Certain Disubstituted *o*-Aminoacetoxy- and Propoxybenzoic and Cinnamic Acids and their *tert*-Butyl Esters

ALEX GRINGAUZ

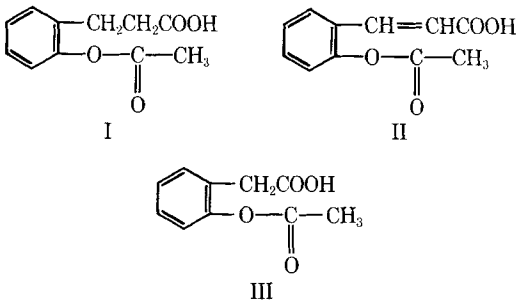
Abstract □ Several *o*-aminoacetoxy- and propoxy derivatives of benzoic and cinnamic acids as well as certain of their *tert*-butyl esters have been prepared as potential analgesics and local anesthetics. The syntheses and biological evaluation of representative compounds are presented.

Keyphrases □ Analgesic properties—derivatives of benzoic, cinnamic acids, esters □ Anesthetic properties—derivatives of benzoic, cinnamic acids, esters □ Benzoic acid, esters (derivatives)—synthesis, biological evaluation □ Cinnamic acid, esters (derivatives)—synthesis, biological evaluation □ IR—analysis □ Bradykinin-induced writhing test—biological analgetic screening

The objective of this work was to synthesize several types of compounds structurally related to acetylsalicylic acid in the hope of obtaining a drug which would overcome some of the disadvantages of aspirin. Ideally the desired agent should have analgesic-antipyretic activity equal to or exceeding that of aspirin. It should have a longer duration of action, possibly as a result of greater stability toward hydrolytic degradation both *in vivo* and *in vitro;* this would make liquid dosage forms possible. It should also exhibit good aqueous solubility. It is also desirable that such a compound produce no, or at least greatly reduced, gastric irritation, ulceration, or bleeding.

DISCUSSION

o-Acetoxyphenylpropionic acid (I) was reported (1) to have analgesic-antipyretic properties similar to aspirin. A recent report (2), however, could not verify this potency. Molecular models indicate that the *trans* isomer of II should be incapable of intramolecularly catalyzed hydrolysis and therefore be more stable. Of the two vinylogs of aspirin (II), only the *cis* isomer showed activity (2). For similar reasons the preparation of an acetyl derivative of *o*-hydroxyphenylpropiolic acid was attempted. Synthesis of this compound has thus far been unsuccessful. *o*-Acetoxyphenylacetic acid (III), the first homolog of aspirin, was recently prepared (2) and found to lack significant activity.

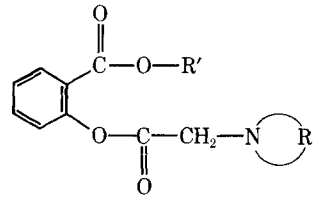


I

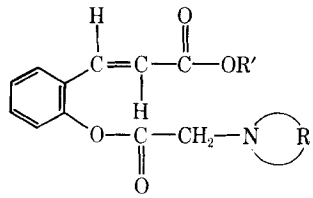
II

III

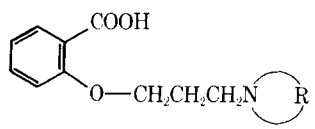
Compounds of Type IV (R′ = H) were synthesized (3) but failed to show pharmacological activity of any significance. Their hydrolytic decomposition rate was considerably greater than aspirin (5–42 times). Since acid functions such as carboxyl groups tend to sharply lower biological potency (4), several esters of IV (R′ = *tert*-butyl) were prepared. Two such esters showed relatively good resistance to *in vitro* hydrolysis (3). This factor alone could alter the absorption and distribution picture in the animal body—and thus possibly its pharmacology. The vinology principle (5) was the rationale for the preparation of several cinnamates V (R′ = H and *tert*-butyl).



IV



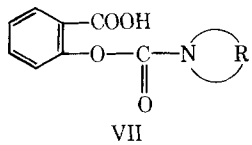
V



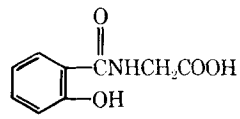
VI

p-Methoxyacetylsalicylic acid has good antipyretic activity (6). *o*-Methoxybenzoic acid also exhibits some activity (7). More recently, it was found (8) that 2-(3-carboxy-4-methoxyphenyl)alanine, a precursor to "phenylalanine aspirin," possessed good analgesic activity. It was therefore deemed of interest to prepare compounds of the *o*-aminopropoxybenzoic acid type (VI) to determine the presence of biological activity. The one member of this series tested for analgesia (XXIV) was, however, devoid of this property.

The synthesis of salicylic acid carbamates of Type VII was unsuccessful (see *Chemistry*). Salicyluric acid (VIII) being the main metabolite of both aspirin and salicylic acid appeared to offer interesting possibilities as a structural moiety. Analgesic-antipyretic activity for the 4-nitro derivative has been claimed (9). Attempts to prepare *o*-aminoacetoxy derivatives were undertaken but were unsuccessful.



VII

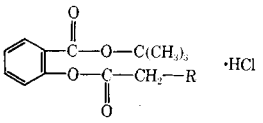


VIII

CHEMISTRY

tert-Butyl aminoacetoxysalicylates (IV) were synthesized by acylation of *tert*-butyl salicylate with bromoacetyl chloride followed by treatment with the appropriate secondary amine. *o*-Coumaric acid was converted to *o*-chloroacetoxycinnamic acid (XVIII) by reaction with chloroacetic anhydride and sodium chloroacetate. Conversion of XVIII to its *tert*-butyl ester (XIX) was accomplished in poor yields by either treatment with isobutylene and H_2SO_4 (9%) or by conversion to the acid chloride with $SOCl_2$ followed by treatment with *tert*-butyl alcohol and pyridine (13%). Reaction of XIX with NaI in acetone followed by the desired amine afforded

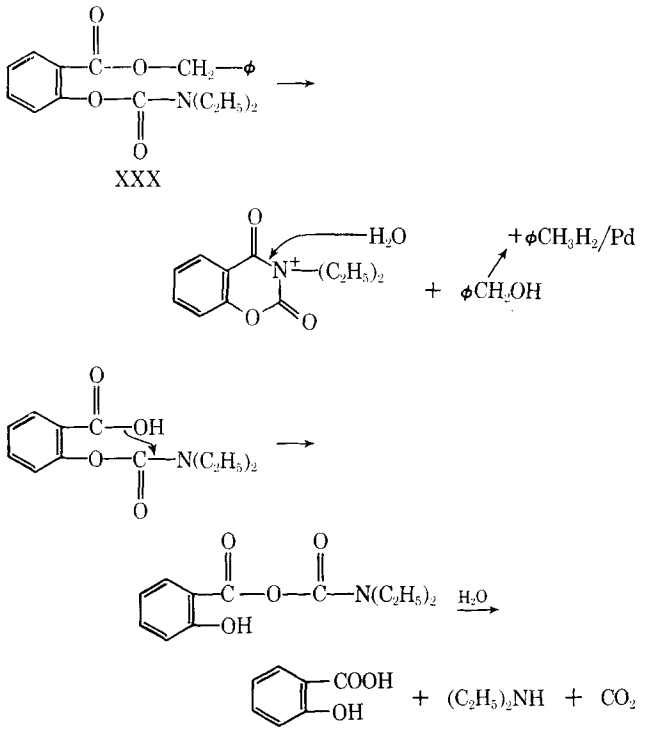
Table I—Disubstituted *tert*-Butyl Aminoacetoxysalicylate Hydrochlorides



Compd.	R	Recrystn.[a] Solvent	M.p. °C.	Anal., % Calcd.	Found
XI	Thiamorpholino	A	177–178[b]	C, 54.60 H, 6.47 N, 3.75	C, 54.49 H, 6.37 N, 3.77[d]
XII	3-Pyrrolino	A	158–159[b]	C, 60.11 H, 6.53 N, 4.12	C, 62.46 H, 6.49 N, 4.28
XIII	Diallylamino	B	141–143[b]	C, 62.03 H, 7.12 N, 3.81	C, 61.42 H, 7.07 N, 3.86
XIV	*cis*-2,6-Dimethylpiperidino	C	186–187[b]	C, 62.55 H, 7.88 Cl, 9.24	C, 62.46 H, 7.73 Cl, 8.92
XV	*cis*-2,5-Dimethylpyrrolidino	C	170–172[b]	C, 61.69 H, 7.63 Cl, 9.59	C, 61.70 H, 7.70 Cl, 9.20
XVI	3-Azabicyclo-[3.2.2]-nonano	D	174–175[b,c]	C, 63.70 H, 7.64 N, 3.54	C, 63.81 H, 7.85 N, 3.43

[a] A = ethyl acetate–ethanol; B = ethanol (95%); C = ethyl acetate–methanol; D = ethyl acetate. [b] Melted with decomposition. [c] Sealed capillary. [d] Sulfur analysis: Calcd. 8.57. Found: 8.55.

V (R′ = *tert*-butyl) as the free base. Conversion to the hydrochloride salt resulted in cleavage of the *tert*-butyl group in at least one instance (see *Experimental*) yielding the aminoacid hydrochloride V (R′ = H). Methyl *o*-(3-bromopropoxy)benzoate (XXIII) was prepared by treatment of methyl salicylate with $NaOCH_3$ and refluxing the product with 1,3-dibromopropane. Reaction of XXIII with the appropriate amine followed by acid hydrolysis of the methyl ester gave VI as the hydrochloride salt. Alternately, VI could be prepared by reaction of methyl salicylate (as the Na salt) with dialkylaminopropyl chloride followed by hydrolysis of the methyl ester.



Scheme I

The carbamate VII (R = diethyl) was attempted but did not lead to the desired product. Benzyl diethylcarbamoylsalicylate (XXX) was synthesized by treating benzyl salicylate with phosgene and reacting the resulting chloroformate with diethylamine. Alternately XXX was also prepared by direct reaction with diethylcarbamoyl chloride. Reductive debenzylation of XXX, however, did not afford VII; salicylic acid was the isolable product. A possible mechanism for this unexpected result is proposed (Scheme I).

EXPERIMENTAL

All melting and boiling points are uncorrected; melting points were determined in capillary tubes. Infrared spectra were obtained in KBr pellets on a Perkin-Elmer 337 instrument. Elemental analyses were done by Smith, Kline & French Laboratories and Alfred Bernhardt, Max-Planck Institute, West Germany. Animal testing was carried out by the Pharmacology Department, Menley & James Laboratories.

***tert*-Butyl Dialkyl or Cycloalkylaminoacetoxysalicylate Hydrochlorides**—tert-*Butyl Salicylate* (*IX*)—This was prepared in 40–50% yield by either treatment of salicyloyl chloride with *tert*-butyl alcohol as described by Cwalina and Gringauz (3) or by H_2SO_4 catalyzed reaction of salicylic acid with excess isobutylene according to McCloskey and Fonken (10).

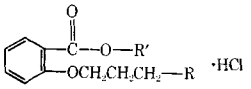
tert-*Butyl Bromoacetoxysalicylate* (*X*)—This was prepared in 68% yield from IX and bromoacetyl chloride according to Cwalina and Gringauz (3).

tert-*Butyl Thiamorpholinoacetoxysalicylate Hydrochloride* (*XI*)—To a solution of 8.10 g. (0.0257 mole) of X in 50 ml. absolute ether there was added dropwise and with stirring 5.15 g. (0.0514 mole) of thiamorpholine[1] in 10 ml. of dry ether. The stirred mixture was refluxed for 6 hr. and filtered. Addition of ethereal HCl precipitated 6.0 g. (62.5%) of the desired salt. Repeated recrystallizations from ethyl acetate–ethanol (70:30) gave m.p. 177–178° dec. The free base could also be obtained in 53% yield, m.p. 83–90° (crude). The five additional analogs similarly prepared are listed in Table I.

***o*-Disubstituted Alkylaminoacetoxycinnamic Acid Hydrochloride**—o-*Coumaric Acid* (*XVII*)—This was prepared in 75–80% yield from coumarin by treatment with aqueous NaOH and yellow HgO according to Seshardi and Rao (11).

[1] A sample of thiamorpholine was supplied by Dr. W. Horrom of Abbott Laboratories, N. Chicago, Ill.

Table II—Disubstituted *o*-3-Aminopropoxybenzoates and Benzoic Acid Hydrochlorides



Compd.	R′	R	Method[a]	M.p. °C.[b]	Anal., % Calcd.	Found
XXIV	CH_3	Diethylamino	A and B	86–88	C, 59.69 H, 8.02	C, 59.79 H, 8.08
XXV	H	Diethylamino		135–137	C, 58.43 H, 7.71	C, 58.19 H, 7.68
XXVI	CH_3	Pyrrolidino	A	139.5–140	C, 60.10 H, 7.40	C, 60.16 H, 7.45
XXVII	H	Pyrrolidino		139–141	C, 58.84 H, 7.05	C, 59.08 H, 7.04
XXVIII	CH_3	Dimethylamino	B	[c]	C, 57.04 H, 7.36	C, — H, —
XXIX	H	Dimethylamino		[d]	C, 55.49 H, 6.99	C, 55.62 H, 7.52

[a] Methods A and B as described in *Experimental* section. [b] Solvent of recrystallization was ethyl acetate–2-propanol, 80:20 for the methyl esters, 50:50 for the acids. [c] Could not be crystallized. [d] Extremely hygroscopic; no valid m.p. was obtainable.

o-*Chloroacetoxycinnamic Acid* (*XVIII*)—A mixture of 50.0 g. (0.302 mole) XVII, 102.5 g. (0.60 mole) of freshly distilled chloroacetic anhydride and 35.6 g. (0.302 mole) of sodium chloroacetate was stirred 15 hr. at 60°. The resultant melt was poured into ice water and stirred until solidification. The crude product obtained was air dried and extracted from unreacted XVII with CH_2Cl_2. Treatment with charcoal and evaporation of solvent afforded 41.0 g. (56.5%) of product which, after recrystallization from benzene–ether melted at 135.0–137.5°.

Anal.—Calcd. for $C_{11}H_9ClO_4$: C, 54.90; H, 3.77; Cl, 14.74. Found: C, 55.16; H, 3.77; Cl, 14.68.

tert-*Butyl* o-*Chloroacetoxycinnamate* (*XIX*)—Direct reaction of XVIII with isobutylene and H_2SO_4 according to McCloskey and Fonken (10) gave a crude yield of 9% with accompanying recovery of XVII and XVIII. A somewhat better yield was obtained by the dropwise addition, at room temperature, of the acid chloride prepared from 34.5 g. (0.143 mole) of XVIII with $SOCl_2$ in dry benzene to a stirred solution of 10.6 g. (0.143 mole) *tert*-butyl alcohol and 11.3 g. (0.143 mole) pyridine. After 6 hr. the mixture was poured into ice water and extracted with ether. Evaporation of the combined, dried (Na_2SO_4) ether extracts afforded a dark oil. Repeated extractions with boiling petroleum ether (30–60°) yielded, on cooling, 5.6 g. (13.3%) of product. Repeated recrystallization from the above solvent gave a m.p. 55–57°.

Anal.—Calcd. for $C_{15}H_{17}ClO_4$: C, 60.71; H, 5.78; Cl, 11.95. Found: C, 60.68; H, 5.75; Cl, 12.06.

tert-*Butyl* o-*Morpholinoacetoxycinnamate Hydrochloride* (*XX*)—To a solution of 4.4 g. (0.00149 mole) XIX in 50 ml. of N_2-purged acetone there was added 2.22 g. NaI similarly dissolved and the mixture refluxed several hours under N_2. The resulting product was treated with 2.58 g. (0.0298 mole) of morpholine in 100 ml. absolute ether and refluxed an additional 3 hr. After filtering the precipitate the residue was treated with HCl gas to yield, after crystallization from 2-propanol, 3.71 g. (65%) of product. Four recrystallizations gave a m.p. 165–167°.

Anal.—Calcd. for $C_{19}H_{26}ClNO_5$: C, 59.47; H, 6.83; Cl, 9.24; N, 3.65. Found: C, 59.00; H, 6.87; Cl, 9.12; N, 3.57.

tert-*Butyl* o-*3-Azabicyclo*-[*3.2.2*]-*nonan-3-ylacetoxycinnamate Hydrochloride* (*XXI*)—This was similarly prepared and recrystallized from ethyl acetate–2-propanol, m.p. 146–147°.

Anal.—Calcd. for $C_{23}H_{32}ClNO_4 \cdot H_2O$: C, 62.85; H, 7.78; N, 3.18. Found: C, 62.70; H, 7.75; N, 3.18.

o-*Diethylaminoacetoxycinnamic Acid Hydrochloride* (*XXII*)—This compound was obtained in 67% yield from XIX and diethylamine. Attempted conversion of the *tert*-butyl ester to its hydrochloride apparently cleaved the ester[2] directly to the free carboxyl group. Repeated recrystallization from 2-propanol gave a m.p. 183–185° dec.

Anal.—Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.43; N, 4.47 Found: C, 57.59; H, 6.52; N, 4.49.

o-Disubstituted Alkylaminopropoxybenzoic Acid Hydrochlorides—*Methyl* o-*3-Bromopropoxybenzoate* (*XXIII*)—To 152 g. (1 mole) methyl salicylate there was added a freshly prepared solution of 23.0 g. (1 mole) Na in 400 ml. absolute methanol. After the addition of 487 g. (2.4 moles) of 1,3-dibromopropane, 300 ml. xylene, and 100 ml. dimethylformamide, the methanol was distilled off and the remaining mixture refluxed 14 hr. Following workup with water, the mixture was washed with 5% NaOH, saturated NaCl, and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave 118 g. (43%) of an oil, b.p. 135–136° (1.2 mm.), n_D^{25} 1.5381, d_4^{25} 1.363.

Methyl o-*3-Diethylaminopropoxybenzoate* (*XXIV*)—*Method A*—To 13.65 g. (0.05 mole) XXIII dissolved in absolute ether there was added 7.31 g. (0.10 mole) diethylamine and the mixture refluxed 18 hr. Filtration of the precipitate, followed by removal of solvent gave 8.3 g. (62.7%) of an oil, b.p. 120–124° (2 mm.), n_D^{30} 1.5094. Treatment with ethereal HCl gave the hydrochloride, m.p. 85–86° (ethyl acetate–2-propanol).

Method B—To a suspension of 0.25 mole of sodium methyl salicylate (prepared as above) in 250 ml. of toluene there was added 37.2 g. (0.25 mole) of 3-diethylaminopropyl chloride and the mixture refluxed 20 hr. Workup as above afforded 14.2 g. (22%) XXIV, b.p. 140–145° (2.5 mm.), n_D^{30} 1.5038. The hydrochloride melted at 86–88°. A mixed melting point with the product obtained by Method A gave no depression. The IR spectra of both salts were identical.

Anal.—Calcd. for $C_{15}H_{24}ClNO_3$: C, 59.69; H, 8.02. Found: C, 59.79, H, 8.08.

o-*3-Diethylaminopropoxybenzoic Acid Hydrochloride* (*XXV*)—Refluxing 10.9 g. (0.0361 mole) XXIV with 5 ml. concentrated HCl and 40 ml. H_2O for 4 hr. gave, after evaporation of the solvent *in vacuo*, an oil. Cooling and repeated scratching with absolute ether afforded 9.1 g. (88%) of product. Three recrystallizations from ethyl acetate–2-propanol (50:50) gave a m.p. 135–137°.

Anal.—Calcd. for $C_{14}H_{22}ClNO_3$: C, 58.43; H, 7.71. Found: C, 58.19; H, 7.68.

Additional analogs of XXIV and XXV were similarly prepared and are listed in Table II.

PHARMACOLOGY

Analgetic screening was performed using the modified bradykinin induced writhing test in mice (12). The compounds were administered at doses equivalent to the ED_{50}[3] of aspirin, on a molecular weight basis, in a volume of 10 ml./kg. Ten mice per group were used for each compound and three groups of controls received the appropriate vehicle. Compounds XI, XV, XVI, XX, XXI, XXII,

[2] Cwalina and Gringauz (*Reference 3*) have shown the ease with which similar *tert*-butyl esters are cleaved under analogous conditions.

[3] The dose which produces analgesia in 50% of the animals tested.

and XXV were tested. Only XI exhibited any activity. When compared to aspirin this activity was insignificant.

Local anesthetic activity was assayed as the ability of the test agent to inhibit the blink reflex in the rabbit when the cornea was lightly stimulated. Butacaine sulfate (Butyn sulfate) was used as a control local anesthetic. Compounds XI, XV, XVI, XX, and XXI were tested and found to have no local anesthetic activity.

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COMMUNICATIONS

Evaluation of an Improved Heidelberg Telemetry Capsule for the Study of Antacids

Keyphrases ☐ Heidelberg FM-transmitting capsule—evaluation ☐ Gastric function assessment—Heidelberg telemetry capsule, evaluation

Sir:

Development of a telemetry system employing the Heidelberg FM-transmitting capsule has provided a convenient methodological approach to the clinical assessment of normal gastric function, as well as disease- and drug-induced alterations in gastric activity. The Heidelberg capsule, while elegant in concept, has been found lacking in dependability, a defect related possibly to transmitter construction. One factor involved in the lack of reliability may have been the relatively large hydrogen-ion sensor that permitted accumulation of particulate matter (*e.g.*, antacids) and mucous debris, thus interfering with normal operation. Furthermore, a relatively high percentage of the capsules did not exhibit a linear response throughout the functional range of pH 1 to 7 during *in vitro* standardization (1).

A modified Heidelberg probe,[1] having a smaller hydrogen-ion sensitive area, has recently been made available. These redesigned telemetry capsules have demonstrated a high degree of *in vitro* reliability with regard to linearity of response in the workable pH range of 1 to 7. The purpose of this study was to evaluate the *in vivo* performance of this modified device.

A FM-signal receiving unit,[1] in belt form, was positioned externally over the stomach area of healthy adult human subjects and connected to a recorder for continuous monitoring of transmitted pH values. Throughout the experimental period the subjects sat erect in an arm chair. Each telemetry capsule was activated by saturation of the hydrogen-ion sensitive end-plate with 0.9% sodium chloride solution, and calibrated in Beckman buffer solutions of pH 2 and 7 at 37°. The capsule was swallowed by the fasted subject, and gastric pH was monitored during the subsequent 50-min. period. After recording baseline pH values (3 to 10 min.), a specified dose of one of four commercial antacid preparations (designated A, B, C, and D) was administered with 30 ml. of water at room temperature: antacid A, 22 ml., suspension; B, 22 ml., suspension; C, 5 ml., suspension; D, two tablets. Each antacid preparation contained aluminum and magnesium hydroxides; formulation C also contained magnesium carbonate and methyl polysiloxane.

The apparent onset and duration of gastric acid buffering activity following administration of the three liquid and one solid antacid formulations are reported in Table I.

Although all of the "improved" Heidelberg capsules were apparently operative, as determined by *in vitro* calibration in buffer solutions and recording of pH signal immediately after swallowing the device, in approximately 14% of the trials (5 of 35 experiments) the anticipated elevation of gastric pH after administration of antacid was not perceived. In 86% of the trials the onset of buffering activity (*i.e.*, elevation of gastric pH above 3.0) following administration of antacid was

[1] Medintron Corp. of America, New York, N. Y.