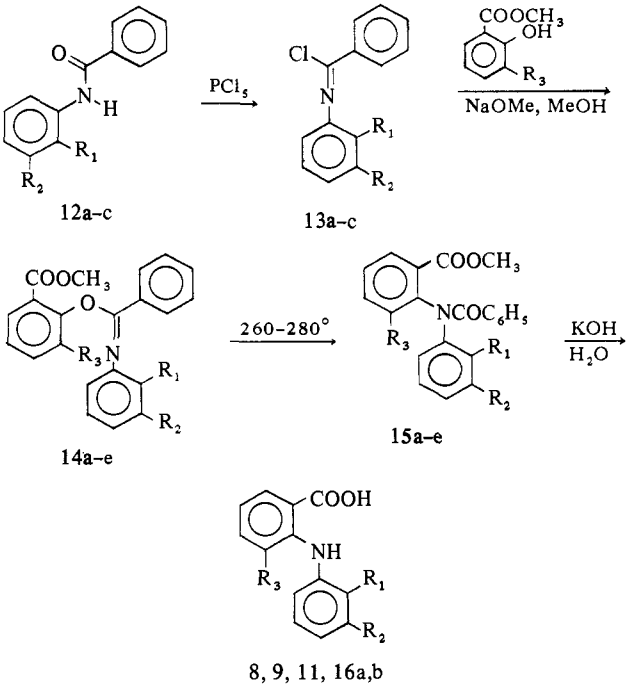
8, R = CH_3
9, R = H



10, R = CH_3
11, R = H

in Scheme I. Substituted benzanilides 12a–c were prepared by the usual method.[8] *N*-Arylbenzimidoyl chlorides **13a–c** were prepared by treatment of the corresponding benzanilides with phosphorus pentachloride.[9] Aryl *N*-arylbenzimidates **14a–c** were prepared by condensation of the corresponding imino chloride with the appropriate phenol in a solution of sodium methoxide in methanol.[10] Chapman rearrangement[11] of these compounds to give substituted methyl *N*-benzoyl-*N*-arylanthranilates **15a–e** proceeded smoothly at 260–280°, despite the steric hindrance of the ortho substituents, as a result of steric acceleration due to

Scheme I



8, 9, 11, 16a,b

†Abstracted in part from the thesis submitted by T. R. W. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1971. Presented in part at Division of Medicinal Chemistry, 160th National Meeting of the American Chemical Society, Chicago, Ill., 1970, MEDI 048. NDEA Title IV Fellow, 1967–1970.