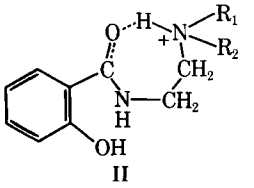

II

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.

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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

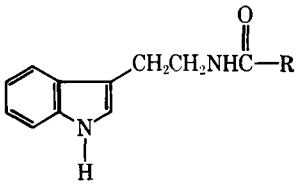
Abstract □ During previous studies on the inhibition of hydroxyindole-*O*-methyltransferase, several *N*-acyltryptamines have been found to be good inhibitors of this enzyme. Substitution of the benzyl or phenyl moiety of *N*-phenylacetyltryptamine or *N*-benzoyltryptamine with halogen atoms further 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

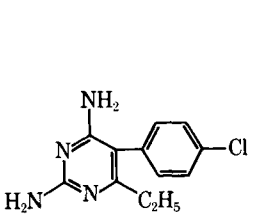
The previous paper (1) reported that several *N*-acyltryptamines had been synthesized and found to be good inhibitors of hydroxyindole-*O*-methyltransferase (HIOMT) *in vitro*. The benzyl or phenyl moiety of *N*-phenylacetyltryptamine (II) and *N*-benzoyltryptamine (III) raised the inhibitory activities 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.

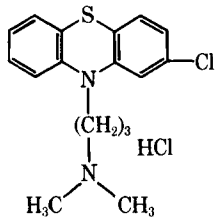
on 1-phenyl-4,6-diamino-2,2-dimethyl-1,2-dihydro-*s*-triazine (VIII) was found to increase the inhibitory activity on dihydrofolic reductase (3). The *m*-bromo (IX) and *m*-chloro (X) derivatives of VIII were both 13-fold better inhibitors than the unsubstituted VIII. It was thus anticipated that substitution of the phenyl moiety of II and III with a halogen atom would also produce a similar effect and result in an increased inhibitory activity of II and of III towards HIOMT.



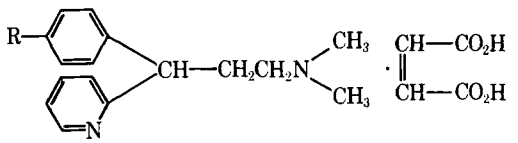
I, R = CH_3–
II, R = $C_6H_5CH_2$–
III, R = C_6H_5–



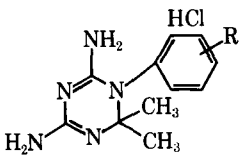
IV



V



VI, R = H
VII, R = Cl



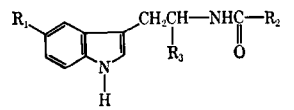
VIII, R = H
IX, R = *m*-Br
X, R = *m*-Cl

An increase of greater than 2.5-fold in inhibitory activity on HIOMT was observed when a chloro group was substituted on the *para*-position of the benzene ring of II to give XV (Table I). The *p*-fluoro group in XIV also gave more than 1.5-fold increase in activity. Substitution of a methyl group on the side chain (see XI), however, resulted in a 1.5-fold loss of inhibitory activity.

In the *N*-benzoyltryptamine series, inhibition of HIOMT was increased by the substitution of a fluorine atom on either the *ortho*- or *meta*-position of the benzene ring of III. Compounds XVIII and XIX were about twice as active as III. The *p*-fluoro group in XX did not seem to change the activity of III. Chlorine substitution gave an even greater increase in the activity of III: an increase of fourfold was observed in *m*-chloro (XXII), 5.5-fold in *p*-chloro (XXIII), and 6.5-fold in *o*-chloro (XXI). Among the dichloro analogs of III, 3,4-disubstitution showed a most profound effect. The 3,5-dichloro compound (XXVI), with both chlorine atoms *meta* to the amide linkage, had an activity comparable to the monosubstituted *m*-chloro compound XXII. Compound XXVI was found to be 3.5 times more active than III. In the 2,4-dichloro compound (XXIV), one chlorine atom is *ortho* and the other one *para* to the amide linkage. The *p*-chloro group apparently did not contribute to the binding of the benzene moiety to the enzyme, as XXIV and the monosubstituted *o*-chloro compound (XXI) were inhibitors of equal activity. A combination of *m*- and *p*- groups offered an additive effect in inhibitory activity: 3,4-dichlorobenzoyltryptamine (XXV) was a better inhibitor than any mono- and any other dichloro compound, being 18-fold more active than the unsubstituted III. The effect of the three adjacent methoxy groups on the inhibiton of HIOMT varied with the *N*-benzoyl and *N*-phenylacetyl series. The 3,4,5-trimethoxyphenyl group improved the inhibitory activity of III by almost twice (see XXVII), whereas a twofold decrease in activity was observed when this group was introduced on II to give XVI. Compound XVII was slightly more active than III. The cyclohexenyl group like the phenyl group was capable of complexing with the enzyme *via* a combination of hydrophobic and donor-acceptor interactions through the π-cloud of the carbon-carbon double bond.

Substitution of a halogen on the 5-position of the indole nucleus exerted an even greater inhibitory effect on HIOMT. Fluorine substitution increased the activity of II by threefold (see XII), and that of III twofold (see

Table I—Inhibition of HIOMT by



Compd.	R_1	R_2	R_3	I_{50},[a] m*M*
I	H	CH_3–	H	1.40[b]
II	H	$C_6H_5CH_2$–	H	0.18[c]
III	H	C_6H_5–	H	0.37[c]
XI	H	$C_6H_5CH_2$–	CH_3	0.27
XII	F	$C_6H_5CH_2$–	H	0.061
XIII	Br	$C_6H_5CH_2$–	H	0.050
XIV	H	*p*-$FC_6H_4CH_2$–	H	0.11
XV	H	*p*-$ClC_6H_4CH_2$–	H	0.068
XVI	H	3,4,5-$(CH_3O)_3C_6H_2CH_2$–	H	0.38
XVII	H	1-Cyclohexenyl	H	0.25
XVIII	H	*o*-FC_6H_4–	H	0.16
XIX	H	*m*-FC_6H_4–	H	0.20
XX	H	*p*-FC_6H_4–	H	0.34
XXI	H	*o*-ClC_6H_4–	H	0.055
XXII	H	*m*-ClC_6H_4–	H	0.10
XXIII	H	*p*-ClC_6H_4–	H	0.066
XXIV	H	2,4-$Cl_2C_6H_3$–	H	0.055
XXV	H	3,4-$Cl_2C_6H_3$–	H	0.020
XXVI	H	3,5-$Cl_2C_6H_3$–	H	0.11
XXVII	H	3,4,5-$(CH_3O)_3C_6H_2$–	H	0.20
XXVIII	F	C_6H_5–	H	0.17
XXIX	Br	C_6H_5–	H	0.070
XXX	F	3,4-$Cl_2C_6H_3$–	H	0.022
XXXI	Br	3,4-$Cl_2C_6H_3$–	H	0.0050

[a] Concentration of an inhibitor giving 50% inhibition of the enzyme. [b] Data from *Reference 4*. [c] Data from *Reference 1*.

XXVIII). Further increases of 3.5-fold and 5-fold were observed in 5-bromo derivatives of II and III, respectively (see XIII and XXIX). A combination of the fluorine atom on C-5 of the indole nucleus and the 3,4-dichloro groups on the benzene moiety resulted in an inhibitor (XXX) which was 17-fold better than III. An even greater increase of 74-fold was achieved by a combined effect of 5-bromo and 3,4-dichlorobenzoyl substitutions. Thus, Compound XXXI was the most active inhibitor prepared.

EXPERIMENTAL[5]

No attempt has been made to obtain maximum yields of all the amides.

Acid Chlorides—*p*-Fluoro- and *p*-chlorophenylacetyl chlorides were prepared from the reaction of the corresponding acid with thionyl chloride in chloroform at room temperature for 15 hr. Similarly, the conversion of 3,4,5-trimethoxyphenylacetic acid to its acid chloride was performed in benzene and in the presence of pyridine. Refluxing 3,4-dichlorobenzoic acid with thionyl chloride afforded 3,4-dichlorobenzoyl chloride. All the above-mentioned acid chlorides were used crude in the following amide syntheses; no attempt has been made to purify these intermediates.

N-Acyltryptamines—*Method A*—A mixture of 10 mmoles of tryptamine or 5-substituted-tryptamine, an equivalent amount of appropriate acid chloride, 12 mmoles of triethylamine, and 30 to 50 ml. of chloroform (dichloromethane was used in the preparation of XVI) was stirred at room temperature for 2 or 15 hr. An equal volume of water was added, and the organic layer was separated and washed successively with 30–50 ml. of 10% HCl, 30–50 ml. of 2 *N* NaOH, and 50 ml. of water. After being dried with anhydrous sodium sulfate the chloroform was evaporated *in vacuo*, and the solid product was recrystallized from a suitable solvent (see Table II). In the case of XVI, the product separated as a yellow oil which solidified upon trituration with petroleum ether (b.p. 30–60°).

See Table II for compounds prepared by this method and their physical constants.

Method B—A solution of 5 mmoles of tryptamine hydrochloride or 5-substituted-tryptamine hydrochloride in 10–20 ml. of water was mixed with 5 ml. of 2 *N* aqueous sodium hydroxide. The addition of 20 ml. of chloroform (in the case of XXI–XXIII, XXVIII, XXIX, and XXXI) or dichloromethane (in the case of XVIII–XX, XXIV, and XXV) dissolved the precipitated free tryptamine, then 5.5 mmoles of the appropriate acid chloride in 5 ml. of the organic solvent was added. The mixture was stirred at room temperature either for 1 hr. or overnight.

For all cases, except XXIII, the product precipitated during the reaction, the organic layer was separated and washed successively with 10% HCl, 2 *N* NaOH, and water. After drying (anhydrous Na_2SO_4) the solvent was evaporated *in vacuo*, and the solid product was recrystallized from a suitable solvent (see Table II). In the preparation of XXV, removal of dichloromethane left a gum which solidified in about 1 hr.

See Table II for compounds prepared by this method and their physical constants.

5-Bromo-3-(β-nitro)vinylindole—A mixture of 6.5 g. (29 mmoles) of 5-bromoindole-3-carboxaldehyde, 1.5 g. of ammonium acetate, and 50 ml. of nitromethane was refluxed with stirring for 2 hr. After cooling, reddish brown solid was collected on a filter and washed with benzene; yield, 7.5 g. (97%), m.p. 190–193°. Recrystallization of this product from absolute methanol gave 5.5 g. (71%), m.p. 192–193.5°; $\lambda_{max.}$ (KBr): 3.10(NH); 6.18, 6.26, 6.40, 6.59, 6.78 (C=C, NO_2); 7.64 μ (NO_2); $\lambda_{max.}$ (C_2H_5OH): 228, 285, and 382 mμ.

Anal.—Calcd. for $C_{10}H_7BrN_2O_2$: C, 45.0; H, 2.64; N, 10.5. Found: C, 44.8; H, 2.90; N, 10.2.

5-Bromotryptamine—To a stirred suspension of 4 g. of lithium aluminum hydride in 150 ml. of tetrahydrofuran was added over a period of 30 min. a solution of 3.0 g. (11 mmoles) of 5-bromo-3-(β-nitro)vinylindole in 40 ml. of tetrahydrofuran. The mixture was refluxed with stirring for 4 hr. Water was added and the mixture was filtered. The filter cake was extracted twice with 75-ml. portions of dichloromethane. The combined organic solutions were evaporated *in vacuo* leaving a pale yellow oil; yield, 2.3 g. (75%). A solution of this free base in benzene was mixed with ether–HCl, and the hydrochloride salt was collected on a filter; yield, 2.0 g. (64%). Two recrystallizations from absolute ethanol–ether gave 0.74 g. (24%), m.p. 286–287°; $\lambda_{max.}$ (KBr): 3.07(NH), 3.31, 3.33, 3.38, 3.42, 3.56, 3.72, 3.86, 3.97, 4.08, 4.20(CH, NH^+); 6.24, 6.29, 6.32, 6.48, 6.63 μ (C=C).

Anal.—Calcd. for $C_{10}H_{12}BrClN_2$: C, 43.6; H, 4.39; N, 10.2. Found: C, 43.8; H, 4.50; N, 10.0.

[5] Melting points are corrected and were taken on a Fisher-Johns or Mel-Temp apparatus. IR spectra were taken with the Perkin-Elmer Spectrophotometer Model 237B. For qualitative UV spectra the Beckman Spectrophotometer Model DB-G was used.

Table II—Physical Constants of *N*-Acyltryptamines

Compd.	Method[a]	Yield, %	M.p., °C	Analysis, % Calcd.	Found
XI	A	53	126–127.5[b]	C, 78.0 H, 6.90 N, 9.58	C, 78.3 H, 6.89 N, 9.29
XII	A	18	130.5–132[c]	C, 73.0 H, 5.78 N, 9.45	C, 72.7 H, 5.93 N, 9.28
XIII	A	85	—[d]	C, 49.2[e] H, 3.44 N, 11.9	C, 49.7 H, 3.59 N, 12.1
XIV	A	33	137–138[c]	C, 73.0 H, 5.78 N, 9.45	C, 73.2 H, 5.75 N, 9.57
XV	A	17	140–141[c]	C, 69.1 H, 5.48 N, 8.96	C, 69.0 H, 5.62 N, 8.95
XVI	A	57	128–129[f]	C, 68.4 H, 6.57 N, 7.60	C, 68.5 H, 6.41 N, 7.74
XVII	A	30	99–102[g]	C, 76.1 H, 7.51 N, 10.4	C, 76.1 H, 7.75 N, 10.3
XVIII	B	82	113–114[g]	C, 72.3 H, 5.36 N, 9.92	C, 72.6 H, 5.12 N, 10.1
XIX	B	68	120–120.5[g]	C, 72.3 H, 5.36 N, 9.92	C, 72.1 H, 5.42 N, 9.93
XX	B	75	144–145[g,h]	C, 72.3 H, 5.36 N, 9.92	C, 72.2 H, 5.15 N, 10.0
XXI	B	51	148–149.5[g]	C, 68.3 H, 5.06 N, 9.38	C, 68.1 H, 4.91 N, 9.45
XXII	B	71	130–131[g]	C, 68.3 H, 5.06 N, 9.38	C, 68.2 H, 4.98 N, 9.42
XXIII	B	77	150–151[g]	C, 68.3 H, 5.06 N, 9.38	C, 68.3 H, 5.07 N, 9.40
XXIV	B	84	126–127[g]	C, 61.3 H, 4.24 N, 8.41	C, 61.5 H, 4.40 N, 8.60
XXV	B	64	112–113[g]	C, 61.3 H, 4.24 N, 8.41	C, 61.2 H, 4.23 N, 8.54
XXVI	A	58	143.5–144.5[g]	C, 61.3 H, 4.24 N, 8.41	C, 61.1 H, 3.98 N, 8.14
XXVII	A	66	164–165.5[g,i]	C, 67.8 H, 6.26 N, 7.90	C, 67.6 H, 6.39 N, 7.78
XXVIII	B	69	115–116[j]	C, 72.3 H, 5.36 N, 9.92	C, 72.5 H, 5.26 N, 9.75
XXIX	B	67	173.5–175[g]	C, 59.5 H, 4.40 N, 8.16	C, 59.8 H, 4.50 N, 8.10
XXX	A	13	132–132.5[c]	C, 58.1 H, 3.73 N, 7.98	C, 58.3 H, 3.82 N, 8.07
XXXI	B	55	143–144[g]	C, 49.5 H, 3.18 N, 6.80	C, 49.3 H, 3.04 N, 6.77

[a] See *Experimental*. [b] Recrystallized from benzene–hexane. [c] Recrystallized from benzene. [d] An oil. [e] Analyzed as the picrate salt, m.p. 151–153° (ethanol). [f] Recrystallized from dichloromethane-petroleum ether (b.p. 30–60°). [g] Recrystallized from aqueous ethanol. [h] A melting point of 144–145° (aq. C_2H_5OH) has been recorded for this compound, prepared by heating a mixture of tryptamine and *p*-fluorobenzoyl chloride in pyridine at 70–80° (5). [i] A melting point of 209–210° (aq. CH_3OH) (5) and 200–202° (CH_3OH) (6) has been reported for this compound. [j] Recrystallized from benzene-heptane.

5-Bromotryptamine hydrochloride (m.p. 290° dec.) has also been prepared from 5-bromophenylhydrazine and γ-aminobutyraldehyde diethyl acetal (7).

Assay—Hydroxyindole-*O*-methyltransferase was isolated from beef pineal gland and purified according to the method of Axelrod and Weissbach (8).

The stock solutions of all the inhibitors, except XII–XIV and XVIII–XX, were prepared in dimethyl sulfoxide (DMSO). Compound XIII was dissolved in 50% DMSO, and Compounds XII, XIV, XVIII–XX were dissolved in propylene glycol. Previous findings showed that the same magnitude of inhibitory activity was obtained regardless of the use of either of these two solvents (4).

Incubation was carried out with *N*-acetylserotonin and *S*-adenosyl-L-methionine-methyl-^{14}C according to the previously described procedure (4).

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Infrared and Thin-Layer Chromatography Determination of Benzoyl Peroxide Degradation Products in Pharmaceuticals

M. GRUBER, R. KLEIN, and MARY FOXX

Abstract □ Infrared qualitative analyses followed by semiquantitative thin-layer chromatography (TLC) were utilized to determine specific degradation products formed at room temperature in pharmaceuticals containing benzoyl peroxide. Studies on pH together with USP benzoate identification tests were employed as qualitative aids. Significant amounts of benzoic acid and/or related acids were encountered as contaminants of all premixed commercially available pharmaceuticals containing benzoyl peroxide, when stored for extended periods at room temperature.

Keyphrases □ Benzoyl peroxide—degradation products □ Degradation, benzoyl peroxide—pharmaceuticals □ IR spectrophotometry—identity □ TLC—identity, analysis

In a previous paper published in this journal, Gruber and Klein (1) evaluated several procedures employed in the testing of benzoyl peroxide stability in pharmaceuticals and demonstrated the inadequacy of conventional titration analyses. In that study, they noted that polarograms of extracts from these preparations exhibited secondary waves other than those associated with benzoyl peroxide which intensified with increasing storage time of the products and were accompanied by decreasing benzoyl peroxide concentration. It was suspected that these waves might be related to intermediates in the oxidative degradation process of benzoyl peroxide.

Extensive investigations have been undertaken by other authors concerning reactions undergone by benzoyl peroxide. Erlenmeyer and Schoenauer (2) found that when heated in the absence of solvent, pure benzoyl peroxide decomposes to yield carbon dioxide and biphenyl with some phenyl benzoate and benzene. In paraffins, (3) the decomposition occurs by homolytic reaction whose products always include carbon dioxide and benzoic acid. DeTar and Long (4) found that decomposition of a very dilute solution of benzoyl peroxide in benzene resulted in the formation of carbon dioxide, benzoic acid, and biphenyl among other end products. When reacted with alcohols (5), benzoyl peroxide yields carbon dioxide, the corresponding aromatic acid, and a carbonyl compound derived from the oxidation of the alcohol. If heated with acetic acid (6), the end products are similar to those found in the absence of solvent, namely carbon dioxide, benzoic acid, phenyl benzoic acid, and benzene.

Little, however, has been written of the decomposition of benzoyl peroxide in aqueous media. It is suspected that this is due to its low solubility and lack of use in this solvent except in pharmaceutical preparations.

When one considers that in pharmaceutical vehicles, not one, but several and different diluents (usually in the form of an emulsion or as a suspension) are dealt with, the complexity of the problem becomes immediately apparent. However, regardless of the solvent system, it is evident from the literature that the end products usually contain either benzoic or a related aromatic acid. This investigation was, therefore, carried out to test the hypothesis that benzoic and/or related acids were in-