boxylic Acid (9). The acrylic acid **2** (2.0 g, 0.06 mol) was dissolved in 700 ml of 95% EtOH containing 0.1 g of I_2. The solution was irradiated with 2537-Å light for 24 hr in a Rayonet reactor while air was bubbled through the solution. Evaporation of the EtOH gave 1.1 g of crude **9**, mp 280–290°. Recrystallization from CH_3CN raised the melting point to 293–294°.

2-Chloro-8-trifluoromethyl[2,1-*b*]thiophene-4-ethylene Oxide (10). The carboxylic acid **9** (2.2 g, 0.066 mol) was refluxed with 20 ml of $SOCl_2$ for 4 hr. The $SOCl_2$ was removed under reduced pressure and the resulting solid was dissolved in *ca.* 100 ml of CH_2Cl_2; this solution was added to a solution of CH_2N_2 in 200 ml of Et_2O [prepared from 4.6 g (0.045 mol) of *N*-nitrosomethylurea[14]] at 0°. The solution was stirred for 4 hr while allowing the temperature to rise to room temperature and then 20 ml of HBr (48%) was added. The resultant crude bromo ketone was dissolved in 200 ml of C_6H_6 and 50 ml of 95% EtOH and allowed to react with 0.5 g of $NaBH_4$ for 15 min. To this reaction medium was added 20 ml of a 20% KOH solution and the mixture was stirred for 15 min. The organic layer was separated and evaporated under reduced pressure to yield 1.3 g of crude **10**, mp 90–95°. Recrystallization raised the melting point to 99–100°.

2-Chloro-8-trifluoromethyl-α-(*N*,*N*-di-*n*-butylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanol Hydrochloride (23). The epoxide **10** (1.8 g, 0.055 mol) was refluxed with 5 ml of $(n\text{-Bu})_2NH$ for 1 hr. The amine was removed under vacuum and the residual oil was chromatographed on an Al_2O_3 column using C_6H_6 as the eluent. The fraction containing the carbinolamine was converted to its HCl salt by passing HCl through the solution for 10 min. Water was removed by refluxing the solution in a Dean-Stark apparatus for 4 hr. Evaporation of the C_6H_6 gave 2.0 g, mp 248–250°. Recrystallization from EtOH–Et_2O raised the melting point to 251–252°.

2-Pyridyl Naphtho[2,1-*b*]thiophen-4-yl Ketone (18). To a stirred suspension of lithium (1.6 g, 0.22 g-atom) in 50 ml of Et_2O, under N_2, 15 g (0.11 mol) of freshly distilled *n*-BuBr was added dropwise. Stirring was continued for 30 min, the solution was cooled to −70°, and 17 g (0.11 mol) of 2-bromopyridine was added dropwise. A solution of 1.25 g (0.055 mol) of naphtho[2,1-*b*]thiophene-4-carboxylic acid in 40 ml of dioxane was added and the solution was stirred at −70° for 3 hr. The cooling bath was removed and when the temperature reached −5° 200 ml of H_2O was carefully added. The mixture was extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$) and the solvent was evaporated. The resultant oil was chromatographed on an Al_2O_3 column using C_6H_6 as the eluent. The yield after recrystallization from EtOH was 0.8 g, mp 118–119°.

2-Pyridylnaphtho[2,1-*b*]thiophen-4-ylcarbinol (37). Method A. A solution of 0.45 g (0.018 mol) of **18** in 150 ml of EtOH containing 2.5 ml of 0.117 *N* HCl and 0.75 g of PtO_2 was hydrogenated at 3.15 kg/cm² for 24 hr. The catalyst was removed by filtering over Celite and the EtOH solution was concentrated to *ca.* 30 ml by evaporation under reduced pressure and was poured into a stirred $NaHCO_3$ solution. The resulting aqueous suspension of the free base was extracted with Et_2O (*ca.* 300 ml). The Et_2O was evaporated and the residue was crystallized from ethanol; the yield was 0.3 g; mp 110–111°.

Method B. A solution of 0.4 g (0.016 mol) of **18** was dissolved in 150 ml of EtOH and 0.5 g of $NaBH_4$ was added and the mixture was stirred at room temperature for 30 min. The EtOH was evaporated under reduced pressure and the residue was dissolved in Et_2O, washed (H_2O), dried (Ca_2SO_4), and evaporated to yield 0.4 g, mp 110–111°.

Acknowledgments. We acknowledge the U. S. Army Medical Research and Development Command under Contract No. DADA17-68-C-8035 for support of this work. This is Contribution No. 1205 from the Army Research Program on Malaria. We thank Dr. Edgar A. Steck for advice and helpful discussion.

References

(1) B. P. Das, J. A. Campbell, F. B. Samples, R. A. Wallace, L. K. Whisenant, R. W. Woodard, and D. W. Boykin, Jr., *J. Med. Chem.*, **15**, 370 (1972).
(2) B. P. Das, R. T. Cunningham, and D. W. Boykin, Jr., *J. Med. Chem.*, **16**, 1361 (1973).
(3) J. W. Panter, D. W. Boykin, Jr., and W. D. Wilson, *J. Med. Chem.*, **16**, 1366 (1973).
(4) E. A. Nodiff, K. Tanabe, C. Seyfried, S. Matsuura, Y. Kondo, E. H. Chen, and M. P. Tyagi, *J. Med. Chem.*, 14, 921 (1971).
(5) E. A. Nodiff, A. J. Saggiomo, M. Shinbo, E. H. Chen, H. Otomasu, Y. Kondo, T. Kikuchi, B. L. Verma, S. Matsuura, K. Tanabe, M. P. Tyagi, and S. Morosawa, *J. Med. Chem.*, **15**, 775 (1972).
(6) P.-L. Chien, D. J. McCaustland, W. H. Burton, and C. C. Cheng, *J. Med. Chem.*, **15**, 28 (1972).
(7) W. T. Colwell, V. Brown, P. Christie, J. Lange, C. Reece, K. Yamamoto, and D. W. Henry, *J. Med. Chem.*, **15**, 771 (1972).
(8) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).
(9) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, 11, 273 (1968).
(10) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(11) C. C. Cheng, *J. Pharm. Sci.*, **60**, 1596 (1971).
(12) J. A. Blanchette and E. V. Brown, *J. Amer. Chem. Soc.*, **73**, 2779 (1951).
(13) J. H. Ford, G. C. Prescott, and D. R. Colingsworth, *J. Amer. Chem. Soc.*, **72**, 2109 (1950).
(14) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1964, p 969.

Antimalarials. 6. Synthesis, Antimalarial Activity, and Configurations of Racemic α-(2-Piperidyl)-4-pyridinemethanols

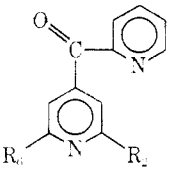
M. P. LaMontagne,* A. Markovac, and P. Blumbergs

Ash Stevens Inc., Detroit, Michigan 48202. *Received October 18, 1973*

Three pairs of racemic α-(2-piperidyl)-4-pyridinemethanols were prepared and tested for antimalarial activity in mice. In each of the three series, catalytic hydrogenation of the precursor pyridyl ketone afforded predominately one isomer. Inversion of this isomer to the other configurational isomer was effected *via* conversion to the oxazolium chloride followed by hydrolysis. The absolute configuration of each isomer was established by examination of the nmr spectra of the 7-aryl-8-oxa-1-azabicyclo[4.3.0]nonane derivatives obtained by treatment of the piperidylcarbinols with formaldehyde. It was thereby determined that the major isomer obtained in the hydrogenation possessed the erythro configuration, whereas the minor isomer was of the threo configuration. The six compounds were tested for antimalarial activity against *Plasmodium berghei* in mice. In each of the three series the threo isomer was significantly more active than the corresponding erythro isomer. All compounds were curative at a dosage of 160 mg/kg or less. Two of the threo isomers were curative at 20 mg/kg and one was active at 10 mg/kg.

In the preceeding papers in this series,[1-4] we reported the preparation and antimalarial activity against *Plasmodium berghei* in mice[5] of a number of α-mono- and dialkylaminomethyl-4-pyridinemethanols containing aryl,[1,2] styryl,[3] benzoyl,[3] and trifluoromethyl[4] substituents in the 2 and 6 positions of the pyridine ring. In an effort to improve further on the already significant degree of antimalarial activity demonstrated by this class of compounds, three pairs of racemic α-(2-piperidyl)-2,6-disubstituted 4-pyridinemethanols were prepared. The 2-piperidyl side

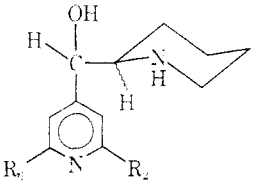
Table I. 4-Aryl 2'-Pyridyl Ketones



Compd	R_2	R_6	Mp, °C (solvent)	Yield,[a] %	Formula	Analyses
1	4-ClC_6H_4	4-ClC_6H_4	186–188 (*i*-PrOH)	81	$C_{23}H_{14}Cl_2N_2O$	C, H, N
2	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	143–145 (*i*-PrOH)	66	$C_{25}H_{14}F_6N_2O$	C, H, N, F
3	4-$CF_3C_6H_4$	CF_3	85–87 (*i*-PrOH–H_2O)	60	$C_{19}H_{10}F_6N_2O$	C, H, N, F

[a]From isonicotinic acid.

Table II. α-(2-Piperidyl)-2,6-disubstituted 4-Pyridinemethanols



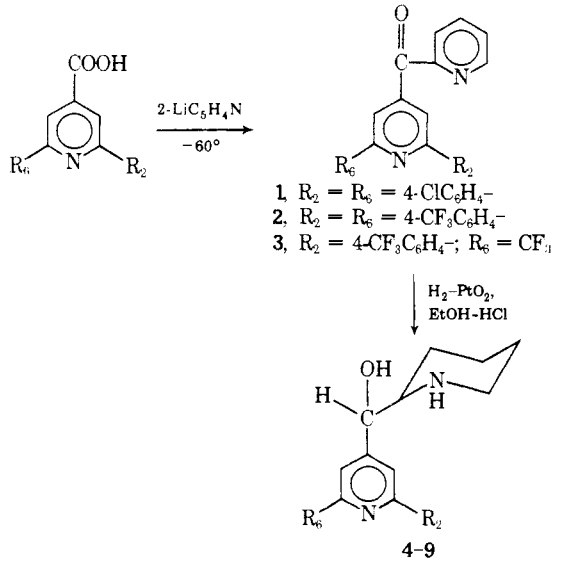
Compd	R_2	R_6	Configuration	Mp, °C (solvent)	Yield, %	Formula	Analyses[a]
4	4-ClC_6H_4	4-ClC_6H_4	Erythro	180–181[b] (*i*-PrOH–H_2O)	50[d]	$C_{23}H_{22}Cl_2N_2O$	
				242–244[c] (CH_3CN)		$C_{23}H_{23}Cl_3N_2O$	Cl
5	4-ClC_6H_4	4-ClC_6H_4	Threo	280–282[c]	55[e]	$C_{23}H_{23}Cl_3N_2O$	
6	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	Erythro	172–174[b] (dioxane–Et_2O–petr ether)	72[d]	$C_{25}H_{22}F_6N_2O$	F
				243–244[c] (*i*-PrOH)		$C_{25}H_{23}ClF_6N_2O$	Cl, F
7	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	Threo	175–178[b] (CH_3CN)	56[e]	$C_{25}H_{22}F_6N_2O$	
				257–258[c] (CH_3OH–*i*-PrOH)		$C_{25}H_{23}ClF_6N_2O$	Cl, F
8	4-$CF_3C_6H_4$	CF_3	Erythro	147–150[b] (Et_2O–petr ether)	40[d]	$C_{19}H_{18}F_6N_2O$	
				172–174[c] (CH_3CN)		$C_{19}H_{19}ClF_6N_2O$	Cl
9	4-$CF_3C_6H_4$	CF_3	Threo	101–103[b] (petr ether)		$C_{19}H_{18}F_6N_2O$	
				241–243[c] (CH_3CN)	81[e]	$C_{19}H_{19}ClF_6N_2O$	Cl, F

[a]In addition to C, H, and N. [b]Free base. [c]HCl salt. [d]From pyridyl ketone. [e]From erythro isomer.

chain has been shown to be effective in imparting activity against *P. berghei* in the 4-quinolyl[6] and 9-phenanthryl[7] series.

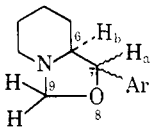
Chemistry. The three pairs of racemic α-(2-piperidyl)-2,6-disubstituted 4-pyridinemethanols were prepared by the procedure of Boykin, *et al.*[6] The two-step sequence is shown in Scheme I. In each case studied, catalytic hydrogenation of the pyridyl ketone afforded both possible racemates as evidenced by tlc analysis. However, one isomer was formed predominantly (80% or more) and this could be purified readily by crystallization. Small amounts of the other isomer could be obtained by extensive work-up of the mother liquors. It was found that the predominant isomer, arbitrarily designated "racemate A," could be inverted to "racemate B" *via* the procedure described by Stevens, *et al.*,[8] shown in Scheme II. The yields in this inversion ranged from 55 to 80%. The physical data for the pyridyl ketones and the piperidylcarbinols are listed in Tables I and II, respectively.

Scheme I



After isolation of the two racemates in each of the three series in pure form, it was next of interest to determine the absolute configuration of each. In the case of racemic phenyl-2-piperidylcarbinols, Crabb and Newton[9] reported that this could be accomplished *via* conversion of the epimeric piperidylcarbinols to the 7-aryl-8-oxa-1-azabicyclo-[4.3.0]nonane derivatives by treatment with formaldehyde. The differences in the chemical shift of the two geminal C_9 protons ($\Delta_{H(9),H(9')}$) and the geminal coupling constant for the same two protons ($J_{H(9),gem}$) could be employed to assign configurations to the amino alcohol precursors. This technique was recently employed also by Olsen[10] in the determination of the configurations of epimeric α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanols. Application of this approach to the present case led to the data shown in Table III. The results obtained by Crabb and Newton[9] and by Olsen[10] are also shown for comparative purposes. The excellent agreement between our results and those of the earlier works indicates that the predominantly formed epimer in the catalytic hydrogenation of each of the three precursor pyridyl ketones possesses the erythro configuration, and the minor isomer has the threo configuration.

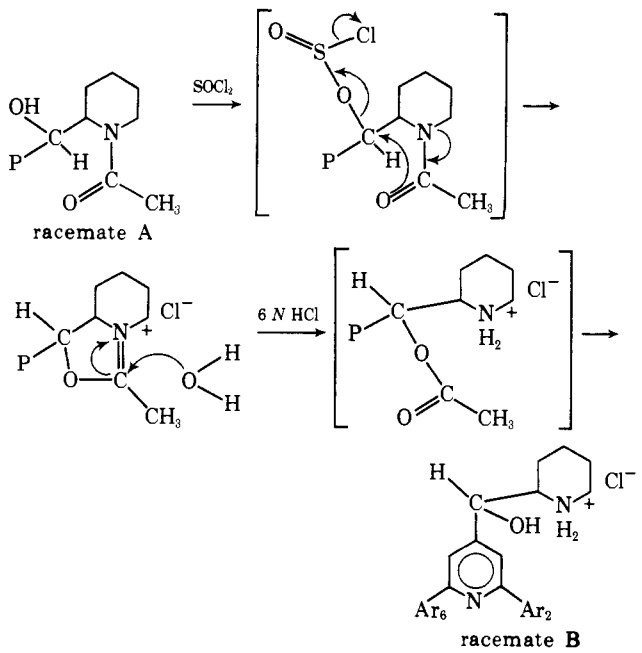
Table III. Nmr Data for 7-Aryl-8-oxa-1-azabicyclo[4.3.0]nonanes[a]



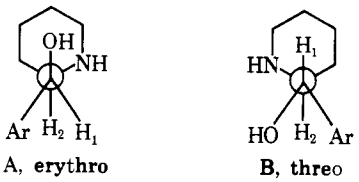
Compd	Ar	Mp, °C	Configuration of H_aH_b	Chemical shift C_9 protons[b]		$\Delta_{H(9)H(9')}$	$J_{H(9)\ gem}$
	Phenyl[f]	172–173[c]	Cis	3.78[e]	4.70[e]	0.92	−1.3
	3,6-Bis(trifluoromethyl)-9-phenanthryl[g]	167–168	Cis	4.17	5.09	0.92	−1.5
10	2,6-Bis(4-chlorophenyl)-4-pyridyl	187–189[d]	Cis	4.07	5.02	0.95	−1.7
11	2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl	167–168	Cis	4.03	5.01	0.98	−1.7
12	2-(4-Trifluoromethylphenyl)-6-trifluoromethyl-4-pyridyl	196–199[d]	Cis	4.00	4.95	0.95	−1.7
	Phenyl[f]	156–157[c]	Trans	4.21[e]	4.64[e]	0.43	−2.7
	3,6-Bis(trifluoromethyl)-9-phenanthryl[g]	181–182	Trans	4.52	4.95	0.43	−2.6
13	2,6-Bis(4-chlorophenyl)-4-pyridyl	145–150[d]	Trans	4.47	4.92	0.45	−3.2
14	2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl	137–139	Trans	4.47	4.90	0.43	−3.2
15	2-(4-Trifluoromethylphenyl)-6-trifluoromethyl-4-pyridyl	82–84	Trans	4.47	4.90	0.43	−3.2

[a]Spectra were obtained on a Varian Model T-60 spectrometer at room temperature in $CDCl_3$ solvent. [b]In δ values relative to TMS, run on free base. [c]Picrate. [d]HCl salt. [e]CCl_4 solvent. [f]Reference 9. [g]Reference 10.

Scheme II. Inversion of α-2′-Piperidyl-4-pyridinemethanol Racemates



The values for the vicinal coupling constants ($J_{H(1)H(2)}$) shown in Table IV are also consistent with the assigned configurations. If one assumes that these compounds exist predominantly in the hydrogen bonded conformations A and B, it would be expected that $J_{H(1)H(2)}$ in the threo isomers (H_1H_2 trans) would be larger than in the erythro isomers (H_1H_2 gauche).



Biological Activity. Antimalarial activity data against *P. berghei* in mice†,[5] are presented in Table V. The data indicate that in the three cases studied, the threo isomer is significantly more active than the corresponding erythro isomer. The same superiority of the threo isomer was observed also in the case of α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanols.[10]

The data of Table V show that the threo isomers are between one and two dose levels more active than the corresponding erythro isomers. In the present series, the erythro isomers are, in general, somewhat less active than most of the corresponding mono- and dialkylaminomethyl derivatives reported earlier.[1,2,4] The threo isomers, on the other hand, are significantly more active than any of the corresponding alkylaminomethyl analogs. Compound **9**, in fact, is the most active 4-pyridinemethanol synthesized to date with five cures at a dosage of 20 mg/kg and a ΔMST of 11.7 days at 10 mg/kg.

Experimental Section‡

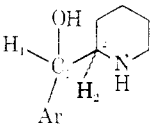
The following procedure is typical of that employed for the synthesis of the three pairs of racemic α-(2-piperidyl)-4-pyridinemethanols as well as the three pyridyl ketone precursors.

2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl 2′-Pyridyl Ketone (2). A solution of 2-bromopyridine (14.3 g, 0.08 mol) in ether (20 ml) was added to a solution of *n*-butyllithium in hexane (1.6 *M*, 56 ml, 0.1 mol) in anhydrous diethyl ether (120 ml) at −70°. The solution was stirred at −70° for 1 hr after which time 2,6-di-*p*-trifluoromethylphenylisonicotinic acid[2] (16.5 g, 0.04 mol) was added. The solution was stirred at −60 to −70° for 2 hr. The reaction mixture was then allowed to warm to *ca.* −10° and poured into ice–water (750 ml). The mixture was extracted with ether (2 × 400 ml). The organic layer was dried and concentrated to dryness under reduced pressure. The resulting crude solid was crystallized

†The antimalarial tests were performed by Dr. Leo Rane of the University of Miami (see ref 5). See footnote *a*, Table V. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Bing T. Poon of the Walter Reed Army Institute of Research.

‡Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were measured on a Varian T-60 model spectrometer using tetramethylsilane as internal standard. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Analyses indicated by element symbols agree with calculated values within ±0.4%.

Table IV. Vicinal Coupling Constants ($J_{H(1)H(2)}$) for Epimeric α-(2-Piperidyl)arylcarbinols[a]



Ar	Nmr chemical shift,[b] C_1H, δ	$J_{H(1)H(2)}$, Hz	Assignment: Erythro–threo system	Assignment: R and S system
3,6-Bis(trifluoromethyl)-9-phenanthryl[e]	c	4.66[d]	Erythro	1*R*2*S*, 1*S*2*R*
2,6-Bis(4-chlorophenyl)-4-pyridyl	5.13	5.0	Erythro	1*R*2*S*, 1*S*2*R*
2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl	4.40	5.0	Erythro	1*R*2*S*, 1*S*2*R*
2-(4-Trifluoromethylphenyl)-6-trifluoromethyl-4-pyridyl	5.10	5.0	Erythro	1*R*2*S*, 1*S*2*R*
3,6-Bis(trifluoromethyl)-9-phenanthryl[e]	c	7.31[d]	Threo	1*R*2*R*, 1*S*2*S*
2,6-Bis(4-chlorophenyl)-4-pyridyl	4.95	7.0	Threo	1*R*2*R*, 1*S*2*S*
2,6-Bis(4-trifluoromethylphenyl)-4-pyridyl	4.28	7.0	Threo	1*R*2*R*, 1*S*2*S*
2-(4-Trifluoromethylphenyl)-6-trifluoromethyl-4-pyridyl	4.95	6.5	Threo	1*R*2*R*, 1*S*2*S*

[a]Spectra were obtained on a Varian T-60 Model spectrometer at room temperature in pyridine-d_5 solvent. [b]See footnote *b*, Table I. [c]Not reported. [d]Measured in DMSO-d_6 solvent. [e]Reference 10.

Table V. Antimalarial Activity against *Plasmodium berghei*

Compd	ΔMST or C[a,b] 10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
4		1.2	11.9 (A)	17.1 (A)	3C
5	0.5	11.5 (A)	5C	5C	5C
6		1.1	10.3 (A)	5C	5C
7	0.3	3C	5C	5C	5C
8	0.3	10.9 (A)	5C	5C	5C
9	11.7 (A)	5C	5C	5C	5C

[a]The test method, described in ref 5, is a highly standardized procedure in which the *P. berghei* causes death of control mice at essentially 6 days. An increase in the mean survival time of five mice by more than 2.5 days beyond this time is statistically significant. Mice surviving more than 60 days are regarded as cured (C). A candidate drug is considered active (A) at a given dosage if one or more mice are alive on day 14. [b]All compounds listed were nontoxic at 640 mg/kg and curative (5C) at 320 mg/kg.

from isopropyl alcohol to yield **2** (12.4 g, 66%).

α-(2-Piperidyl)-2,6-bis(4-trifluoromethylphenyl)-4-pyridinemethanol. Erythro Isomer 6. A mixture of 2,6-bis(4-trifluoromethylphenyl)-4-pyridyl 2′-pyridyl ketone (9.44 g, 0.02 mol), platinum oxide (600 mg, prereduced), ethanol (300 ml), and concentrated hydrochloric acid (2.2 ml) was shaken in a Parr hydrogenation apparatus under 45 psi of hydrogen for 8 hr. The resulting combined mixture of three such reductions was filtered and the solvent was removed under reduced pressure. The residue was dissolved in warm methanol and the solution was poured over a column of Dowex 1-X2 (OH^- form). The eluent was concentrated to a small volume, cooled, and filtered to yield crude title compound. This material was recrystallized twice from a dioxane–ether–petroleum ether (bp 30–60°) mixture to yield 17.5 g of pure title compound, mp 172–174°. Concentration of the mother liquors gave a second crop, 3.2 g, mp 170–172°, for a total yield of 20.7 g (72%).

A sample of the free base (5.9 g, 8.1 mmol) was suspended in methanol (60 ml) and acidified to pH 2 with concentrated hydrochloric acid (1.5 ml). The solution was diluted with water to 130 ml, cooled, and filtered and the product was dried to yield 6.05 g (95%) of crude hydrochloride, mp 242–243°. The material was recrystallized twice from 2-propanol to yield 4.8 g of the pure hydrochloride salt, mp 243–244° dec.

α-2′-[(*N*-Acetyl)piperidyl]-2,6-bis(4-trifluoromethylphenyl)-4-pyridinemethanol (*N*-Acetyl Derivative of 6). A suspension of α-2′-piperidyl-2,6-bis(4-trifluoromethylphenyl)-4-pyridinemethanol (**6**) free base (19.22 g, 0.04 mol) in methanol (150 ml) was cooled in an ice bath and treated portionwise with acetic anhydride (three 10-ml portions at 30-min intervals). The solution was allowed to warm to room temperature, diluted with water (400 ml), and made basic with aqueous sodium hydroxide. The resulting mixture was extracted with chloroform (70 ml × 5). The chloroform extract was washed with water and dried. Removal of the solvent and crystallization of the residue from a mixture of chloroform and benzene gave the title compound, 15.8 g (76%), mp 171–173°. *Anal.* ($C_{27}H_{24}F_6N_2O_2$) C, H, N, F.

α-(2-Piperidyl)-2,6-bis(4-trifluoromethylphenyl)-4-pyridinemethanol. Threo Isomer 7. The *N*-acetyl derivative of **6** (15.7 g, 0.03 mol) was added portionwise over a 5-min period to cold (0°) thionyl chloride (130 ml). The solution was allowed to stand at room temperature overnight. The excess thionyl chloride was removed at reduced pressure. The residual solid was stirred with 6 *N* hydrochloric acid (300 ml) for 1 hr at room temperature and then heated on a steam bath for 3 hr. After charcoaling, the solution was made basic with 30% aqueous sodium hydroxide solution and the mixture was extracted with chloroform. The chloroform extract was washed with water and dried ($MgSO_4$) and the solvent was removed under reduced pressure. A gummy residue remained which solidified upon addition of an ether–petroleum ether mixture to yield 12 g of the crude title compound, mp 173–176°. Recrystallization from acetonitrile gave 9.1 g of product, mp 176–179°. Concentration of the mother liquors gave a second crop, 1.5 g, mp 175–178°, for a total of 10.6 g (74%).

The free base (19.5 g, 0.041 mol) was dissolved in hot methanol (300 ml). The solution was acidified with concentrated hydrochloric acid to pH 2 and diluted with water to 600 ml. A solid slowly formed. The mixture was cooled in an ice bath for 3 hr and filtered, and the solid was washed with water and dried to yield 20.8 g (99%) of product, mp 257–258°.

Synthesis of 1-Azabicyclo[4.3.0]nonane Derivatives of α-(2-piperidyl)-4-pyridinemethanols. The following is a typical procedure used for the conversion of the α-2-piperidylcarbinols to 7-aryl-8-oxa-1-azabicyclo[4.3.0]nonane derivatives.

A solution of *threo*-α-2′-piperidyl-2,6-bis(4-trifluoromethylphenyl)-4-pyridinemethanol (0.2 g) in MeOH (4 cc) containing 37% aqueous formaldehyde (0.26 cc) was heated at reflux 17 hr. The solution was cooled and filtered to afford the azabicyclononane derivative **14** (0.14 g, 68%). *Anal.* ($C_{26}H_{22}F_6N_2O$) C, H, N.

The following derivatives were prepared as described above. Epimer **4** was converted to the derivative **10** in 60% yield. The compound was purified as the HCl salt *via* recrystallization from CH_3CN. *Anal.* ($C_{24}H_{23}Cl_3N_2O$) C, H, N.

Epimer **6** afforded derivative **11** (65%). *Anal.* ($C_{26}H_{22}F_6N_2O$) C, H, N.

Compound **8** upon treatment as described above gave **12** (60%). *Anal.* ($C_{20}H_{19}ClF_6N_2O$) C, H, N.

Epimer **5** gave **13** (50%). *Anal.* ($C_{24}H_{23}Cl_3N_2O$) C, H, N.

Similarly, epimer **9** afforded the derivative **15**. *Anal.* ($C_{20}H_{18}F_6N_2O$) C, H, N.

Acknowledgment. This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DADA17-69-C-9065. This is Contribution No. 1211 from the Army Research Program on Malaria. The advice and timely suggestions of Drs. T. R.

Sweeney and B. T. Poon of the Walter Reed Army Institute of Research are gratefully acknowledged.

References

(1) P. Blumbergs, M. P. LaMontagne, A. Markovac, J. G. Moehring, A. B. Ash, and C. L. Stevens, *J. Med. Chem.*, **15**, 808 (1972).
(2) A. Markovac, M. P. LaMontagne, P. Blumbergs, A. B. Ash, and C. L. Stevens, *J. Med. Chem.*, **15**, 918 (1972).
(3) M. P. LaMontagne, *J. Med. Chem.*, **16**, 68 (1973).
(4) M. P. LaMontagne, A. Markovac, and M. S. Ao, *J. Med. Chem.*, **16**, 1040 (1973).
(5) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(6) D. W. Boykin, A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, 11, 273 (1968).
(7) (a) E. A. Nodiff, A. J. Saggiomo, M. Shinbo, E. H. Chen, H. O. Otomasu, Y. Kondo, T. Kikuchi, B. L. Verma, S. Matsuura, K. Tanabe, M. P. Tyagi, and S. Morosawa, *J. Med. Chem.*, **15**, 775 (1972); (b) E. A. Nodiff, K. Tanabe, C. Seyfreid, S. Matsumura, Y. Kondo, E. H. Chen, and M. P. Tyagi, *ibid.*, 14, 921 (1971).
(8) C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amine, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. D. Pillai, and J. W. Stoddard, *J. Org. Chem.*, **31**, 2593 (1966).
(9) T. A. Crabb and R. F. Newton, *J. Heterocycl. Chem.*, **3**, 418 (1966).
(10) R. E. Olsen, *J. Med. Chem.*, **15**, 207 (1972).

Substituent Effects upon the Base Hydrolysis of Penicillins and Cephalosporins. Competitive Intramolecular Nucleophilic Amino Attack in Cephalosporins

Joseph M. Indelicato,* Theresa Teipen Norvilas, Ralph R. Pfeiffer, William J. Wheeler, and William L. Wilham

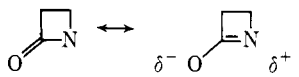
The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206. *Received October 23, 1973*

The chemical reactivity of a series of β-lactam antibiotics was found to be sensitive to steric strain and to inductive effects. Steric strain as reflected by the β-lactam ir carbonyl frequency correlates with the log of the rate constant for base hydrolysis. Insignificant changes in β-lactam reactivity resulted from C-6- and -7-acylamido side-chain modification in penicillins and cephalosporins. Cephalosporins that have α-amino-containing acylamido side chains may undergo intramolecular nucleophilic attack at the β-lactam, while ampicillin cannot because of steric hindrance. In contrast, substituent effects as a result of substitution at the C-3 methylene of cephalosporins were significant and correlate with σ_1 values and calculated electron densities at the β-lactam carbonyl.

Two classes of extremely valuable clinical antibiotics, the penicillins and cephalosporins, are β-lactam-containing compounds that interfere with the three-dimensional crosslinking of peptidoglycan strands by an enzyme, transpeptidase,[1] during the final stage of cell wall biosynthesis.[2] This enzyme cleaves the C-terminal D-alanine residue from a peptide chain which terminates with D-alanylalanine on one peptidoglycan strand and replaces it with a free amino group connected to a neighboring peptidoglycan strand. Strominger has proposed that the penicillins and cephalosporins resemble the D-alanylalanine peptide fragment and that transpeptidase mistakes the β-lactam-containing molecule as its substrate. When the β-lactam opens, the transpeptidase becomes irreversibly acylated and inactive.[3]

Because acylation of transpeptidase is necessary for antibacterial activity, the chemical reactivity of the β-lactam moiety of a penicillin or cephalosporin may reflect its antibiotic activity. A number of such correlations have been explored.

Woodward has suggested that isolated β-lactams, due to resonance stabilization, are considerably less reactive than the strained penicillin β-lactam.[4] Simple amides and isolated β-lactams **1** may exist in a planar resonance stabilized configuration **2**. However, in penicillins and cephalosporins the nitrogen bond to the carbonyl function cannot become planar because of ring strain. The infrared carbonyl frequencies of isolated β-lactams (1730 cm^{-1}) and penicillins (1775 cm^{-1}) reflect these differences in strain and resonance stabilization. Morin, *et al.*, have shown a qualitative correlation between the infrared β-lactam carbonyl frequency (a proposed measure of acylation ability) of a series of penicillins and cephalosporins and their antibacterial activity.[5] (A qualitative correlation is all that should be expected because antibacterial activity depends upon factors such as enzyme recognition, cell permeability, and β-lactamase resistance in addition to acylating ability.[6]) Hermann's CNDO/2 calculations of the inductive effect of 3-methylene substituents upon cephalosporin β-lactam reactivity also correlate with gram-negative antibacterial activity.[7] Sweet and Dahl, using X-ray structure analysis, have correlated the carbonyl and carbon–nitrogen bond lengths of penicillins and cephalosporins with their antibacterial activity.[8] These investigators have also suggested (from qualitative literature data) a correlation between the ease of base hydrolysis of the β-lactam moiety and antibacterial activity. The effect of 6-acylamido substitution in penicillins upon the reactivity of the β-lactam ring has been examined by Kinget and Schwartz.[9]



1 **2**

The effect of substituents on the reactivity of isolated β-lactams was first reported by Holley and Holley[10] and more recently by Washkuhn and Robinson.[11] The effect of ring size on ring-fused β-lactam reactivity has been studied by Earle,[12] *et al.*, and Moll.[13] To our knowledge a quantitative comparison of the relative reactivities of a series of penicillins and similarly substituted cephalosporins has not been previously reported.

Our purposes for this study were threefold: (1) to further examine Morin's prediction that the infrared carbonyl frequency of a series of β-lactam antibiotics correlates with the β-lactam reactivity; (2) to correlate linear free energy substituent constant values with the relative rate constants of base hydrolysis of 3-methylene-substituted cephalosporins; and (3) to examine the effect of various acylamido side chain moieties upon the observed hydrolysis rate constants of penicillins and cephalosporins.

Results and Discussion

β-Lactam Infrared Frequency, a Measure of Chemical Reactivity. Morin (using methyl esters) assumed that