Inhibition of Synaptosomal Accumulation of *l*-Norepinephrine II: *N*-Aryloxyalkylphentermines, Quaternary *d*-Amphetamines, and 3-Aryloxypropylamines

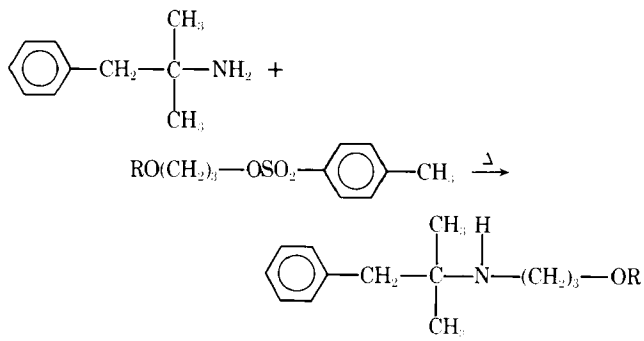
JAMES C. SCHAEFFER, ARTHUR K. CHO ˣ, and JOSEPH F. FISCHER

Abstract □ The inhibitory potencies of a series of *N*-substituted phentermines on the synaptosomal uptake of *l*-norepinephrine were found to be similar to those of the corresponding amphetamines. Quaternization of *N,N*-dimethyl-*d*-amphetamine diminished, but did not abolish, its inhibitory potency, indicating that a permanently charged cation is also effective. Since the addition of an aromatic moiety at the end of a four-atom chain originating at the nitrogen of amphetamine or phentermine significantly increased inhibitor strength, several 3-aryloxypropylamines and 4-phenylbutylamine were tested, but they were much weaker inhibitors than *dl*-amphetamine. Thus, the observed increase in inhibitor potency apparently was not simply the result of a specific interaction of the "nonmimic" portion of the *N*-substituted amphetamines or phentermines.

Keyphrases □ *l*-Norepinephrine—inhibition of synaptosomal accumulation by a series of *N*-substituted phentermines, corresponding amphetamines, and 3-substituted propylamines, compared □ Phentermines, *N*-substituted—inhibition of synaptosomal accumulation of *l*-norepinephrine □ Amphetamines, *N*-substituted—inhibition of synaptosomal accumulation of *l*-norepinephrine □ Propylamines, 3-substituted—inhibition of synaptosomal accumulation of *l*-norepinephrine □ Structure–activity relationships—inhibition of synaptosomal accumulation of *l*-norepinephrine by *N*-substituted phentermines, amphetamines, and 3-substituted propylamines

In a previous report from this laboratory, the relative inhibitory effects of a series of *N*-substituted amphetamines on the accumulation of ^{3}H-*l*-norepinephrine by a nonstriatal synaptosome preparation were described (1). The purpose of the study was to develop a specific inhibitor of the *l*-norepinephrine uptake mechanism by employing the "nonclassical inhibitor" principle (2, 3). This principle utilizes the concept that inhibitor specificity can result not only from the site of the substrate–receptor interaction but also through interactions with other regions remote from this center; these other regions depend on more distant physical and/or topographical features of both the oversized inhibitor and the macromolecules to which it binds.

In the previous study (1), *N*-substitution of a butyl group was found to reduce markedly inhibitory efficacy. However, through the introduction of a terminal, hydrophobic, aromatic moiety, a substantial portion of the lost inhibitor potency was regained. Furthermore, the addition of a second α-methyl group to *dl*-amphetamine, as in phentermine, did not alter inhibitor strength significantly (1).



Scheme I—Method A

The present report describes additional studies on this general problem; three factors in the structural requirements for inhibition were examined. Initially, the effect of an additional α-methyl group on selectivity was explored through a series of *N*-substituted phentermine derivatives. The importance of the structural features surrounding the positively charged nitrogen then was investigated. Although the absolute requirement of a cationic species had been demonstrated (1), no evidence was presented concerning ligand toleration about a quaternized nitrogen. Finally, the relative inhibitory potencies of several primary amines representing the "nonmimic" portions of the corresponding nonclassical inhibitors were compared to see if the inhibitory enhancement observed was independent of the amphetamine moiety.

EXPERIMENTAL

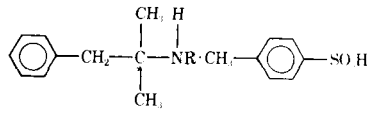
Chemicals—Phentermine[1], *p*-hydroxyphentermine[1], tritiated *l*-norepinephrine[2] (4–10 Ci/mmole), and choline chloride[3] were obtained commercially. Trimethylethylammonium iodide and trimethylheptylammonium iodide were synthesized[4]. All other compounds used were prepared by methods described here.

Method A (Scheme I) was employed to synthesize III–VI (Table I). Compound VII was prepared from 4-phenoxybutyl bromide and phentermine, as indicated by Method B (Scheme II). These syntheses were carried out in the identical manner as those previously reported for the corresponding amphetamines (1). The Eschweiler–Clarke methylation of *S(d)*-amphetamine afforded *N,N*-dimethyl-*d*-amphetamine (XIX) (4). The quaternization of this compound with the appropriate alkyl halide provided VIII–X (Table II) (Method C, Scheme III). Azide replacement of toluenesulfonate followed by lithium aluminum hydride reduction (Method D, Scheme IV) gave the 3-aryloxypropylamines listed in Table III. Compound XVII was prepared by reacting equimolar amounts of toluenesulfonic acid hydrate and 4-phenylbutylamine[3] in acetone.

Synthetic Procedures[5]—*General Procedure (Method C)*—Fifty millimoles of *d*-amphetamine (6.75 g) was slowly added with cooling to 12.8 g of 88% formic acid. To this mixture was added 11.25 ml of formaldehyde (150 mmoles). After the vigorous evolution of gas had ceased, the mixture was heated at 90–100° for 8 hr.

[1] Pennwalt Corp., Rochester, N.Y.
[2] New England Nuclear Corp., Boston, Mass.
[3] Aldrich Chemical Co., Milwaukee, Wis.
[4] By Dr. D. J. Jenden, Department of Pharmacology, UCLA Center for the Health Sciences.
[5] Melting points were determined on a Mel-Temp apparatus and are not corrected. Either mulls or liquid films were used to obtain IR spectra on an Infracord instrument (Perkin-Elmer). Elemental analyses were performed by H. King, Department of Chemistry, UCLA Center for the Health Sciences.

Table I—Analytical Data for *N*-Alkyl- and 3-Aryloxypropylphentermine *p*-Toluenesulfonates[a]



Compound	R	Method	Recrystallization Solvent	Yield[b], %	Melting Point	Analysis, %	Calc.	Found
III	$-(CH_2)_3CH_3$	A	Acetone	46	140–142°	C H	66.80 8.28	66.59 8.11
IV	$-(CH_2)_3O-C_6H_5$	A	Ethanol	55	209–212°	C H	68.53 7.30	68.50 7.27
V	$-(CH_2)_3O-C_{10}H_7$	A	Acetone	40	184–186°	C H	71.25 6.98	71.20 6.86
VI	$-(CH_2)_3O-C_{10}H_7$	A	Acetone–methanol (10:1)	35	196–199°	C H	71.25 6.98	71.23 6.86
VII	$-(CH_2)_4O-C_6H_5$	B	Acetone–ethanol (2:1)	34	176–178°	C H	69.05 7.51	68.96 7.52

[a] All compounds were uniform by TLC (free base, methanol) and exhibited spectra compatible with their proposed structures. [b] Minimum recrystallized yield from last step in synthetic sequence.

The reaction mixture then was allowed to cool to room temperature, and 25 ml of 4 *M* HCl was added.

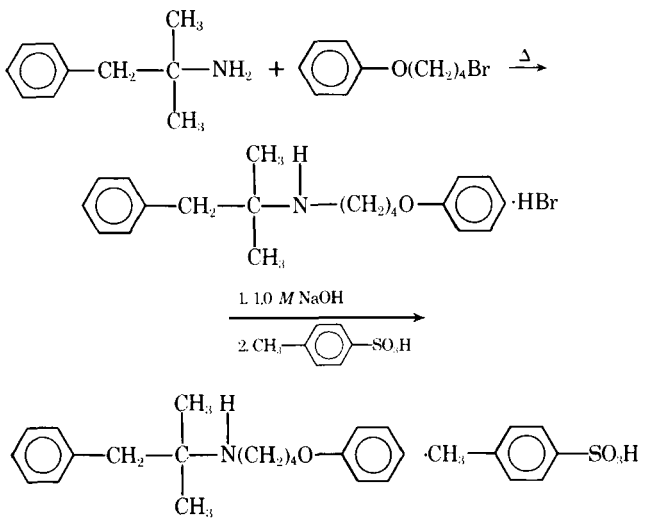
The resulting basic mixture was extracted twice with 100-ml portions of benzene. The benzene extracts were combined, dried with magnesium sulfate, and spin evaporated to an oil, which was vacuum distilled. The fraction distilling between 111 and 113°/30 mm was collected (3.4 g). This material was dissolved in 100 ml of ether, and dry hydrogen chloride was bubbled through the solution. The precipitate that formed was filtered, recrystallized from acetone, and dried under high vacuum over phosphorus pentoxide at 100°. Two grams of *N,N*-dimethyl-*d*-amphetamine hydrochloride (20%), which melted[6] at 183–186°, was obtained. This material had a specific rotation[6] of +15.1°, exhibited no N–H bands in the IR spectrum, and gave the following analysis. Calc. for C, 66.14; H, 9.08. Found: C, 66.18; H, 8.99.

A mixture of 1.63 g of *N,N*-dimethyl-*d*-amphetamine (free base, 10 mmoles), 10 mmoles of the appropriate alkyl halide, and 25 ml of ether was allowed to stand for 7–10 days at 0–5°. The resulting precipitate was filtered, recrystallized from the appropriate solvent, and dried under high vacuum over phosphorus pentoxide at 60°. The physical properties of these compounds and the solvents of recrystallization are presented in Table II.

General Procedure (Method D)—A mixture of 2.5 mmoles of the appropriate 3-aryloxypropyl *p*-toluenesulfonate (1), 10 ml of dimethylformamide, 1 ml of water, and 195 mg of sodium azide (3 mmoles) was heated at 65–70° for 19 hr. After 100 ml of 1 *N* NaOH had been added to the mixture, it was extracted with two 25-ml portions of ether. The extract was backwashed with water, dried with magnesium sulfate, and spin evaporated to an oil; this oil exhibited a strong IR band at 2100 cm^{-1}, characteristic of azides.

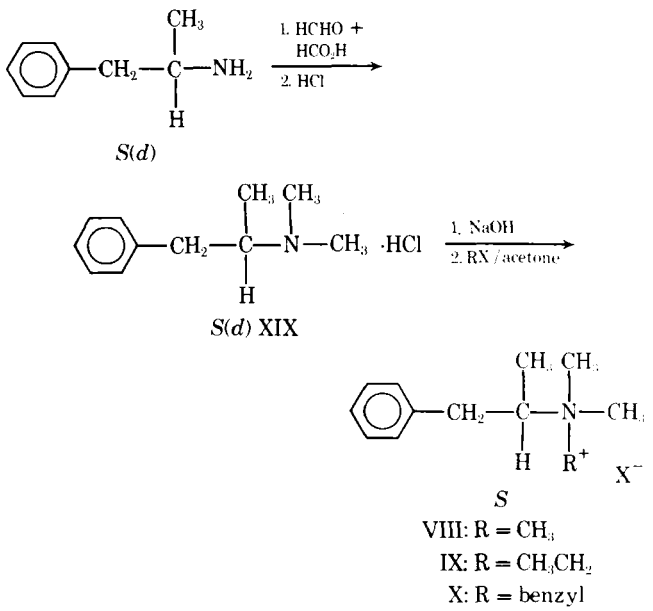
To this material were added 25 ml of anhydrous ether and 190 mg of lithium aluminum hydride (5.0 mmoles). After this mixture was refluxed for 5 hr, 100 ml of 1 *N* NaOH was slowly added. The resulting mixture was extracted with two 50-ml portions of ether, which were combined and dried with magnesium sulfate, and the solvent was removed under vacuum. The residue was converted to the appropriate organic acid salt, recrystallized, and dried. The physical properties and solvents for recrystallization are given in Table III.

Filtration Assay—Male Sprague–Dawley rats, 180–200 g, were



VII

Scheme II—Method B



S(*d*) XIX

S

VIII: R = CH_3

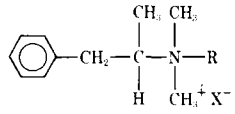
IX: R = CH_3CH_2

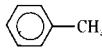
X: R = benzyl

Scheme III—Method C

[6] Reference 4 reported mp 182–183° and [α] +13.1°.

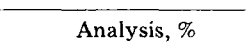
Table II—Analytical Data for α-Methylphenethyldimethylammonium Halides

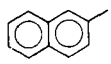


Compound[a]	R	X^-	Recrystallization Solvent	Yield[b], %	Melting Point	Analysis, %	Calc.	Found
VIII	CH_3—	I	Acetone	66	200–202°[c]	C	47.22	47.41
						H	6.60	6.64
IX	CH_3CH_2—	I	Ethanol	8	133–136°	C	48.91	49.02
						H	6.95	6.80
X		Br	Ether–methanol (2:1)	30	205–208°	C	64.67	64.53
						H	7.24	7.23

[a] Prepared using Method C. [b] Minimum recrystallized yield from last step in synthetic sequence. [c] This compound was prepared through a different route in Ref. 4, mp 197–198°.

Table III—Analytical Data for 3-Aryloxypropylamine Salts[a]



Compound[b]	R	X	Recrystallization Solvent	Yield[c], %	Melting Point	Analysis, %	Calc.	Found
XI[d]		Toluenesulfonic acid	Acetone	30	170–174°	C	59.42	59.31
						H	6.55	6.66
XII		Toluenesulfonic acid	Acetone	23	164–167°	C	64.31	64.23
						H	6.20	6.15
XIII		Benzoic acid	Ether	36	136–137°	C	74.28	74.25
						H	6.55	6.62

[a] All compounds were uniform by TLC (free base, methanol). [b] Prepared using Method D. [c] Minimum recrystallized yield from azide formation step. [d] Previously prepared by treating 3-phenoxypropyl bromide with ammonia [J. V. Brahn *et al.*, *Ber.*, **70B**, 979(1937)].

killed by decapitation. The corpus striatum and cerebellum of each brain was rapidly removed by dissection. The remainder of the brain was homogenized, and a synaptosome-enriched tissue fraction was obtained (5). The test compounds were incubated with an aliquot of this preparation (protein concentration 15–20 mg/ml) in Krebs–Ringer phosphate containing nialamide for 5 min before addition of ^{3}H-*l*-norepinephrine (final concentration 1 μM).

Five minutes later, the uptake was quenched by addition of ice-cold 0.9% NaCl containing 100 μM of unlabeled substrate. The resulting mixture was filtered through a cellulose acetate filter assembly[7] (0.8-μm filter) (6). The net accumulation of ^{3}H-*l*-norepinephrine was determined by liquid scintillation counting. The details of these procedures were described previously (1).

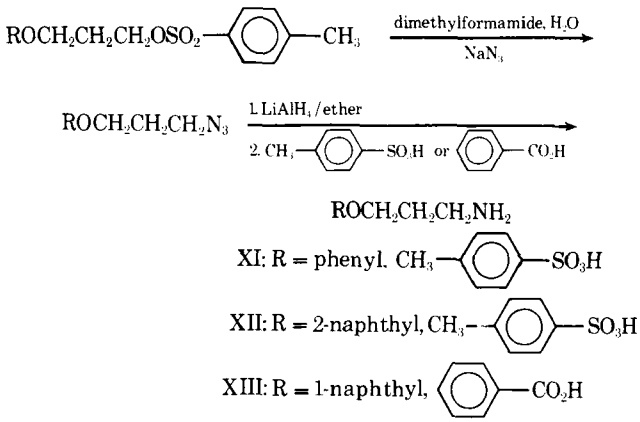
RESULTS AND DISCUSSION

In Table IV the effects of the phentermine and analogous *dl*-amphetamine-derived inhibitors on the accumulation of *l*-norepinephrine are compared. With the exception of VI and VII, the two series appeared parallel. *para*-Hydroxylation (II) did not noticeably alter the potency of either compound (I, IA, II, and IIA). The addition of an *N*-butyl group (III) to phentermine resulted in a six- to sevenfold drop in inhibitor strength, while the same change in the amphetamine series caused a ninefold loss. In either series, the introduction of a phenyl (IV) or naphthyl (V and VI) ring at the end of a four-atom chain from the nitrogen brought about a two- to threefold increase in potency when compared to the simple *N*-butyl analogs. A five-atom chain (VII) was more favorable in the amphetamine case.

Overall, none of the compounds was more potent than the simple amines themselves. However, a properly placed aromatic moiety can partially overcome the initial unfavorable interactions associated with *N*-butylation. Although the amphetamine and phentermine derivatives exhibited similar inhibitory potencies for nonstriatal accumulation, greater differences may be expected in the striatal system, which has different stereochemical as well as structural requirements (7–10).

The monomethylation of *d*-amphetamine to *N*-methyl-*d*-amphetamine did not change inhibitor strength, but the introduction of a second methyl group caused a sevenfold decrease in inhibitory power (1). When the nitrogen was quaternized by the addition of a third methyl group (VIII, Table V), an additional threefold loss occurred. Since it is unlikely that VIII can penetrate membranes, at least part of the accumulative mechanism being blocked must involve interaction with the external synaptosomal membrane. Similar findings were reported for the methiodides of cocaine and imipramine (11). These compounds interfered with the accumulation of norepinephrine by cortex slices at concentrations of 1 and 0.2 μM, respectively.

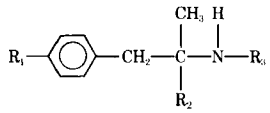
The inactivity of XIV–XVI (Table V) points out that the inhibition of VIII is specific and not associated with a general ionic or detergent-like action. The addition of larger substituents, as in IX and X, did not alter inhibitor strength, so apparently only minimal steric factors are associated with the interaction of a fourth nitrogen ligand and the anionic carrier site. Choline (XIV) was shown to be accumulated by a similar preparation at micromolar concentrations (12, 13), and similar observations have been made in this laboratory (14) employing the same preparations used in this study. Therefore, there appears to be very little competition between



Scheme IV—Method D

[7] Millipore Corp., Bedford, Mass.

Table IV—Inhibition of Synaptosomal Uptake of *l*-Norepinephrine by *N*-Substituted Amphetamines and Phentermines[a]



Compound	R_1	R_2	R_3	I_{50}, μM[b]
I	H	CH_3	H	1.6
IA[c]	H	H	H	1.3
II	OH	CH_3	H	2.4
IIA	OH	H	H	1.1
III	H	CH_3	$-(CH_2)_3CH_3$	10.8
IIIA	H	H	$-(CH_2)_3CH_3$	12.3
IV	H	CH_3	$-(CH_2)_3O-$ 	4.9
IVA	H	H	$-(CH_2)_3O-$ 	4.4
V	H	CH_3	$-(CH_2)_3O-$ 	7.2
VA	H	H	$-(CH_2)_3O-$ 	5.2
VI	H	CH_3	$-(CH_2)_3O-$ 	3.4
VIA	H	H	$-(CH_2)_3O-$ 	5.8
VII	H	CH_3	$-(CH_2)_4O-$ 	6.7
VIIA	H	H	$-(CH_2)_4O-$ 	2.1

[a] Substrate concentration was 1 μM *l*-norepinephrine. [b] The I_{50} values were determined as previously described (1). All values are the average of two or more independent measurements. The variation in each multiple determination was less than 25%. [c] Amphetamine analogs are represented in the A series.

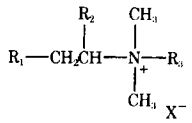
these two compounds for the *l*-norepinephrine transport system.

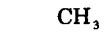
The introduction of an aromatic moiety at the end of a four- or five-atom chain from the terminal nitrogen of amphetamine or phentermine caused a two- to fivefold increase in inhibitor strength when compared with the corresponding *N*-butyl derivative (Table IV). This increment in inhibitor potency could be the result of a nonspecific hydrophobic interaction, but it could also be the result of the nonmimic amine end of the molecule interacting with the transport system at a second site. If the latter were the case, the increase in inhibitor strength could be the result of two separate interactions.

In an attempt to resolve this question, XI–XIII and XVII were prepared and tested. As can be seen from Table VI, these compounds did inhibit *l*-norepinephrine accumulation but were much less effective than the corresponding amphetamine derivatives (A series). If a simple summation effect were involved, the stronger the nonmimic amine the more potent should be the combined nonclassical inhibitor. However, 3-phenoxypropylamine (XI) was two- to threefold more potent than 4-phenylbutylamine (XVII), and 3-(2-naphthyloxy)propylamine (XII) was two- to threefold stronger than 3-(1-naphthyloxy)propylamine (XIII), and the inhibitory potency of the substituted amphetamines had a different relative order so this apparently is not the case. Differences in I_{50} values of two to threefold are significant.

An alternative explanation might be that both the mimic and nonmimic moieties may compete for a common site on the carrier. Since all simple primary amines listed in Table VI are much less potent than *dl*-amphetamine (I_{50} = 1.3 μM), they may be considered competitive antagonists of the binding of the amphetamine moiety in this model. Thus, the I_{50} values of the corresponding

Table V—Inhibition of Synaptosomal Uptake of *l*-Norepinephrine by Quaternary Amines[a]



Compound	R_1	R_2	R_3	X^-	Optical Isomer	I_{50}, μM[b]
XIV	OH	H	CH_3	Cl	—	>100[c]
XV	H	H	CH_3	I	—	>100[c]
XVI	$CH_3(CH_2)_4-$	H	CH_3	I	—	294
VIII		CH_3	CH_3	I	*S(l)*	22.0
IX		CH_3	CH_3CH_2	I	*S*	21.6
X		CH_3		Br	*S*	22.2

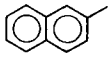
[a] Substrate concentration was 1 μM *l*-norepinephrine. [b] The I_{50} values were determined as previously described (1). All values are the average of two or more independent measurements. The variation in each multiple determination was less than 25%. [c] No inhibition at 100 μM.

nonclassical inhibitor should be somewhere between the I_{50} values of its components. The stronger the nonmimic interaction, the closer the I_{50} of the nonclassical inhibitor should be to the value of its nonamphetamine part.

The data for the 3-phenoxypropyl (XI and IVA) and 4-phenylbutyl (XVII and XVIIA) compounds appear to qualitatively support this hypothesis. However, the results of the 2-naphthyl (XII and VIA) and 1-naphthyl (XIII and VA) studies do not, since the two- to threefold change in nonmimic strength has little effect on the potency of the corresponding nonclassical inhibitor. Furthermore, *N*-phenethyl-*dl*-amphetamine (I_{50} = 7.3 μM) is a weaker inhibitor than either of its parts; the I_{50} of phenethylamine is 6.0 μM (1). Therefore, unfavorable steric factors apparently are associated with the secondary amine structure of this nonclassical inhibitor and cannot be accounted for by this simple competition theory.

Another possibility is that the substituted amphetamines are inhibiting by a nonclassical mechanism but that the optimal configuration has not yet been reached. Thus, the binding of the amphetamine portion of the molecule to the normal substrate site could be perturbed by the interaction of the nonmimic moiety so that the affinity of the combined molecule is only comparable to the simple amphetamine moiety. If this is the nature of the inhibition, it should be possible to devise a nonclassical inhibitor whose interactions are more complementary. Because of its dependency on an adjacent area as well as the normal *l*-norepinephrine binding site,

Table VI—Inhibition of Synaptosomal Uptake of *l*-Norepinephrine[a] by R—X—$(CH_2)_3NH_2$

Compound	R	X	I_{50}, μM[b]
XI		O	10.8
IVA[c]			4.4
XVII		CH_2	23.9
XVIIA			2.7
XII		O	13.4
XIA			5.8
XIII		O	30.5
VA			5.2

[a] Substrate concentration was 1 μM *l*-norepinephrine. [b] The I_{50} values were determined as previously described (1). All values are the average of two or more independent measurements. The variation in each multiple determination was less than 25%. [c] Corresponding nonclassical inhibitor derived from *dl*-amphetamine.

this type of inhibitor is more likely to serve as a selective tool for studying the uptake of neurotransmitters by different tissues and brain regions.

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[x] To whom inquiries should be directed.

Synthesis and Biological Evaluation of Tetrakis(acetylsalicylato)-μ-dicopper(II)

DAVID A. WILLIAMS [*], DONALD T. WALZ [‡], and WILLIAM O. FOYE [*x]

Abstract □ The synthesis of a copper–aspirin chelate, previously reported to be a more active anti-inflammatory agent than aspirin itself, is given. Reaction of potassium acetylsalicylate with cupric sulfate gave a stable copper complex, which analysis and molecular weight determination showed to be a 4:2 chelate structure. Oil–water partition measurements showed the complex to be 10-fold more oil soluble than aspirin. Biological evaluation in rats showed the copper complex of aspirin to be approximately equal to aspirin in reducing carrageenan-induced inflammation, but it was 1.7 times more active than aspirin in reducing the primary lesion of adjuvant arthritis. Whereas aspirin produced a 50% or greater incidence of GI erosions at doses of 100–300 mg/kg in rats, the copper complex caused no erosions in doses up to 1200 mg/kg.

Keyphrases □ Tetrakis(acetylsalicylato)-μ-dicopper(II)— synthesis, biological evaluation, anti-inflammatory activity, physical properties □ Biological evaluation—tetrakis(acetylsalicylato)-μ-dicopper(II), anti-inflammatory activity, rats □ Aspirin–copper complex—synthesis, biological evaluation, anti-inflammatory activity, physical properties □ Copper–aspirin complex—synthesis, biological evaluation, physical properties □ Anti-inflammatory agents, potential—synthesis and biological evaluation of aspirin–copper complex

In 1956, Chenoweth (1) postulated that the salicylates may exert "some if not all" of their biological actions through their ability to bind metal ions, a property that isomers of salicylic acid lack. To test this postulate, a series of substituted salicylic acids and heterocyclic analogs was prepared; their metal-binding avidities were compared with several biological effects to determine possible parallels (2, 3). With hindered (3,5- and 3,6-disubstituted) salicylic acids, for instance, both metal-binding ability and anti-inflammatory activity were lowered (4).

Table I—Oil–Water Partition Coefficients

Compound	pH	K^a
Aspirin–copper complex	4.1	1.3
Salicylic acid	4.1	9.0
Aspirin	4.3	0.11

[a] $K = \frac{C_{\text{oleyl alcohol}}}{C_{\text{water}}}$

Table II—Anti-Inflammatory Activities

Compound	Dose, mg/kg po	Antiedema, Δ, ml (0 *versus* 3 hr)
Aspirin–copper complex	50	+0.40[a]
	100	+0.31[a]
	200	+0.26[a]
Aspirin	50	+0.34[a]
	100	+0.27[a]
	200	+0.20[a]
Controls		+0.55

[a] $p = 0.00$.

Sorenson (5) recently reported that copper chelates of some anti-inflammatory agents, including aspirin, gave marked increases in anti-inflammatory activity compared with the activities of the unchelated agents. Anti-inflammatory activity was also observed for copper chelates of some ligands having no anti-inflammatory properties at all in the nonchelated state. These findings indicate that the copper complexes may be active metabolites of many anti-inflammatory agents. Since the copper(II) complex of