Comparative Stability of Benzamide, Salicylamide, and Some *N*-Substituted Derivatives

K. T. KOSHY*

Abstract □ The comparative stability of benzamide, salicylamide, and some *N*-substituted derivatives were determined in 1.00 *N* perchloric acid and 1.00 *N* sodium hydroxide to elucidate the effect of the substituents on the rates of hydrolysis. Results indicated that in both media benzamide was less stable than salicylamide and *N*-(2-diethylaminoethyl)-benzamide was less stable than the corresponding salicylamide derivative. This clearly demonstrated the marked stabilizing effect of the hydroxyl group in the ortho position. Benzamide and *N*-(2-diethylaminoethyl) benzamide were less stable in alkaline than in acid medium. An opposite effect was noticed in salicylamide and other *N*-substituted salicylamide derivatives. This may be due to stability of the phenolate ions due to resonance effect and consequent resistance to nucleophilic attack by hydroxide ions. Substitution of alkyl or aminoalkyl groups on the amide nitrogen markedly increased the stability of salicylamide; a phenyl group on the nitrogen also had a protective effect, but less than that of alkyl or aminoalkyl groups. The inhibitory effect of these substituents on the rate of hydrolysis of salicylamide is presumed to be due to steric hindrance.

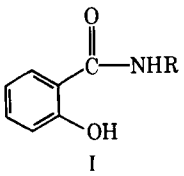
Keyphrases □ Salicylamide, *N*-substituted derivatives—stability □ Benzamide, *N*-substituted derivatives—stability □ Hydrolysis rates—salicylamides, benzamides □ pH effect—salicylamides, benzamides hydrolysis □ UV spectrophotometry—analysis

The kinetics of the hydrolysis of amides has been investigated by several workers, although the literature is sparse compared to that relative to the saponification of esters. The effect of ring substituents on the rate of hydrolysis of aromatic amides has been reported (1–4). Reid (1) studied the hydrolysis of several ring-substituted benzamides in aqueous solution at 100° and found that benzamide was hydrolyzed faster than the substituted compounds. One of the compounds included in his study was salicylamide. Meloche and Laidler (2) made a systematic study on the effect of ring substituents in the acid and base hydrolysis of aromatic amides. These authors noted that in alkaline hydrolysis, the activation energy is lowered and the rate increased by electron-withdrawing groups, whereas electron-releasing substituents increased the activation energy and decreased the rate. In the acid hydrolysis of the amides, on the contrary, the activation energy is lowered by electron-releasing substituents and raised by electron-attracting ones. Leisten (3) studied the constitutional effects on the hydrolysis of amides in concentrated acid solutions. His result showed that in strongly acid conditions polar effects are large; electron-attracting substituents accelerate the hydrolysis and electron-donating substituents retard it. Bolten and Henshall (5) studied the hydrolysis of four unsubstituted and three *N*-substituted aliphatic amides in aqueous solution catalyzed by cation exchange resin. They noticed that *N*-methylacetamide and *N*,*N*′-dimethylacetamide were more resistant to hydrolysis than acetamide, but gave no explanation to this observation. Brodie and Szekely (6) studied the hydrolysis of salicylamide under conditions designed to simulate gastrointestinal environment and reported that it was resistant to cleavage.

Salicylamide and *N*-substituted salicylamides have been investigated for their analgesic and antipyretic properties. There are patented procedures (7–9) for the preparation of *N*-(2-dialkylaminoethyl)salicylamides. During the course of investigation of one of these compounds, *N*-(2-diethylaminoethyl)salicylamide, it was found to be unusually resistant to hydrolysis. This report concerns the stability of this compound and a comparison of its stability with salicylamide and a few structurally similar *N*-alkyl and *N*-aminoalkylsalicylamides. Benzamide and *N*-(2-diethylaminoethyl)benzamide were also included in this study in order to elucidate the effect of the phenolic hydroxyl group on the stability of these compounds.

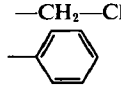
EXPERIMENTAL

Chemicals—The salicylamide derivatives used in this study had the general structure I.



I

where R represented

(*a*)	—H	Salicylamide[1] (m.p. 140–142°)
(*b*)	$-CH_2-CH_2-N-(C_2H_5)_2HCl$	*N*-(2-Diethylaminoethyl)-salicylamide hydrochloride (Compound MA593)[2] (m.p. 97–98°)
(*c*)	$-CH_2-CH_2-N-(CH_3)_2HCl$	*N*-(2-Dimethylaminoethyl)-salicylamide hydrochloride (Compound MA569)[2] (m.p. 133–136°)
(*d*)	$-CH_2-CH_2-N[CH-(CH_3)_2]_2HCl$	*N*-(2-Diisopropylaminoethyl)salicylamide hydrochloride (Compound MA631)[2] (m.p. 149–152°)
(*e*)	$-CH_2-CH_2-CH_3$	*N*-*n*-Propylsalicylamide
(*f*)	$-CH_2-CH_2-CH-(CH_3)_2$	*N*-Isopentylsalicylamide
(*g*)		Salicylanilide[3] (m.p. 138–140°)

N-*n*-Propyl and *N*-isopentylsalicylamides were prepared by refluxing methylsalicylate with an excess of the corresponding amine

[1] Monsanto Chemical Co.
[2] Synthesized by Miles Chemical Therapeutics Research Laboratory.
[3] Matheson Coleman & Bell, East Rutherford, N. J.

for several hours. The course of the reaction was monitored by GLC. When the reaction was complete as indicated by the disappearance of the methylsalicylate peak on the chromatogram, the excess of amine was removed by distillation under reduced pressure. *N-n*-Propylsalicylamide was recrystallized from a 2:1 mixture of methanol and water (m.p. 59–63°). *N*-Isopentylsalicylamide was recrystallized from absolute ethanol (m.p. 39–41°).

Benzamide (m.p. 125–126°) was used.[4] *N*-(2-Diethylaminoethyl)-benzamide was prepared according to the classical Schotten-Baumann reaction from benzoyl chloride and 2-diethylaminoethylamine. The purified amide was a liquid at room temperature. The oxalate salt (m.p. 133–135°) was readily formed from acetone on reacting with calculated amount of oxalic acid.

Analytical Procedures.—In order to study the rate of hydrolysis of the various compounds, analytical procedures were required to determine the concentrations of the intact molecules or of their degradation products. The procedures used are summarized below:

For Compounds MA593, MA569, MA631, Salicylamide N-n-Propylsalicylamide and N-Isopentylsalicylamide—The products of hydrolysis of these compounds are salicylic acid and the corresponding amines. The undegraded compounds all have similar UV absorption spectra with a broad maximum at about 300 mμ in both acidic and neutral aqueous solutions. Salicylic acid also absorbs in this region. In basic medium, the absorption peak for these compounds shifts to 326 mμ, while no change occurs in the spectrum of salicylic acid. The amines formed from the compounds do not have any significant absorption at these wavelengths. The absorption spectra for Compound MA593 and salicylic acid in neutral and in basic media are shown in Fig. 1 as a typical example. The analytical procedure for these compounds in the presence of their degradation products involved determining the absorbances at 297 mμ and 326 mμ in sodium hydroxide–disodium hydrogen phosphate buffer, pH 12, and calculating the concentrations of the parent compounds remaining in solution by solving a pair of simultaneous equations. The absorption measurements were made using a spectrophotometer[5] and 1-cm. silica cells.

For Salicylanilide—In basic medium, salicylanilide has two peaks, one at 270 mμ and the other at 334 mμ. Salicylic acid and aniline have no absorption in this medium at 334 mμ. Therefore, the absorbance at 334 mμ in pH 12 buffer was used to determine the concentration of salicylanilide.

For benzamide and N-(2-Diethylaminoethyl)benzamide—Direct spectrophotometric measurements were not applicable to the analysis of these compounds due to interference from benzoic acid. Therefore, benzamide was separated from benzoic acid by extraction with chloroform from an alkaline solution. The chloroform extract was washed with water, dried with anhydrous sodium sulfate, and the absorbance determined at 264 mμ. *N*-(2-Diethylaminoethyl)benzamide was separated from benzoic acid by extraction with ethyl ether from a basic solution. The ether extract was washed with water and then extracted with 0.001 *N* HCl. The absorbance of the solution was determined at 224 mμ and the concentration calculated. There was no interference from 2-diethylaminoethylamine.

Procedure for Studying the Rate of Hydrolysis—A 0.005 *M* solution of each compound was prepared in a 100-ml. volumetric flask in the appropriate medium which had been preheated to the temperature at which the hydrolysis was studied. The flask was placed in a water bath maintained at 90 ± 1° and aliquots withdrawn at suitable intervals and analyzed for the residual amount of each compound according to the procedure outlined above.

The hydrolysis was studied in 0.2 *M* buffer solutions in the pH range 2–8, in 1.00 *N* perchloric acid, and in 1.00 *N* sodium hydroxide. The buffer systems were phosphoric acid–monobasic sodium phosphate at pH 2 and 3, acetic acid–sodium acetate at pH 4 and 5, and monobasic–dibasic sodium phosphate at pH 6, 7, and 8.

RESULTS AND DISCUSSION

The hydrolysis of Compound MA593 was studied in greater detail than the other compounds; in buffers pH 2–8, 1.00 *N* NaOH, and in 1.00 *N* perchloric acid. All the other compounds were hydrolyzed only in 1.00 *N* perchloric acid and in 1.00 *N* NaOH except salicylanilide, which was hydrolyzed only in the acid medium.

[4] Fisher Scientific Co.
[5] Beckman model DB.

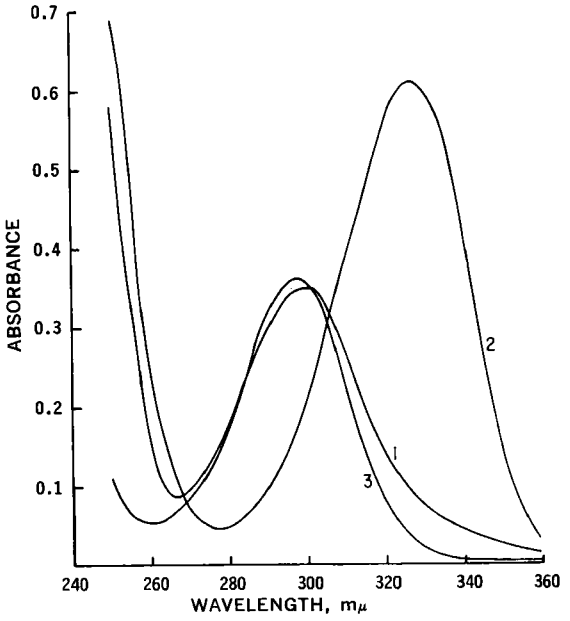


Figure 1—*Absorption spectra of 1.0 × 10⁻⁴ M solutions of Compound MA 593 and salicylic acid. Key: 1, MA 593 in water; 2, MA 593 in buffer, pH 12; 3, salicylic acid in water and in buffer, pH 12.*

Compound MA593 was highly resistant to hydrolysis in buffers in the pH range 2–8. In fact, there was no detectable hydrolysis at pH 2–5 at 90° for a period of 125 hr.

The effect of buffer species as general base catalysts was checked by hydrolyzing Compound MA593 in solutions pH 2–8 at 90° using different concentrations of the buffer components at each pH. No general base catalysis was noticed.

The effect of ionic strength on the hydrolysis of Compound MA593 was studied in 1.00 *N* perchloric acid at 90° in the presence of varying amounts of potassium chloride. The hydrolysis rate was not affected by changes in the ionic strength of the medium.

As expected, all the compounds studied followed a pseudo first-order rate of hydrolysis. This is illustrated in Fig. 2 which is a plot of the logarithm of the concentration against time for the hydrolysis in 1.00 *N* perchloric acid at 90°. The rate constants were calculated from the slopes of these lines and similar data for the hydrolysis in 1.00 *N* NaOH and are shown in Table I.

Comparing benzamide to salicylamide and *N*-(2-diethylaminoethyl)benzamide to Compound MA593, there were marked differences in the rate constants both in the acidic and basic medium. In both pairs, the compound containing the hydroxyl group was considerably less susceptible to hydrolysis. This is in agreement with the findings by Reid (1) who found that benzamide was hydrolyzed faster than salicylamide. According to Leisten (3), *ortho*-substituents in benzamide retard hydrolysis independently of their electrophilic or nucleophilic nature and the effect is clearly steric. In the case of salicylamide and Compound MA593 in the acid medium, in addition to this steric effect, the possibility of protection by intramolecular hydrogen bonding is also present.

Table I illustrates the protection afforded by *N*-alkyl and *N*-aminoalkyl substituents on salicylamide. The *N*-aminoalkyl compounds, MA593, MA569, and MA631 were about 10 to 15 times as stable as salicylamide. This protective effect in the acid medium was at first suspected to be due to the presence of the tertiary amine group in these compounds. But experiments with the *N*-alkyl derivatives, *N*-*n*-propyl, and *N*-isopentylsalicylamides showed these compounds to be just as resistant to hydrolysis as the *N*-aminoalkylsalicylamides. (Figure 2 and the data in Table I show the two *N*-alkylsalicylamide derivatives to be slightly more stable in acid than the *N*-aminoalkylsalicylamides. However, the two *N*-alkyl-substituted salicylamides were hydrolyzed in an aqueous medium containing 10% ethanol for solubility reasons. It was subsequently found that when MA593, MA569, and MA631 were hydrolyzed in the same medium, their rates of hydrolysis were diminished to an extent comparable to that of *N*-*n*-propyl and *N*-isopentylsalicylamide.) This finding that an alkyl or an aminoalkyl substituent on the amide nitrogen of salicylamide markedly increases its resistance

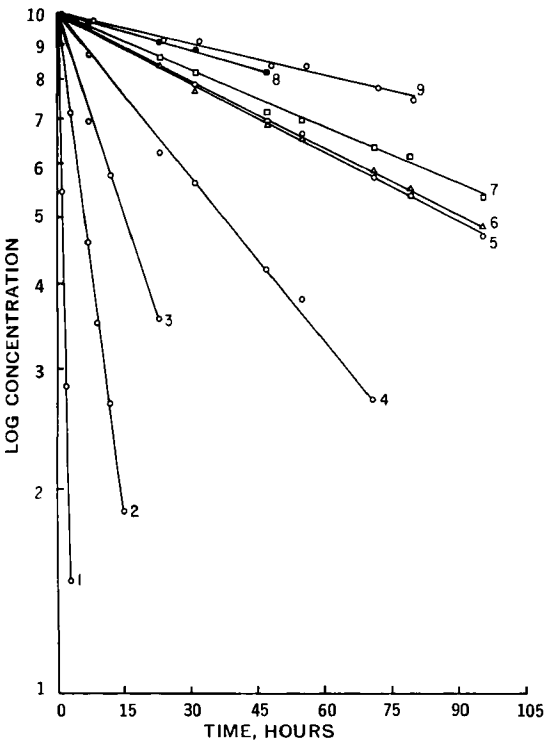
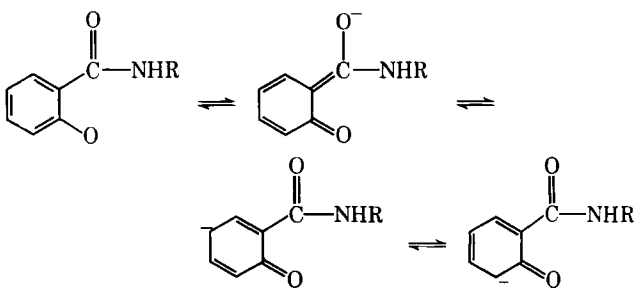


Figure 2—*Pseudo first-order plot of the hydrolysis of amides in 1.00* N *perchloric acid at 90°. Key: 1, benzamide; 2, salicylamide; 3,* N-*(2-diethylaminoethyl)benzamide; 4, salicylanilide; 5, MA 569; 6, MA 593; 7, MA 631; 8,* N-*isopentylsalicylamide; 9,* N-*propylsalicylamide.*

to hydrolysis is significant and believed not to have been reported in the literature.

Benzamide and *N*-(2-diethylaminoethyl)benzamide were more readily hydrolyzed in the base than in the acid medium. Meloche and Laidler (2) noticed similar results for the hydrolysis of benzamide and few *para* substituted derivatives. The hydrolysis of salicylamide however, exhibited a reverse trend—faster in the acid medium than in the basic medium. Though not as marked, a similar trend was noticed in the case of *N*-aminoalkylsalicylamides (MA593, MA569, and MA631) and *N*-alkylsalicylamides (*N*-*n*-propyl and *N*-isopentyl). In 1.00 *N* sodium hydroxide, all the salicylamides mentioned above would be existing as phenolate ions or in their resonance forms shown below:



Such resonance forms obviously make the ion more stable. Representing the basic hydrolysis of amides by the $B_{AC}2$ mechanism (11),

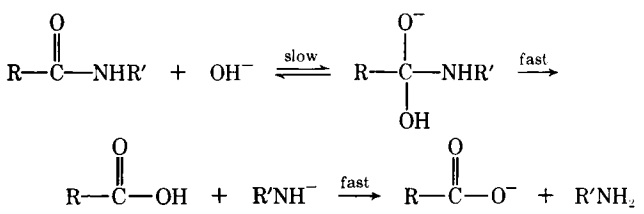


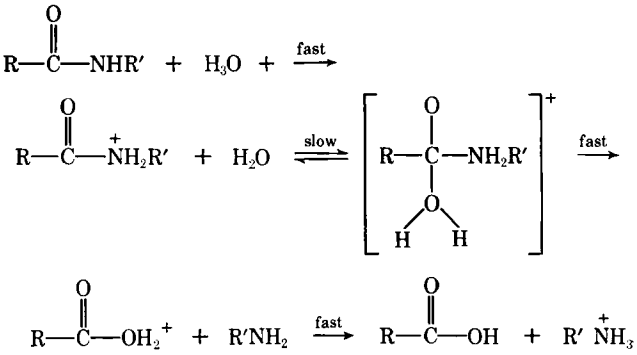
Table I—First-Order Rate Constants for the Hydrolysis of Amides in 1.00 *N* Perchloric Acid and in 1.00 *N* NaOH at 90°

Amide	Rate Constant, hr.$^{-1}$ × 10^3 1.00 *N* $HClO_4$	1.00 *N* NaOH
Salicylamide	112.5	55.8
MA593	7.7	3.2
MA569	7.7	5.0
MA631	6.5	5.2
N-*n*-Propylsalicylamide	3.4[a]	4.42
N-Isopentylsalicylamide	4.2[a]	3.6
Salicylanilide	18.2[a]	—
Benzamide	628.0	4650.0
N-(2-Diethylaminoethyl)benzamide	47.4	240.0

[a] Samples hydrolyzed in a medium containing 10% ethanol.

it may be noted that the rate-determining step is the nucleophilic attack by the hydroxide ion. It can, therefore, be seen that the negatively charged phenolate ion and its resonance forms would repel attack by hydroxide ions. This may account for the increased stability of these compounds in strongly basic medium. Alkyl and aminoalkyl substitution on the amide nitrogen of the salicylamides further enhanced their stability in the basic medium. It may be due to the slight electron-donating properties of alkyl groups, but more likely to steric effect.

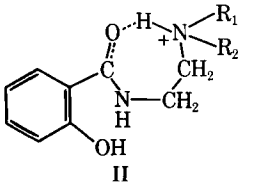
It is interesting that in the acid medium salicylanilide was intermediate in stability between salicylamide and the other *N*-substituted salicylamides. Representing the acid hydrolysis of amides by the well recognized $A_{AC}2$ mechanism (11) the increased resistance of



salicylanilide compared to salicylamide can be explained on the basis that the phenyl group being electrophilic would reduce the basicity of the nitrogen and would make it less susceptible to attack by the proton in the first step of the hydrolysis mechanism. But this explanation cannot be extended to the *N*-alkyl and the *N*-aminoalkyl derivatives of salicylamide. Alkyl group being weakly electron-donating should increase the basicity of the amide nitrogen and facilitate attack by the proton and accelerate the rate. The experimental data, however, show a reverse trend. Obviously, the greater stability of *N*-alkyl and *N*-aminoalkylsalicylamides cannot be explained on the basis of inductive effect.

Garrett (10) in his study on the hydrolysis of selected esters found that diethylaminoethylsalicylate hydrochloride was highly resistant to hydrogen ion-catalyzed hydrolysis and noticed no significant general base catalysis. It is noteworthy that Compound MA593, which is a structurally similar amide, behaves in an analogous manner. In explaining the mechanism of hydrolysis of diethylaminoethylacetylsalicylate hydrochloride, the above author postulated the formation of a cyclic compound formed by internal hydrogen bonding as an intermediate prior to nucleophilic attack by water molecule. In the case of Compounds MA593, MA569, and MA631, in acid medium, their protonated species could possibly be involved in the formation of cyclic intermediate as shown in Structure II.

However, formation of the cyclic intermediate may not be too likely since it is a seven-membered transition. But more important, such an intermediate would impart more positive character to the carbonyl carbon and thus make it more susceptible to nucleophilic attack by water. This should cause an acceleration in the rate of



II

hydrolysis if one assumes the same rate-determining step as shown in the amide hydrolysis mechanism shown earlier. In addition, the formation of a cyclic intermediate is not possible for *N*-*n*-propyl and *N*-isopentylsalicylamide and therefore cannot account for the increased stability of *N*-alkyl and *N*-aminoalkylsalicylamides.

The $A_{AC}2$ mechanism for the hydrolysis of amides requires that substituents should exert only weak polar effects, but when suitably situated, they should exert strong steric effects (11). The effect of the alkyl and the aminoalkyl substituents on the amide nitrogen in retarding the rate of acid hydrolysis of salicylamide appears to be primarily due to steric hindrance.

SUMMARY

The hydrolysis of *N*-(2-diethylaminoethyl)salicylamide was studied in buffers of pH 2–8. There was no detectable degradation at 90° in pH 2–5 buffers after 125 hr. Slow hydrolysis was noticed at pH 6, 7, and 8.

The rates of hydrolysis of salicylamide, salicylanilide, benzamide, *N*-(2-diethylaminoethyl)benzamide, and *N*-*n*-propyl-, *N*-isopentyl-, *N*-(2-diethylaminoethyl)-, *N*-(2-dimethylaminoethyl)-, and *N*-(2-diisopropylaminoethyl)salicylamides were studied in 1.00 *N* perchloric acid and in 1.00 *N* NaOH at 90°. In the acid medium, salicylanilide was more stable than salicylamide which in turn was more stable than benzamide. Aminoalkyl substituent on the nitrogen increased the stability of benzamide. Salicylamide was more stable in basic than in acidic medium, probably due to the protection afforded by the negative charge on the phenolate ion. The *N*-alkyl and *N*-aminoalkylsalicylamides were highly resistant to acid and base hydrolysis. This appeared to be due to combined steric hindrance by the hydroxyl group in the *ortho* position and the alkyl and aminoalkyl groups on the nitrogen.

REFERENCES

(1) E. E. Reid, *Am. Chem. J.*, **21**, 284(1899); **24**, 397(1900).
(2) I. Meloche and K. J. Laidler, *J. Am. Chem. Soc.*, **73**, 1712 (1951).
(3) J. A. Leisten, *J. Chem. Soc.*, **1959**, 765.
(4) J. T. Edward and S. C. R. Meacock, *ibid.*, **1957**, 2000.
(5) P. D. Bolten and T. Henshall, *ibid.*, **1962**, 1226.
(6) D. C. Brodie and I. J. Szekely, *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 414(1951).
(7) British pat. 862,721, Miles Laboratories, Inc.
(8) British pat. 874,206, Knoll A. G. Chemiche Fabriken.
(9) British pat. 903,718, Knoll A. G. Chemiche Fabriken.
(10) E. R. Garrett, *J. Am. Chem. Soc.*, **80**, 4049(1958).
(11) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 785, 786.

ACKNOWLEDGMENTS AND ADDRESSES

Recived September 19, 1968 from the *Product Development Laboratory, Consumer Products Division, Miles Laboratories, Inc., Elkhart, Ind. 46514*

Accepted for publication November 15, 1968.

The author wishes to thank L. S. Shankle for technical assistance.

* Present address: The Upjohn Company, Kalamazoo, Mich. 49001

Hydroxyindole-*O*-Methyltransferase III: Influence of the Phenyl Moiety on the Inhibitory Activities of Some *N*-Acyltryptamines

BENG T. HO, WILLIAM M. McISAAC, and L. WAYNE TANSEY

Abstract □ During previous studies on the inhibition of hydroxyindole-*O*-methyltransferase, several *N*-acyltryptamines have been found to be good inhibitors of this enzyme. Substitution of the benzyl or phenyl moiety of *N*-phenylacetyltryptamine or *N*-benzoyltryptamine with halogen atoms further enhanced the inhibitory activity. Among all the halogen-substituted inhibitors, the 3,4-dichloro substitution offered the highest activity. An increase in inhibition of the enzyme was also observed when a fluorine or bromine atom was placed on C-5 position of the indole nucleus. A combination of the 5-bromo and 3,4-dichlorobenzoyl substitutions resulted in the most active inhibitor.

Keyphrases □ *N*-Acyltryptamines—synthesis □ Hydroxyindole-*O*-methyltransferase inhibition—*N*-acyltryptamines □ Structure-activity relationship—*N*-acyltryptamines □ IR spectrophotometry—identity, structure □ UV spectrophotometry—identity

The previous paper (1) reported that several *N*-acyltryptamines had been synthesized and found to be good inhibitors of hydroxyindole-*O*-methyltransferase (HIOMT) *in vitro*. The benzyl or phenyl moiety of *N*-phenylacetyltryptamine (II) and *N*-benzoyltryptamine (III) raised the inhibitory activities eight and four times, respectively, over *N*-acetyltryptamine (I). This increase in activity could be attributed to the increase in affinity of the phenyl group to the enzyme by both hydrophobic bonding and donor-acceptor interaction (1). Biologically active compounds bearing a halogen atom on their structures, such as antimalarial pyrimethamine (IV),[1] tranquilizer chlorpromazine (V),[2] and many others have been well documented. The *p*-chloro group of the potent oral antihistamine chlorpheniramine maleate[3] (VII) gave a 20-fold increase in potency over the nonchlorinated pheniramine[4] (VI) (2). Substitution of a halogen atom

[1] Daraprim, Burroughs Wellcome & Co. (U.S.A.), Inc., Tuckahoe, N. Y.
[2] Thorazine, Smith Kline & French, Philadelphia, Pa.
[3] Chlor-Trimeton Maleate, Schering Corp., Bloomfield, N. J.
[4] Trimeton, Schering Corp., Bloomfield, N. J.