3-Ethylamino-3-methyl-2-butyl acetate. A 17-g. portion (0.13 mole) of 3-ethylamino-3-methyl-2-butanol (XIII) was converted to the acetate ester by heating on the steam bath for 3 hr. with 18 g. (0.17 mole) of acetic anhydride. The ester (13.9 g., 61% yield) had b.p. 88–92° at 24 mm. n_D^{25}, 1.4268.

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.21; H, 10.97; N, 8.10.

The hydrochloride had m.p. 157–160°.

Anal. Calcd. for $C_9H_{20}ClNO_2$: C, 51.54; H, 9.61; N, 6.68. Found: C, 51.94; H, 9.43; N, 6.75.

Acknowledgment. The authors express their thanks to Air Reduction Chemical Co., New York, for generous samples of *t*-acetylenic carbinols; to Messrs. W. L. Brown, G. M. Maciak, H. L. Hunter, R. M. Hughes, Alfred Brown, and David Cline of the Lilly Research Laboratories, Indianapolis, Ind., for the analytical determinations; and to Eli Lilly and Co. for the support of this work.

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CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, PURDUE UNIVERSITY]

Synthesis and Stability Studies of Certain Disubstituted Aminoacetoxybenzoic Acids

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Received August 11, 1960

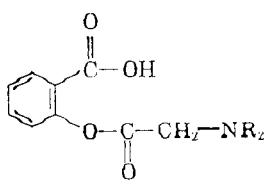
Five disubstituted aminoacetoxybenzoic acids were synthesized as their hydrochloride salts. Their hydrolysis rates were determined and compared with those of aspirin.

Aspirin is probably the most widely used chemical medicinal agent. Production in the United States alone was 18.0 million pounds in 1957.[2]

Despite its great utility and popularity, however, acetylsalicylic acid has two major drawbacks. It has poor solubility in aqueous media and, more important, it has a tendency to hydrolyze in the presence of only traces of moisture.

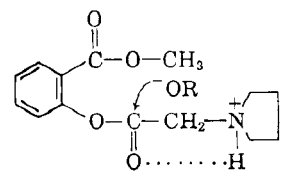
The purpose of this study is to synthesize compounds similar to aspirin which, it is hoped, might, due to steric and/or electronic factors be more stable to hydrolysis and water soluble.

The desired structure is:



A

Garrett[3] showed that a group of hindered acylsalicylic acids were more resistant to acid-catalyzed hydrolysis than aspirin. Garrett[4] also showed that B was resistant to hydrogen ion catalyzed hydrolysis, due to a "proton shield" effect. However, the compound was very susceptible to nucleophilic catalysis. He explains this as an electrophilic-nucleophilic catalysis whereby the hydrogen of the protonated amine hydrogen bonds with the carbonyl oxygen, thus facilitating attack on the carbonyl carbon.



B

Kagan and Birkenmeyer[5] have described reactions which support the hypothesis that the carboxylate anion of acylsalicyclic acid can participate in a neighboring group nucleophilic attack on the carbonyl carbon of the acyl moiety and on the carbon atom *alpha* to the carbonyl group.

EXPERIMENTAL

o-Disubstituted aminoacetoxybenzoic acid. a. tert-Butyl salicylate. Method A. Silver salicylate, 54 g. (0.22 mole), *tert*-butyl chloride, 61 g. (0.66 mole) and 150 ml. of dry thiophene-free benzene were agitated in a closed container, protected from light, during a 24-hr. period. The mixture was filtered and the filtrate concentrated under reduced pressure. The resulting oil was treated with 5% sodium bicarbonate solution, the aqueous layer extracted with ether and the combined oil and ethereal extracts dried over calcium chloride.

After removal of the ether the residue was fractionated at 16–18 mm. yielding 23.5 g. (48%) of a product distilling at 120–123°, n_D^{25} 1.5029, d^{27} 1.0579.

Method B: Salicyloyl chloride, obtained from 0.2 mole of salicyclic acid and prepared according to a modification of Wolffenstein's[6] method, was added dropwise to a well-

(1) Abstracted from a dissertation submitted to the Graduate School of Purdue University in partial fulfillment for the Ph.D. degree. Present address: Brooklyn College of Pharmacy, Long Island University.

(2) U. S. Tariff Commission, *Synthetic Organic Chemicals, Report 203.* U. S. Government Printing Office, Washington, D. C., 1958, p. 33.

(3) E. R. Garrett, *J. Am. Chem. Soc.*, **79**, 3401 (1957).

(4) E. R. Garrett, *J. Am. Chem. Soc.*, **79**, 5206 (1957).

(5) F. Kagan and R. D. Birkenmeyer, *J. Am. Chem. Soc.*, **81**, 1086 (1959).

(6) R. Wolffenstein, German Patent **284,161** (1914); *Chem. Zentr.*, *I*, 1290 (1915).

stirred mixture of 37 g. (0.35 mole) of anhydrous sodium carbonate and 38 ml. (0.25 mole) of *tert*-butyl alcohol. Stirring was continued for a total of 12 hr. The mixture was then poured into 200 ml. of water. The oily layer was separated and the aqueous layer as well as the residual sodium chloride–sodium carbonate mixture were extracted with ether. The oil and combined ethereal extracts were dried over calcium chloride. After removal of the ether the residue was fractionated yielding 18.0 g. (46%) of product distilling at 118–120° at 16 mm., n_D^{25} 1.5035, d^{27} 1.0579.

Molecular Refractivity: Calcd. 52.58. Found: product A: 54.06; product B: 53.79.

b. tert-Butyl bromoacetoxysalicylate. Into a 250-ml. three-necked flask, equipped with a mercury-sealed stirrer, addition funnel and drying tubes, and maintained at −50° in a Dry Ice–acetone bath, there was placed 25.0 g. (0.129 mole) of *tert*-butyl salicylate, 20.2 g. (0.2 mole) of triethylamine and 50 ml. of absolute ether. To the well-stirred mixture there was added dropwise, 23.6 g. (0.15 mole) of bromoacetyl chloride, diluted with an equal volume of absolute ether, over a 4-hr. period. Stirring was continued for an additional 10 hr.

The solid mixture was transferred to a beaker and treated with ice water. The resulting suspension was extracted with ether, filtered and dried over calcium chloride. The ether was evaporated with an air jet yielding a mass of crystals which were washed with and recrystallized from petroleum ether (b.p. 30–60°). There was obtained 10.9 g. (42%) of product. A repeatedly recrystallized sample melted at 56–57°.

Anal. Calcd. for $C_{13}H_{15}BrO_4$: C, 49.52; H, 4.76; Br, 25.3. Found: C, 49.67; H, 4.77; Br, 25.6.

c. tert-Butyl morpholinoacetoxysalicylate. To a solution of 8.0 g. (0.0254 mole) of *tert*-butyl bromoacetoxysalicylate in 50 ml. of absolute ether in a 250-ml. three necked flask equipped with a mercury-sealed stirrer, addition funnel, reflux condenser and drying tubes, there was added, dropwise, 4.6 g. (0.055 mole) of morpholine in 10 ml. of absolute ether. The stirred mixture was refluxed for 4 hr. The morpholine hydrobromide was filtered off and the ethereal solution evaporated yielding 6.3 g. (77%) of a crystalline product, which upon recrystallization from petroleum ether–ether (80:20) melted at 95–96°. The hydrochloride was prepared in the usual manner and recrystallized from ethyl acetate–isopropyl alcohol (80:20); m.p. 178–179° with decomposition.

The piperidino, pyrrolidino, diethylamino and diisopropylamino analogs of the above compound were prepared in a similar manner except that the oily free bases were converted to their hydrochlorides since it was found impossible to obtain them as bases in crystalline forms in good yields (see Table I).

d. o-Morpholinoacetoxybenzoic acid. Into a well-cooled solution of 5.0 g. (0.0155 mole) of *tert*-butyl morpholinoacetoxysalicylate in 70 ml. of absolute ether there was passed dry hydrogen chloride gas until the hydrochloride initially formed went into solution (5–10 min.). The ethereal solution was evaporated to dryness and the solid residue recrystallized from ethyl acetate–isopropyl alcohol (80:20). The yield was 3.8 g. (81.5%). A repeatedly recrystallized sample melted at 168–169° with decomposition.

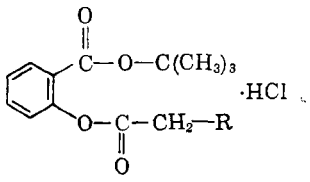
The piperidino, pyrrolidino, diethylamino and diisopropylamino analogs of the above compound were prepared in a similar manner. In some instances the product was obtained as an oil and was solidified by repeated washings with absolute ether and trituration in the cold. (see Table II).

Methyl morpholinoacetoxysalicylate. This compound was prepared by two methods. It was synthesized from methyl iodoacetoxysalicylate and morpholine in a manner analogous to the *tert*-butyl analog. The recrystallized product melted at 177–179°.

The compound was also prepared by the esterification of *o*-morpholinoacetoxybenzoic acid hydrochloride by diazomethane in ether. After recrystallization it melted at 179–180°. A mixed melting point of the products obtained by the above methods produced no depression. The infrared spectra of the two products were identical.

TABLE I

o-DISUBSTITUTED *tert*-BUTYL AMINOACETOXYSALICYLATES



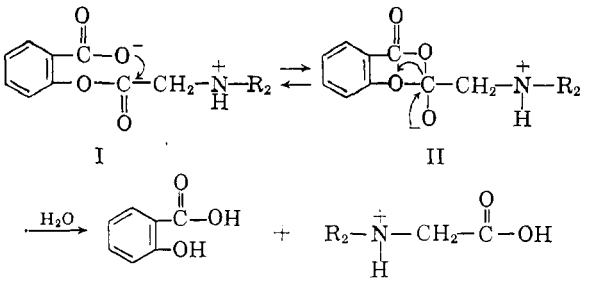
R	M.P.[b]	C Calcd.	C Found[e]	H Calcd.	H Found
Morpholino[a]	178–179[c] 95–96[d]	63.53	63.71[f]	7.21	7.16[f]
Piperidino[a]	154–155[c]	60.75	59.81	7.36	7.15
Pyrrolidino[a]	162–163[c]	59.72	59.15	7.08	7.10
Diethylamino[a]	139–140[c]	59.12	58.28	7.60	7.63
Diisopropylamino[a]	164–165[c]	61.36	61.54	8.13	8.11

[a] Recrystallized from ethyl acetate–isopropyl alcohol (80:20). [b] All melting points are uncorrected and were taken in capillary melting point tubes. [c] Melted with decomposition. [d] Free base. [e] Analyses were performed by the Alfred Bernhardt Laboratories, Max-Planck Institut, Mülheim, W. Germany. [f] Analyzed as the free base.

Hydrolysis rates. These were determined for the compounds indicated in the tables at 27.0 ± 0.1° at *p*H 2.1 ± 0.1, and in the case of *o*-morpholinoacetoxybenzoic acid also at *p*H 8.0 ± 0.1. The increase in the color intensity due to formation of ferric-salicylate complex was followed on a Beckman DU Spectrophotometer at 530 mμ. The concentration of the compounds used was of the order of 10^{-5} moles per 100 ml. Rate constants were calculated by the method of least squares for first order kinetics.

DISCUSSION

The rate determining step is presumably I to II. The presence of I in the anionic form favors cyclization since the carboxylate ion is more nucleophilic than the carboxyl group. In the case of the



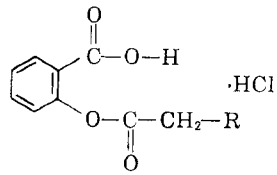
diisopropyl analog, steric interference to the formation of the activated cyclic intermediate II is apparently significant (see Table III). However, its hydrolysis rate is still 6.3 times faster than aspirin.[7]

Methyl pyrrolidylacetylsalicylate hydrochloride (B) is resistant to acid catalyzed hydrolysis due to

(7) The hydrolysis rate of aspirin as determined in this study was 0.0777 × 10^{-5} sec.$^{-1}$ at *p*H 2.1 and 27°. Garrett[3] reports 0.0562 × 10^{-5} sec.$^{-1}$ at *p*H 2.5 and 25°.

TABLE II

o-DISUBSTITUTED AMINOACETOXYBENZOIC ACIDS

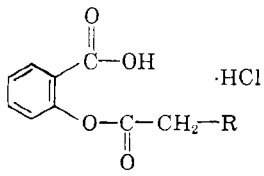


R	M.P.[b]	C		H		N		Cl	
		Calcd.	Found[d]	Calcd.	Found	Calcd.	Found	Calcd.	Found
Morpholino[a]	168–169[c]	51.74	51.51	5.35	5.50	4.65	4.59	11.75	11.73
Piperidino[a]	165–166[c]	56.09	55.79	6.05	6.19	4.71	4.72	—	—
Pyrrolidino[a]	165–166[c]	54.63	53.44	5.65	5.81	—	—	12.41	12.70
Diethylamino[a]	151–152[c]	54.26	53.79	6.33	6.62	4.87	5.07	—	—
Diisopropylamino[a]	151–152[c]	57.05	56.22	7.02	7.08	—	—	11.23	11.25

[a] Recrystallized from ethyl acetate–isopropyl alcohol. (80:20). [b] All melting points are uncorrected and were taken in capillary melting point tubes. [c] Melted with decomposition. [d] Analyses were performed by the Alfred Bernhardt Laboratories, Max-Planck Institut, Mülheim, W. Germany.

TABLE III

HYDROLYSIS RATES AND ISOELECTRIC POINTS OF *o*-DISUBSTITUTED AMINOACETOXYBENZOIC ACIDS



R	k × 10^5 sec.$^{-1}$[a,b]	Ip[d]
Morpholino	3.03 ± 0.078	8.8
	1.19 ± 0.048[c]	—
Piperidino	1.20 ± 0.043	5.2
Pyrrolidino	3.25 ± 0.0046	5.6
Diethylamino	2.13 ± 0.0082	5.6
Diisopropylamino	0.419 ± 0.0075	6.3

[a] Determined at 27.0 ± 0.1° at *p*H 2.1 ± 0.1. [b] Buffers: *p*H 2.1-equal volumes of 0.01*M* hydrochloric acid and 0.0047*M* potassium chloride containing 0.4 g. of ferric ammonium sulfate dodecahydrate; *p*H 8.0-equal volumes of 0.032*M* phenobarbital and 0.01*M* sodium phenobarbital. [c] At *p*H 8.0 ± 0.1. [d] Isoelectric points were determined by potentiometric titration.

a "proton shield" effect. However, Garrett[3] found it to be susceptible to nucleophilic catalysis. In I the neighboring carboxylate acts as the nucleophile, even in acidic medium. The hydrogen bonding of the protonated amine hydrogen with the carbonyl oxygen and the inductive effect of the quaternary nitrogen, both facilitate the nucleophilic attack on the carbonyl carbon of the acyl moiety. These factors then, may explain the more rapid hydrolysis of the disubstituted aminoacetoxybenzoic acids hydrochlorides in comparison to aspirin.

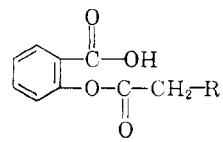


FIG. 1 Hydrolysis rates of *o*-disubstituted aminoacetoxybenzoic acids *p*H 2.1

R = I. *N*-morpholino
II. *N*-piperidino
III. *N*-pyrrolidino
IV. *N*,*N*-diethylamino
V. *N*,*N*-diisopropylamino

It is of interest to note the unexpectedly low value obtained for the hydrolysis of the morpholino analog in an alkaline medium. A possible relationship of *p*H, at the respective isoelectric points of these aminoacids, to their rates of hydrolysis might exist. However, this aspect was not investigated at this time.

Acknowledgment. The authors express their appreciation to Dr. M. W. Carter of the Statistics and Computer Laboratory for his help in the statistical evaluation of the kinetic data.

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