[Bis(2,2-dimethyl-1-aziridinyl) and Bis(1-aziridinyl)] Phosphinates. (A) *O*-(*p*-Carbomethoxyphenyl)carbamato-*N*-*p*-phenyl Esters (4 and 5). A solution of 2,2-dimethylaziridine (1.423 g, 0.02 mol) and triethylamine (2.024 g, 0.02 mol) in dry ether (80 ml) was cooled to −10 to −15° (ice-salt bath), and 3 (4.042 g, 0.01 mol) in dry DME (20 ml) was added dropwise keeping the temperature below −8°. After continued stirring for 2 hr, the precipitated solids were collected and repeatedly extracted with DME. The combined extracts were evaporated and the residue was dried *in vacuo* and then recrystallized from a mixture of methylene chloride and ether (1:1) to yield 4 in analytical purity: yield 61%; mp 142–144°; nmr δ 1.43 (s, 12 H), 2.26 (d, 4 H, J = 14 Hz), 3.93 (s, 3 H), 7.08–8.17 (m, 8 H). *Anal.* ($C_{23}H_{28}N_3O_6P$) C, H, N, P.

Compound 5 was synthesized in the same manner, using unsubstituted aziridine instead of 2,2-dimethylaziridine: yield 72%; mp 140–142°; nmr δ 2.26 (d, 8 H, J = 14 Hz), 3.93 (s, 3 H), 7.07–8.17 (m, 8 H). *Anal.* ($C_{19}H_{20}N_3O_6P$) C, H, N, P.

(B) *N*-*p*-(Carbomethoxyphenyl)carbamato-*O*-*p*-phenyl Esters (15 and 16). These compounds were synthesized in an analogous manner as 4 and 5, respectively, using the phosphorodichloridate 14. However, the products 15 and 16 remained in solution after precipitation of the triethylamine hydrochloride and were obtained from the filtrates by evaporation of the solvent and recrystallization of the residues from methylene chloride–ether (1:1). 15 gave a yield of 57%; mp 101–104°; nmr δ 1.42 (s, 12 H), 2.25 (d, 4 H, J = 14 Hz), 3.86 (s, 3 H), 6.86–8.01 (m, 8 H). *Anal.* ($C_{23}H_{28}N_3O_6P$) C, H, N, P. 16 gave a yield of 38%; mp 153–154°; nmr δ 2.32 (d, 8 H, J = 15 Hz), 3.95 (s, 3 H), 6.95–8.08 (m, 8 H). *Anal.* ($C_{19}H_{20}N_3O_6P$) H, N, P; C: calcd, 54.68; found, 54.14.

(C) *p*-(Benzyloxy)phenyl Esters (19 and 20). These compounds were prepared by reacting 18 with 2,2-dimethylaziridine and aziridine, respectively, in the presence of an equivalent amount of triethylamine, under similar conditions as described in the synthesis of 4, except that ether was used as the only solvent. After separation of the precipitated triethylamine hydrochloride, the desired products, 19 and 20, respectively, were crystallized from the filtrates and then recrystallized from ether. 19 gave a yield of 58%; mp 83–85°; nmr δ 1.42 (s, 12 H), 2.24 (d, 4 H, J = 14 Hz), 5.04 (s, 2 H) 7.07 (q, 4 H), 7.39 (s, 5 H). *Anal.* ($C_{21}H_{28}N_2O_3P$) C, H, N. 20 gave a yield of 73%; mp 38–40°; nmr δ 2.30 (d, 8 H, J = 15 Hz), 5.10 (s, 2 H), 7.13 (q, 4 H, J = 9 Hz), 7.48 (s, 5 H). *Anal.* ($C_{17}H_{19}N_2O_3P$) C, H, N.

Attempted Syntheses of 7a and 7b (Scheme I). Method A. Reaction of the phosphorodichloridate 6 with aziridine (or 2,2-dimethylaziridine), at −15°, led to mixtures of partially polymerized degradation products, from which only tris(1-aziridinyl)phosphine oxide[15] (TEPA) could be isolated and identified.

Method B. A solution of ethyl bis(2,2-dimethyl-1-aziridinyl)-phosphinylcarbamate (9, AB-132)[7] in dry toluene was heated to boiling. Immediate formation of the isocyanate 10 was observed [ir 2225 cm^{-1} (C=N=O)]. Reaction of the latter with 2 resulted in opening of the aziridine rings (nmr) and polymerization.

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Local Anesthetic Azabicyclo-*N*-alkylanilides

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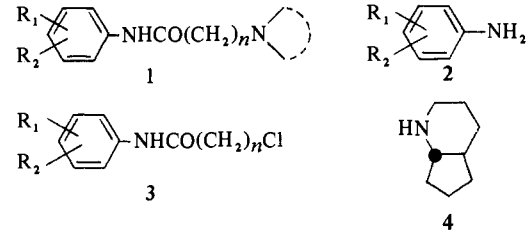
The synthesis of a series of azabicyclo-*N*-alkylanilides and the preliminary evaluation of their local anesthetic activities are described. The azabicyclic moieties are *cis*- and *trans*-octahydro-1*H*-pyrindine, *cis*- and *trans*-decahydroquinoline, *cis*- and *trans*-decahydro-1*H*-cyclohepta[*b*]pyridine, and *trans*-hexahydro-1*H*-cyclopenta[*b*]pyrrole. *trans*-6′-Chloro-2,3,4,4a,5,6,7,7a-octahydro-1*H*-1-pyrindine-1-propiono-*o*-toluidide (14a, rodocaine) was approximately four times more potent than lidocaine and had a considerably longer duration of action.

Since the introduction of lidocaine,[1] the literature has recorded many derivatives containing the aminoalkylanilide grouping.[2–4] Most local anesthetics[5–7] are characterized by a lipophilic portion and a hydrophilic moiety linked together by an intermediate chain.[1] Relatively little structural modification has been introduced into the amine portion or hydrophilic moiety.[5–7]

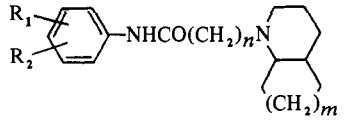
As part of an effort to develop new local anesthetic agents, with properties corresponding to chemical stability, high potency, low toxicity, rapid onset of action, and absence of local irritation, a series of azabicyclo-*N*-alkylanilides of general formula 1 was prepared. One of the objectives of this study was to incorporate the amine portion into a bicyclic ring system. Thus in 1, -N< corresponded to *cis*- or *trans*-octahydro-1*H*-pyrindine, *cis*- or *trans*-decahydroquinoline, *cis*- or *trans*-decahydro-1*H*-cyclohepta[*b*]pyridine, or *trans*-hexahydro-1*H*-cyclopenta[*b*]pyrrole, *n* was either methylene or ethylene, and R_1 and R_2 were methyl or chlorine.

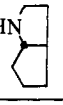
Chemistry. The compounds were synthesized by conventional methods. Reaction of appropriate anilines 2 with



either chloracetyl chloride or 3-chloropropionyl chloride afforded the corresponding ω-chloroalkylanilides (3). Displacement of the ω-chlorine of 3 with various bicyclic sec-

Table I



Compd	R_1	R_2	n	m	A/B	Methods[a]	Crystn solvent	Yield purified, %	Mp, °C	Formula[b]
5	2-Me	6-Me	1	1	Cis	A	*i*-Pr_2O	42	137-138	$C_{18}H_{26}N_2O$
6	2-Me	6-Me	1	1	Trans	A	*i*-Pr_2O	54	132-133	$C_{18}H_{26}N_2O$
7	2-Me	6-Cl	1	1	Cis	A	*i*-Pr_2O	68	117-118	$C_{17}H_{23}ClN_2O$
8	2-Me	6-Cl	1	1	Trans	A	*i*-Pr_2O-*i*-PrOH	50	187-188	$C_{17}H_{23}ClN_2O \cdot HCl$
9	2-Cl	6-Cl	1	1	Cis	A	*i*-PrOH	55	260-261	$C_{16}H_{20}Cl_2N_2O \cdot HCl$
10	2-Cl	6-Cl	1	1	Trans	A	*i*-Pr_2O	50	138	$C_{16}H_{20}Cl_2N_2O$
11	2-Me	6-Me	2	1	Cis	A	*i*-Pr_2O-*i*-PrOH	72	202-203	$C_{19}H_{28}N_2O \cdot HCl$
12	2-Me	6-Me	2	1	Trans	A	*i*-PrOH-Me_2CO	53	205-206	$C_{19}H_{28}N_2O \cdot HCl \cdot H_2O$
13	2-Me	6-Cl	2	1	Cis	A	*i*-Pr_2O-Me_2CO	42	190-191	$C_{18}H_{25}ClN_2O \cdot HCl$
14a	2-Me	6-Cl	2	1	Trans	B	*i*-Pr_2O	79	109-110	$C_{18}H_{25}ClN_2O$
14b	2-Me	6-Cl	2	1	(+)-Trans	B	*i*-Pr_2O	75	121-122	$C_{18}H_{25}ClN_2O$
14c	2-Me	6-Cl	2	1	(−)-Trans	B	*i*-Pr_2O	82	120-121	$C_{18}H_{25}ClN_2O$
14d	2-Me	6-Cl	2	1	Trans	B	*i*-Pr_2O-MeOH	83	207-208	$C_{18}H_{25}ClN_2O \cdot HCl$
15	2-Cl	6-Cl	2	1	Cis	A	*i*-Pr_2O-*i*-PrOH	49	203-204	$C_{17}H_{22}Cl_2N_2O \cdot HCl$
16	2-Cl	6-Cl	2	1	Trans	B	*i*-Pr_2O	65	117-118	$C_{17}H_{22}Cl_2N_2O$
17	2-Me	6-Me	1	2	Cis	B	*i*-Pr_2O	33	142-143	$C_{19}H_{28}N_2O$
18	2-Me	6-Me	1	2	Trans	A	*i*-Pr_2O	29	125-126	$C_{19}H_{28}N_2O$
19	2-Me	6-Cl	1	2	Trans	A	*i*-PrOH	45	210-211	$C_{18}H_{25}ClN_2O \cdot HCl$ $0.5H_2O$[c]
20	2-Cl	6-Cl	1	2	Trans	A	*i*-Pr_2O-Me_2CO	42	160-161	$C_{17}H_{22}Cl_2N_2O$
21	2-Me	6-Me	2	2	Cis	B	*i*-PrOH	62	227-228	$C_{20}H_{30}N_2O \cdot HCl$
22	2-Me	6-Cl	2	2	Cis	B	Me_2CO	14	219-220	$C_{19}H_{27}ClN_2O \cdot HCl$
23	2-Me	6-Cl	2	2	Trans	B	*i*-PrOH	33	190-191	$C_{19}H_{27}ClN_2O \cdot HCl$
24	2-Cl	6-Cl	2	2	Trans	A	*i*-Pr_2O-EtOH	52	201-202	$C_{18}H_{24}Cl_2N_2O \cdot HCl \cdot H_2O$
25	2-Me	6-Me	1	3	Cis	B	Me_2CO	41	191-192	$C_{20}H_{30}N_2O \cdot (COOH)_2$[d]
26	2-Me	6-Me	1	3	Trans	B	*n*-Hexane	62	113-114	$C_{20}H_{30}N_2O$
27	2-Me	6-Cl	1	3	Cis	B	*n*-Hexane	77	100-101	$C_{19}H_{27}ClN_2O$
28	2-Me	6-Cl	1	3	Trans	B	*n*-Hexane	31	81-82	$C_{19}H_{27}ClN_2O$
29	2-Cl	6-Cl	1	3	Cis	B	*n*-Hexane	26	137-138	$C_{18}H_{24}Cl_2N_2O$
30	2-Cl	6-Cl	1	3	Trans	B	*n*-Hexane	45	113-114	$C_{18}H_{24}Cl_2N_2O$
31	2-Me	6-Me	2	3	Cis	B	PhH	30	108-109	$C_{21}H_{32}N_2O$
32	2-Me	6-Me	2	3	Trans	B	Me_2CO-EtOH	57	154-155	$C_{21}H_{32}N_2O \cdot (COOH)_2$
33	2-Me	6-Cl	2	3	Cis	B	Me_2CO	83	161-162	$C_{20}H_{29}ClN_2O \cdot (COOH)_2$
34	2-Me	6-Cl	2	3	Trans	B	Me_2CO	62	151-152	$C_{20}H_{29}ClN_2O \cdot (COOH)_2$
35	2-Cl	6-Cl	2	3	Cis	B	Me_2CO-*n*-hexane	47	128-129	$C_{19}H_{26}Cl_2N_2O$
36	2-Cl	6-Cl	2	3	Trans	B	Me_2CO	54	167-168	$C_{19}H_{26}Cl_2N_2O \cdot (COOH)_2$
37	2-Cl	5-Cl	2	1	Trans	B	Me_2CO	69	156-157	$C_{17}H_{22}Cl_2N_2O \cdot (COOH)_2$
38	2-Me	3-Cl	2	1	Trans	A	*i*-Pr_2O	50	91-92	$C_{18}H_{25}ClN_2O$
39	2-Me	4-Cl	2	1	Trans	A	*i*-Pr_2O-Me_2CO	75	156-158	$C_{18}H_{25}ClN_2O \cdot HCl \cdot H_2O$[e]
40	2-Me	5-Me	2	1	Trans	B	Me CO	76	166-167	$C_{19}H_{28}N_2O \cdot (COOH)_2$
41	2-Me	3-Me	2	1	Trans	B	*i*-Pr_2O-EtOH	47	77-78	$C_{19}H_{28}N_2O \cdot HCl$
42	2-Me	4-Me	2	1	Trans	B	Me_2CO	63	150-151	$C_{19}H_{28}N_2O \cdot (COOH)_2$
43	2-Me	6-Me	$C(CH_3)H$	1	Trans	B	Me_2CO	59	298-299	$C_{19}H_{28}N_2O \cdot HCl$
44	2-Me	5-Me	2	2	Trans	B	Me_2CO	55	119-120	$C_{20}H_{30}N_2O \cdot (COOH)_2$
45	2-Me	6-Cl	2	1	Trans		B	Me_2CO	92	155-156	$C_{17}H_{23}ClN_2O \cdot (COOH)_2$

[a] Methods refer to the Experimental Section. [b] *Anal.* for C, H, and N. [c] C: calcd, 59.02; found, 58.27. [d] C: calcd, 65.32; found, 64.70. [e] C: calcd, 57.60; found, 56.88.

ondary amines gave the desired azabicyclo-*N*-alkylanilides (Table I). The azabicyclic compounds were prepared by known methods.[8-13] Pure cis and trans diastereoisomers were obtained either by fractional crystallization or by fractional freezing at −20°. *trans*-6′-Chloro-2,3,4,4a,5,6,7,7a-octahydro-1*H*-pyrindine-1-propiono-*o*-toluidide (**14a**) was resolved in its (+) and (−) enantiomers **14b** and **14c**. Fractional crystallization of the *d*-camphorsulfonic acid salt of **14a** afforded **14c**. **14b** was crystallized from the mother liquor. Alternatively, **14b** and **14c** were also prepared by resolution of *trans*-2,3,4,4a,5,6,7,7a-octahydro-1*H*-1-pyrindine (**4**) with *d*-camphorsulfonic acid as resolving agent, followed by reaction of the respective enantiomers with 3,6′-dichloropropiono-*o*-toluidide.

Pharmacology. The compounds tested showed a local anesthetic profile. For screening of conduction anesthesia, male Wistar rats of 200 ± 5 g body weight were used. Drug-induced nerve block was assessed by measuring the rapidity of response to a noxious stimulus (H_2O at 55°) applied to the hind 5 cm of the tail.[14] Each rat was given two perineural injections of a 0.1-ml solution each in the base of the tail.[15] The solution was either saline (controls) or saline containing the compound to be tested. The pH of the solution was kept between 6.3 and 7.3. Compounds that could not be dissolved under these circumstances were not tested. Reaction times of tail withdrawal were measured at time intervals between 0.5 and 120 min after injection. Reaction times of control animals never exceeded 6 sec. A score one was given for a direct tail withdrawal between 6 and 10 sec, a score two for a slow tail withdrawal between 6 and 10 sec,

Table II. Conduction Anesthesia

Compd	Dose[a]	n^b	pr^c	Duration, min	n with score 4	3	2	1	Seizures[d]	Mortality[d]
11	2.5	6	4	35	1	2	1		6	0
12	2.5	5	5	40	2	1	2		5	0
	0.63	5	0							
13	2.5	6	5	60	2	2	1		6	0
14a	5.0	15	15	100	9	3	3		5	5
	2.5	29	29	75	11	14	3	1	19	0
	1.25	20	20	45	4	12	3	1	2	0
	0.63	23	13	20		3	6	4	0	0
	0.16	20	5	<20			3	2	0	0
14b	5.0	5	5	100	5				5	5
	2.5	10	10	75	4	5	1		10	0
	1.25	4	4	40	1	1	2		2	0
14c	5.0	5	5	100	3	1	1		5	5
	2.5	12	12	70	9	2	1		12	0
	1.25	5	5	50		3	2		5	0
15	2.5	3	2	20		1	1		1	0
21	2.5	3	1	20			1		0	0
22	2.5	6	4	120	2	2			6	0
23	2.5	6	5	80	4	1			6	1
24	2.5	6	6	90	3	2	1		6	0
31	2.5	6	5	100	2	2	1		6	1
32	2.5	3	3	100		2	1		1	0
33	2.5	3	3	55		1	1	1	1	0
34	2.5	3	1	20			1		0	0
38	2.5	3	3	35		2	1		0	0
39	2.5	3	1	55		1			0	0
40	2.5	3	1	30			1		0	0
41	2.5	3	2	30		1		1	0	0
44	2.5	6	5	50	1	2	2		0	0
45	2.5	5	5	40	2		3		0	0
	1.25	5	3	30		1	1	1	0	0
	0.63	5	1					1		
Lidocaine	20.0	15	15	80	12	2	1		15	15
	10.0	10	10	45	6	1	3		10	0
	5.0	10	8	35	3	2	2	1	1	0
	2.5	10	5	25		1	3	1	0	0
	1.25	10	1	<20			1		0	0
	0.63	10	1	<20			1		0	0

[a] 2 × 0.1 ml of the test solution, dose in mg/ml. [b] Number of test animals. [c] Number of animals with positive response. [d] 1 × 0.4 ml of the test solution.

a score three (subsurgical analgesia) for a slow reaction time exceeding 10 sec, and a score four (surgical analgesia) for no reaction.

Side effects and toxicity were measured on the same rats 8 hr after the initial injections. A single iv injection of 0.4 ml of the test solution was given into the tail and seizures and mortality were recorded during the next 24 hr. The irritancy was assessed by measuring the swelling of the hindpaw after local injection.[16]

Results and Discussion

The results are summarized in Table II. All compounds tested had a rapid onset of action (<1 min), showed local anesthetic activity, and gave no signs of irritation at the site of injection. The structure–activity relationship was not clear since the compounds with a methylene group as intermediate chain (n = 1) were invariably insoluble under the test circumstances. However, the following observations could be made. 2,6-Substitution in the phenyl group was optimal. In the octahydro-1*H*-pyrindine and decahydroquinoline series were the trans compounds better than the corresponding cis compounds; replacement of a methyl group by a chlorine atom improved the potency, while replacement of both methyl groups by chlorine atoms decreased the activity, presumably owing to a reduced solubility. In the decahydro-1*H*-cyclohepta[*b*]pyridine series the situation was reversed; cis compounds were better than the corresponding trans compounds and replacement of a methyl by chlorine decreases activity.

trans-6′-Chloro-2,3,4,4a,5,6,7,7a-octahydro-1*H*-1-pyrindine-1-propiono-*o*-toluidide (**14a**) was found to be approximately four times more potent than lidocaine. The (+) and (−) enantiomers **14b** and **14c** showed no appreciable differences in potency or duration of action, in contrast to the recent observation that the *S* configurations of both mepivacaine and bupivacaine were significantly longer acting than their respective enantiomers.[17] Owing to these screening results, **14a** has been selected for further investigation.

Experimental Section

Melting points were taken on a Tottoli melting point apparatus and are corrected. All compounds were routinely checked for their structure by uv and ir spectrometry (uv on a Beckman DI-2A and ir on a Perkin-Elmer 421). Optical rotations were taken on a Perkin-Elmer 141 polarimeter. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3,2′,5′-Trichloropropionanilide (3a). To a solution of 2,5-dichloroaniline (60.5 g, 0.5 mol) in AcOH (400 ml) was added dropwise 3-chloropropionyl chloride (69.8 g, 0.55 mol) while the temperature was kept below 15°. The resulting mixture was stirred at room temperature for an additional 2 hr. An aqueous solution of NaOAc (200 g in 500 ml of H_2O) was added and the precipitate collected by filtration. Crystallization from CH_2Cl_2–*n*-hexane afforded pure **3a** (82 g, 65%), mp 134–135°. *Anal.* ($C_9H_8Cl_3NO$) C, H, N.

Method A. *cis*-2,3,4,4a,5,6,7,7a-Octahydro-1*H*-1-pyrindine-1-propiono-2′,6′-xylidide Hydrochloride (11). A suspension of 3-

chloropropiono-2',6'-xylidide (7.0 g, 0.033 mol), *cis*-octahydro-1*H*-pyrindine HCl (3.75 g, 0.03 mol), Na_2CO_3 (7.5 g, 0.06 mol), and KI (0.1 g) in 4-methyl-2-pentanone (250 ml) was stirred and refluxed for 72 hr. After cooling, H_2O was added. The organic layer was separated and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The oily residue was converted into its HCl salt in *i*-Pr_2O–*i*-PrOH HCl. Crystallization from *i*-Pr_2O–*i*-PrOH gave pure **11** (7.27 g, 72%), mp 202–203°. *Anal.* ($C_{19}H_{28}N_2O \cdot HCl$) C, H, N.

Method B. *cis*-3,4,4a,5,6,7,8,8a-Octahydro-1(2*H*)-quinolinepropiono-2',6'-xylidide Hydrochloride (21). A suspension of 3-chloropropiono-2',6'-xylidide (7.0 g, 0.033 mol), *cis*-decahydroquinoline HCl (5.27 g, 0.03 mol), and $NaHCO_3$ (8.4 g, 0.1 mol) in EtOH (200 ml) was stirred and refluxed overnight. After cooling the mixture was concentrated *in vacuo* and 2 *N* aqueous HCl was added. The mixture was extracted with *i*-Pr_2O; the aqueous layer was alkalized with 50% NaOH and extracted with *i*-Pr_2O. The organic layer was separated and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Conversion of the residue to its HCl salt and crystallization from *i*-PrOH afforded pure **21** (6.5 g, 62%), mp 227–228°. *Anal.* ($C_{20}H_{30}N_2O \cdot HCl$) C, H, N.

Resolution of *trans*-2,3,4,4a,5,6,7,7a-Octahydro-1*H*-pyrindine (4). A mixture of **4** (78 g, 0.624 mol) and (+)-camphor-10-sulfonic acid monohydrate (144.7 g, 0.624 mol) was boiled in Me_2CO (1250 ml) and allowed to cool. The crystalline precipitate was collected by filtration, which afforded crude (+)-base *d*-camphorsulfonate (94 g). Several recrystallizations from MeCN gave 36 g of pure (+)-*trans*-2,3,4,4a,5,6,7,7a-octahydro-1*H*-pyrindine *d*-camphorsulfonate (**4a**): mp 155–156°; $[\alpha]^{24}D$ +27.7° (MeOH). *Anal.* ($C_8H_{15}N \cdot C_{10}H_{16}O_4S$) C, H, N.

The resolution liquor was allowed to stand at room temperature for another 3 days. The precipitate was removed by filtration and filtrate was concentrated *in vacuo*. The residual crude (−)-base *d*-camphorsulfonate was resistant to several attempts of crystallization and was consequently converted to base in the usual way. Conversion of the latter base to **14** according to method B gave 14b.

Conversion of the base corresponding to **4a**, to 14 according to method B afforded 14c.

Resolution of *trans*-6'-Chloro-2,3,4,4a,5,6,7,7a-octahydro-1*H*-1-pyrindine-1-propiono-*o*-toluidide (14a). A mixture of **14a** (9.6 g, 0.03 mol) and (+)-camphorsulfonic acid monohydrate (6.96 g, 0.03 mol) was boiled in EtCOMe (40 ml). The solvent was removed *in vacuo* and the residue dissolved and boiled in *i*-Pr_2O until crystallization started. The crystalline precipitate was collected by filtration yielding 9 g of crude **14b** as *d*-camphorsulfonate: mp 137–139°; $[\alpha]^{24}D$ +19.5° (MeOH). Several crystallizations from EtCOMe (until constant rotation), followed by conversion to base in the usual way, and recrystallization from *i*-Pr_2O afforded 0.5 g of **14b**: mp 121–122°; $[\alpha]^{24}D$ +40° (MeOH). *Anal.* ($C_{18}H_{25}ClN_2O$) C, H, N.

The resolution liquor was evaporated *in vacuo*. The residual *d*-camphorsulfonate of 14c was triturated with EtOAc (10 ml), the precipitate removed by filtration, and the filtrate concentrated to dryness yielding 2 g of **14c** as *d*-camphorsulfonate salt: $[\alpha]^{24}D$ −8° (MeOH). Conversion to base in the usual way and crystallization from *i*-Pr_2O afforded a pure 0.1 g of **14c**: mp 120–121°; $[\alpha]^{24}D$ −41.5° (MeOH). *Anal.* ($C_{18}H_{25}ClN_2O$) C, H, N.

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Chemical Transformations of Antibiotic X-537A and Their Effect on Antibacterial Activity†

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A number of derivatives of the polyether antibiotic X-537A have been tested *in vitro vs. Bacillus* E and *Bacillus* TA and the results clearly indicate that all the oxygen functions involved in ligand formation with cations and intramolecular hydrogen bonding (as revealed by X-ray analysis) contribute to the biological activity of the antibiotic. In addition, a number of derivatives at the C-5 position of the aromatic chromophore exhibited a qualitative correlation between their partition coefficients (octanol–water) and *in vitro* activity.

The isolation of antibiotic X-537A (**1**) was first reported[1] in 1951. The structure,[2,3] biosynthesis,[4,5] and nitration[6] of the antibiotic have been discussed in earlier communications. The studies reported here involve a number of chemical modifications of the antibiotic and the resulting effects that were observed in the *in vitro* antibacterial activity against *Bacillus* E and *Bacillus* TA.

The X-ray crystallographic analysis of the barium salt of the antibiotic[3,7] revealed an unsymmetrical complex (Figure 1) in which the cation was bound by nine ligands, six of which involved oxygens from one antibiotic molecule, two were from a second antibiotic molecule, and the ninth ligand

†Microanalytical and spectral data will appear immediately following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-73-397.