EXPERIMENTAL[1]

***N*-(2,3,4,5,6-Pentafluorobenzyloxy)phthalimide**—A mixture of 25 g (0.0957 mole) of 2,3,4,5,6-pentafluorobenzyl bromide, 15.6 g (0.0957 mole) of *N*-hydroxyphthalimide, 10.1 g (0.1 mole) of triethylamine, and 150 ml of dimethylformamide was stirred at room temperature for 19 hr and then on a steam bath for 2 hr. The majority of the solvent was removed under reduced pressure.

A solution of the residual material in methylene chloride was washed with 10% sodium carbonate solution and dried over anhydrous magnesium sulfate. The solvent was evaporated. Crystallization of the residue from acetone–hexane gave 27.4 g (83%) of buff crystals, mp 140–142°. An analytical sample was prepared by recrystallizing a portion from acetone–hexane, and buff crystals, mp 141–143°, were obtained.

Anal.—Calc. for $C_{15}H_6F_5NO_3$: C, 52.49; H, 1.76; F, 27.68. Found: C, 52.63; H, 1.76; F, 27.99.

***O*-(2,3,4,5,6-Pentafluorobenzyl)hydroxylamine Hydrochloride**—Fifteen grams (0.295 mole) of hydrazine hydrate was added to a suspension of 51.5 g (0.15 mole) of *N*-(2,3,4,5,6-pentafluorobenzyloxy)phthalimide in 87 ml of dimethylformamide and 870 ml of methanol at 60°. The mixture was stirred at ambient temperature for 3 hr and was then acidified to pH 2 by the addition of 2 *N* hydrochloric acid. The phthalylhydrazide was removed by filtration, and the filtrate was evaporated to dryness. The residue was treated with 200 ml of 2 *N* sodium hydroxide solution and extracted with ether (3 × 100 ml).

The combined ether extracts were dried over anhydrous magnesium sulfate, and anhydrous hydrogen chloride was bubbled through the ether solution. The solid which separated was collected by filtration, giving 31.1 g. Crystallization from ethanol gave 21.2 g, and an additional 5.1 g was obtained by concentrating the filtrate. The combined solids were recrystallized from ethanol, giving 20.4 g of white plates, mp 215° (sublimes[2]). An additional 4.2 g of white plates, mp 215° (sublimes[2]), was obtained by concentrating the filtrate. The total yield was 24.6 g (66%).

Anal.—Calc. for $C_7H_4F_5NO{\cdot}HCl$: C, 33.68; H, 2.02; Cl, 14.21; F, 38.06. Found: C, 33.77; H, 2.24; Cl, 14.29; F, 37.38.

[1] Melting points (Thomas Hoover apparatus) are corrected. The IR spectra were recorded on a Perkin-Elmer 241 spectrophotometer. NMR spectra were taken on a Varian A60 instrument. Mass spectra were recorded on a Consolidated Electrodynamics Corp. 21-110B mass spectrometer. The compounds were subjected to IR, NMR, and mass spectrometry, and the results were consistent with structures assigned.

[2] Drying the compound under high vacuum at elevated temperature will result in loss by sublimation.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1975, from the *Fertility Research Department, The Upjohn Company, Kalamazoo, MI 49001*

Accepted for publication June 25, 1975.

The author thanks D. J. Williams for technical assistance and the Physical and Analytical Chemistry Research Department of The Upjohn Co. for supplying analytical data.

New Compounds: Derivatives of Methyl 2-Aminoacetyl-4,5-dimethoxyphenylacetate

P. CATSOULACOS

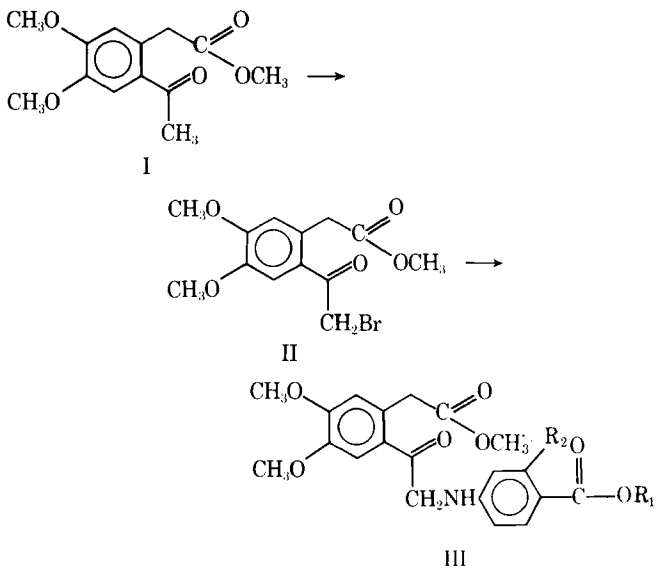
Abstract □ Methyl 2-bromoacetyl-4,5-dimethoxyphenylacetate was prepared by reacting cupric bromide with methyl 2-acetyl-4,5-dimethoxyphenylacetate. Aminoacetyl derivatives formed on condensation of substituted *p*-aminobenzoic esters with the bromoacetyl derivative. Some prepared compounds were tested for local anesthetic and anti-inflammatory activities.

Keyphrases □ 2-Aminoacetyl-4,5-dimethoxyphenylacetate derivatives—synthesized, evaluated for local anesthetic and anti-inflammatory activity □ Anesthetics, local, potential—derivatives of 2-aminoacetyl-4,5-dimethoxyphenylacetate synthesized, evaluated □ Anti-inflammatory agents, potential—derivatives of 2-aminoacetyl-4,5-dimethoxyphenylacetate synthesized, evaluated

In view of the importance of the local anaesthetic activity of α-aminoketone derivatives (1–3), it was decided to condense methyl 2-bromoacetyl-4,5-dimethoxyphenylacetate with esters of *p*-aminobenzoic acid and *p*-aminosalicylic acid.

DISCUSSION

Methyl 2-acetyl-4,5-dimethoxyphenylacetate (I) (4) was halogenated with cupric bromide (5) to give the corresponding bromoacetyl derivative (II) in a 50% yield. Treatment of II with methyl and ethyl esters of *p*-aminobenzoic and *p*-aminosalicylic acid produced the aminoacetyl compounds (III) in good yields (Scheme I).



Scheme I

Table I—Anti-Inflammatory Evaluation of Two Derivatives of Methyl 2-Aminoacetyl-4,5-dimethoxyphenylacetate

Compound	Concentration, *M*	Inhibition, %
III*b*	5.4×10^{-6}	8
	5.1×10^{-7}	5
III*c*	1.6×10^{-5}	6
	1.6×10^{-6}	4

Table II—Physical Data of Methyl 2-Aminoacetyl-4,5-dimethoxyphenylacetate Derivatives

Compound	R_1	R_2	Yield, %	Melting Point	Recrystallization Solvent	Formula	Analysis, %	Calc.	Found
III*a*	CH_3	H	73	164–166°	Ethyl acetate	$C_{21}H_{23}NO_7$	C	62.84	62.95
							H	5.73	5.91
							N	3.49	3.48
III*b*	C_2H_5	H	79	154–155°	Ethyl acetate–hexane	$C_{22}H_{25}NO_7$	C	63.59	63.70
							H	6.07	6.10
							N	3.38	3.52
III*c*	CH_3	OH	63	184–186°	Chloroform–methanol	$C_{21}H_{23}NO_8$	C	60.42	60.54
							H	5.56	5.71
							N	3.36	3.43
III*d*	C_2H_5	OH	70	180–182°	Chloroform–methanol	$C_{22}H_{25}NO_8$	C	61.24	61.80
							H	5.84	6.20
							N	3.25	3.30

Compound IIIc, as its hydrochloride salt, was tested for local anesthetic activity in the guinea pig cornea and showed appreciable activity at a 0.5% (w/v) concentration, possessing an average activity of 40 min.

Compounds III*b* and III*c* were also tested *in vitro* for anti-inflammatory activity using the Tomlinson *et al.* (6) method (Table I).

EXPERIMENTAL[1]

Methyl 2-Bromoacetyl-4,5-dimethoxyphenylacetate (II)—Methyl 2-acetyl-4,5-dimethoxyphenylacetate (I), 50.4 g (0.2 mole), and cupric bromide, 89.4 g (0.4 mole), were dissolved in 1 liter of methanol, and the solution was heated under reflux for 3 hr. During this time, a white precipitate formed and the solution lightened in color. The reaction mixture, after filtration, was evaporated *in vacuo* to a paste. The paste was dissolved in chloroform.

The organic layer was washed with water, dried over sodium sulfate, and evaporated to yield a crystalline compound. Crystallization from ether gave 33.1 g (50%) of II, mp 112–114°; IR: ν_{max} 1735 ($COOCH_3$) and 1690 ($COCH_2Br$) cm^{-1}; NMR: τ 2.58 and 3.15 (two aromatic protons), 5.5 ($COCH_2Br$), 6 ($2CH_3O$), 6.05 (CH_2COOCH_3), and 6.25 ($COOCH_3$).

Anal.—Calc. for $C_{13}H_{15}BrO_5$: C, 47.13; H, 4.53. Found: C, 47.40; H, 4.62.

Methyl 2-Aminoacetyl-4,5-dimethoxyphenylacetate Derivatives—To a solution of II (3.31 g, 10 mmoles) in 150 ml of anhydrous benzene was added *p*-aminobenzoic or *p*-aminosalicylic ester (20 mmoles), and the mixture was heated under reflux for 5 hr. The solvent was evaporated under reduced pressure, and the residue was dissolved in chloroform. The organic layer was washed several times with water and dried over magnesium sulfate. After evaporation of the solvent, the residue was crystallized from the appropriate solvent.

IR and NMR spectra of the reported compounds were as expected. Physical data for the products obtained are given in Table II.

[1] Melting points were determined on a Gallenkamp melting-point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 521 instrument in potassium bromide. NMR spectra were determined with a Varian Associates A-60 instrument, using deuterochloroform as the solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, Nuclear Research Center "Demokritos."

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 25, 1975, from the *Greek Atomic Energy Commission, Nuclear Research Center "Demokritos," Chemistry Department, Athens, Greece.*

Accepted for publication July 3, 1975.