Table I—Fluorescence Method for Nitrofurantoin Determination (Relative Fluorescence Intensity per Microgram [a])

Sample[b]	Trial[c]	Nitrofurantoin Reacted, μg							
		0.25	0.50	0.75	1.00	5.00	10.00	Mean[d]	SD
Water (1.0 ml)	1	124.8	100.7	99.9	100.3	100.1	62.7	106.4	10.7
	2	95.1	100.3	99.1	94.1	109.2	90.0	99.6	6.0
	3	113.3	93.6	93.9	92.9	88.6	72.5	96.5	9.7
Rabbit plasma (0.1 ml)	1	109.5	95.1	95.8	108.3	94.1	84.0	100.6	7.6
	2	109.5	119.5	107.8	119.3	115.9	107.5	114.4	5.5
	3	75.9	88.3	79.5	85.0	84.5	64.8	82.6	4.9
Rabbit plasma (0.5 ml)	1				87.3				
	2				99.0				
	3				102.5				

[a] Blank values were subtracted. [b] Blank values for water and 0.1 and 0.5 ml of rabbit plasma were 7.8, 10.6, and 27.6 relative fluorescence intensity units, respectively. [c] $n = 3$. [d] The mean and standard deviation were calculated between 0.25 and 5 μg since the 10-μg values seemed unreliable.

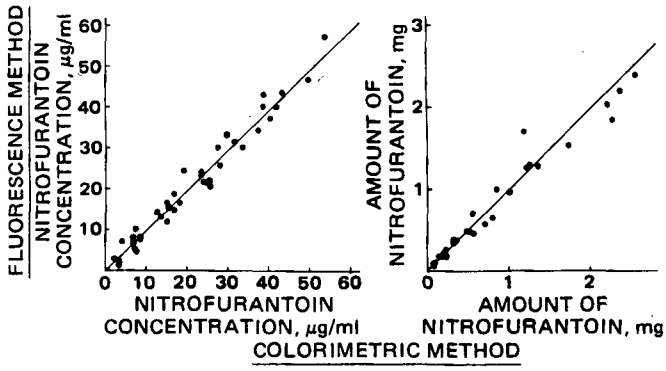


Figure 1—*Comparison of values obtained by the fluorescence and colorimetric methods for the determination of I in plasma (left) and urine (right).*

three rabbits dosed with I were assayed by the fluorescence and colorimetric methods. Figure 1 shows that good correlations were obtained for the values determined by the two methods in both plasma ($y = 0.980x + 0.125$, $r = 0.982$) and urine ($y = 0.980x - 0.026$, $r = 0.999$).

The fluorescence method for I is 10 times more sensitive than the colorimetric method, and it appears to be specific for I. It should be useful for the determination of microamounts of the drug for pharmacokinetic studies and other purposes.

REFERENCES

(1) J. D. Conklin and R. D. Hollifield, *Clin. Chem.*, 11, 925 (1965).
(2) *Ibid.*, 12, 690 (1966).
(3) W. D. Manson and B. Sandmann, *J. Pharm. Sci.*, 65, 599 (1976).
(4) T. Uno and H. Taniguchi, *Jpn. Anal.*, 21, 76 (1972).
(5) S. Nakano, H. Taniguchi, and T. Furuhashi, *Yakugaku Zasshi*, 92, 411 (1972).
(6) H. Taniguchi, K. Mikoshiba, K. Tsuge, and S. Nakano, *ibid.*, 94, 717 (1974).
(7) J. A. Buzard, D. M. Vrablic, and M. F. Paul, *Antibiot. Chemother.*, 6, 702 (1956).

ACKNOWLEDGMENTS

The authors thank Professor T. Miyasaka and Dr. H. Arai, Showa University, for valuable advice.

Phenylfurans IV: Spasmolytic 3-Diethylamino-2,2-(dimethyl)propyl Esters of 5-Substituted Phenyl-2-furancarboxylic Acids

HOMER A. BURCH *x, RONALD E. WHITE *, GEORGE C. WRIGHT *, and MARVIN M. GOLDENBERG ‡

Received February 15, 1979, from the **Chemical Research Division and the* ‡*Biological Research Division, Norwich-Eaton Pharmaceuticals, Division of Morton-Norwich Products, Inc., Norwich, NY 13815.* Accepted for publication August 1, 1979.

Abstract □ A series of 3-diethylamino-2,2-(dimethyl)propyl 5-substituted phenyl-2-furancarboxylates was prepared and found to be pharmacologically active *in vitro* as GI tract nonanticholinergic smooth muscle spasmolytic agents. One of the more active compounds in the series contained the 5-(4-nitrophenyl) group.

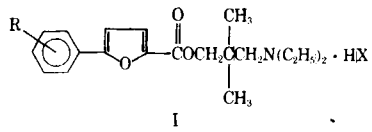
Keyphrases □ Phenylfurans—3-diethylamino -2,2- (dimethyl)propyl esters of 5-substituted phenyl-2-furancarboxylic acids, synthesis, potential use as spasmolytic agents □ Spasmolytic agents—3-diethylamino-2,2-(dimethyl)propyl esters of 5-substituted phenyl-2-furancarboxylic acids, synthesis and pharmacological properties

The syntheses and pharmacological properties of 1- and 3-amino- and 1-amino-5-hydroxy-2,4-imidazolidinedione derivatives of 5-phenyl-2-furancarboxaldehydes have been described (1–3). This paper discusses the synthesis and *in vitro* pharmacological evaluation of a series of esters (I) derived from 3-diethylamino-2,2-(dimethyl)propanol (III) and 5-phenyl-2-furancarboxylic acids (II) (4). These compounds have potential use as spasmolytic agents (5).

DISCUSSION

Synthesis—The key intermediates in the synthesis of the esters were the appropriately substituted 5-phenyl-2-furancarboxylic acids (II). The acids generally were obtained in modest yields through the coupling of a substituted phenyldiazonium salt with 2-furancarboxylic acid. Several acids were prepared by oxidation of the corresponding 5-phenyl-2-fur-

0022-3549/80/0100-0107$01.00/0



I

Table I—Evaluation of 5-Substituted Phenyl-2-furancarboxylic Esters

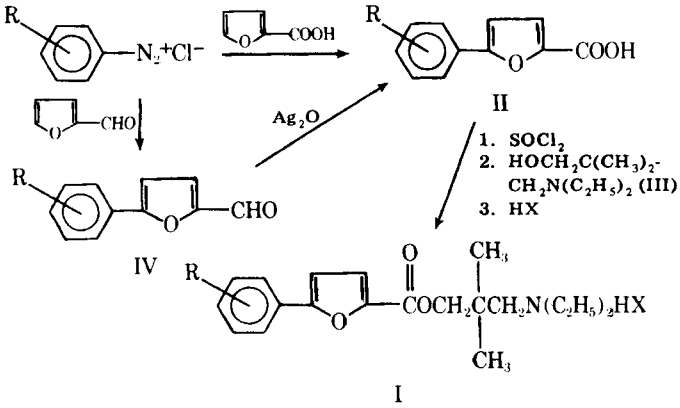
Compound	R	Melting Point	Yield, %	Crystallization Solvent[a]	Formula		Analysis, % Calc.	Analysis, % Found	Concentration, μg/ml	Inhibitory Action on Ileal Contractions *In Vitro*[b]	Acetylcholine-Induced Contractions, % of control[c]
Ia	4-F	134–138°	49	I	$C_{20}H_{26}FNO_3 \cdot HCl$	C	62.58	62.55	0.3	0.7	90
						H	7.09	7.02	1	0.09	93
						N	3.65	3.56			
Ib	4-Cl	139–143°	53	E	$C_{20}H_{26}ClNO_3 \cdot HCl$	C	60.00	60.03	1	1.4	119
						H	6.80	6.84	3	0.01	80
						N	3.50	3.45			
Ic	4-Br	154–157°	25.5	A	$C_{20}H_{26}BrNO_3 \cdot HCl$	C	54.01	54.16	1	1.7	93
						H	6.12	6.23	3	0.05	105
						N	3.15	3.02			
Id	2,3-Cl_2	168–175°	82	I	$C_{20}H_{25}Cl_2NO_3 \cdot HCl$	C	55.25	55.06	1	0.7	57
						H	6.03	5.94	10	0.01[d]	96
						N	3.22	3.13			
Ie	3,4-Cl_2	136–138°	41	I	$C_{20}H_{25}Cl_2NO_3 \cdot HCl$	C	55.25	55.42	1	2.1	103
						H	6.03	6.06	3	0.006	95
						N	3.22	3.14			
If	4-NO_2	179–182°	45	E	$C_{20}H_{26}N_2O_5 \cdot HCl$	C	58.46	58.51	1	0.1	100
						H	6.62	6.84	3	0.01	100
						N	6.82	6.96			
Ig	2-NO_2, 4-CH_3	146–148°	58	I	$C_{21}H_{28}N_2O_5 \cdot HCl$	C	59.36	59.38	1	1.1	107
						H	6.88	7.04	10	0.001	84
						N	6.59	6.49			
Ih	3-CF_3	119–123°	39	I	$C_{21}H_{26}F_3NO_3 \cdot HCl$	C	58.13	58.37	1	0.9	108
						H	6.27	6.33	3	0.1	92
						N	3.23	3.19			
Ii	4-CF_3	162–164°	65	EA	$C_{21}H_{26}F_3NO_3 \cdot HCl$	C	58.13	58.23	1	0.7	57
						H	6.27	6.50	10	0.01[d]	96
						N	3.23	3.15			
Ij	3,4-F_2	133–135°	47	EA–A	$C_{20}H_{25}F_2NO_3 \cdot HCl \cdot 1/2H_2O$[e]	C	58.74	58.60	1	0.3	117
						H	6.66	6.50	3	—[f]	101
						N	3.43	3.37			
Ik	3-CH_3O	138–140°	52	E	$C_{21}H_{29}NO_4 \cdot C_4H_4O_4$	C	63.14	63.17	1	0.5	93
						H	6.99	7.14	3	0.7	99
						N	2.95	3.01			
Il	4-CH_3O	133–136°	46	EA	$C_{21}H_{29}NO_4 \cdot HCl$	C	63.71	63.40	1	0.4	86
						H	7.64	7.65	3	0.008	102
						N	3.54	3.56			
Im	H	113–115°	75	BP	$C_{20}H_{27}NO_3 \cdot HCl$	C	65.65	65.45	1	0.7	108
						H	7.71	7.74	3	0.09	94
						N	3.83	3.85			

[a] E = ethanol, I = 2-propanol, A = acetone, BP = benzene–petroleum ether, and EA = ethyl acetate. [b] As determined by the ratio of two frequencies of electrical stimulation, one before and one after the drug, that caused equal muscle contraction (8). The estimation of inhibition is predicted on the lines representing contractions (at frequencies of electrical stimulation of 0.3, 1, 3, and 10 Hz) being parallel before and after drug administration. Two to 10 ileal strips were used to ascertain the activity of each compound. [c] Concentration of acetylcholine in the bath was 0.01 μg/ml. [d] The estimate of activity given in this case applied only to a frequency of 1 Hz and is different at other frequencies of stimulation because the lines are nonparallel. [e] Water by Karl Fischer method: calc., 2.20; found, 2.0%. [f] The frequency–response lines are nonparallel, and values do not apply.

ancarboxaldehydes (IV). Evidence for arylation of the furan ring at the 5-position was presented previously (6).

Subsequent ester formation occurred readily *via* the reaction of the acid chloride of II with III (Scheme I).

Pharmacology—This series of compounds was evaluated to discover



I

Scheme I

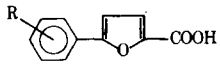
nonanticholinergic therapeutic agents capable of exerting a spasmolytic effect through inhibition of contraction of the small and large intestines induced by motor nerve electrical stimulation. The activity of each compound was determined initially by using the isolated rabbit ileum following transmural electrical- and acetylcholine-induced excitation of the smooth muscle (7).

A compound's efficacy was judged by whether it caused parallel displacement or depression of the contractile responses of the isolated rabbit ileum evoked by increasing electrical stimulation frequencies. An inactive compound did not shift the frequency–response line. If the contractile responses at any particular stimulation frequency were equal before and after drug administration, a numerical value of 1 was assigned to describe the lack of response change. An active inhibitory compound had a value of <1. A nonspecific depression of contractile responses following the various stimulation frequencies elicited a nonparallel shift of these responses.

The results of *in vitro* pharmacological testing are found in Table I. When tested at 1 μg/ml, six esters (Ia, If, and Ii–Il) displaced contractile responses of the isolated rabbit ileum. The estimation of inhibitory action for these compounds was ≤0.7. Increasing the concentration of each agent to 3 or 10 μg/ml shifted the frequency–response curves and caused profound inhibition by nearly all of the esters.

Another criterion for evaluating activity was the ability of the compound not to exhibit substantial antagonism of acetylcholine-induced

Table II—5-Substituted Phenyl-2-furancarboxylic Acids



Compound	R	Melting Point	Synthetic Method[a]	Yield, %	Crystallization Solvent[b]	Formula	Analysis, %	Calc.	Found
II*a*	4-F	199–202°	A	13.9	A	$C_{11}H_7FO_3$	C	64.08	64.10
							H	3.42	3.48
II*b*	4-Cl	195–197°	A	34	A	$C_{11}H_7ClO_3$	C	59.35	59.36
							H	3.17	3.13
II*c*	4-Br	205–206°	A	31	B	$C_{11}H_7BrO_3$	C	49.47	49.54
							H	2.64	2.60
							Br	29.29	30.19
II*d*	2,3-Cl_2	259–261°	A	35.9	A	$C_{11}H_6Cl_2O_3$	C	51.39	51.36
							H	2.35	2.38
							Cl	27.58	27.37
II*e*	3,4-Cl_2	234–238°	A	44.4	A	$C_{11}H_6Cl_2O_3$	C	51.39	51.54
							H	2.35	2.41
II*f*	4-NO_2	255–257°	A	56	C	$C_{11}H_7NO_5$	C	56.66	56.86
							H	3.03	3.09
							N	5.67	5.91
II*g*	2-NO_2, 4-CH_3	197–200°	A	32.5	A	$C_{12}H_9NO_5$	C	58.30	58.04
							H	3.67	3.68
							N	5.67	5.59
II*h*	3-CF_3	208–210°	A	21.3	A	$C_{12}H_7F_3O_3$	C	56.26	56.24
							H	2.75	2.84
II*i*	4-CH_3	180–183°	B	20	D	$C_{12}H_{10}O_3$	C	56.26	55.92
							H	2.75	2.80
II*j*	3,4-F_2	212–214°	B	47	D	$C_{11}H_6F_2O_3$	C	58.94	58.55
							H	2.70	2.76
II*k*	3-CH_3O	163–166°	B	25	A	$C_{12}H_{10}O_4$	C	66.05	65.93
							H	4.62	4.67
II*l*	4-CH_3O	172–176°	B	32	D	$C_{12}H_{10}O_4$	C	66.05	66.38
							H	4.62	4.56
II*m*	H	151–152°	B	78	E	$C_{11}H_8O_3$	C	70.21	69.92
							H	4.29	4.27

[a] A = arylation of 2-furancarboxylic acid, and B = oxidation of 5-substituted phenyl-2-furancarboxaldehyde. [b] A = acetone, B = acetonitrile, C = acetic acid, D = benzene, and E = ether.

contractions. All esters failed to cause a dose-related inhibition of acetylcholine-induced contractions.

These findings demonstrate this class of compounds to be pharmacologically active as GI tract nonanticholinergic smooth muscle spasmolytic agents. The spectra of pharmacological effectiveness of I*f* were reported elsewhere (8).

EXPERIMENTAL[1]

5-Substituted Phenyl-2-furancarboxylic Acids (II)—*Method A*—To the diazonium salt of 2,3-dichloroaniline (289 g, 1.78 moles) in a mixture of 400 ml of water and 900 ml of concentrated hydrochloric acid at 0° were added a solution of 2-furancarboxylic acid (184 g, 1.6 moles) in 660 ml of acetone and a solution of cupric chloride (40 g) in 80 ml of water. Cooling was necessary to keep the temperature below 35°. After the exothermic reaction ceased, the mixture was stored at room temperature for 2 days; it was then poured into 6 liters of water, and the resulting mixture was stirred for 2 hr. The crude II*d* was collected by filtration, washed with water, and dried at 60°. Purification was achieved by recrystallization.

Compounds II*a*–II*h* were prepared similarly from the appropriately substituted anilines.

Method B—A solution of silver nitrate (120 g, 0.71 mole) in 243 ml of water was added with stirring to a solution of sodium hydroxide (56 g, 1.4 moles) in 243 ml of water. 5-Phenyl-2-furancarboxyaldehyde (6) (63 g, 0.37 mole) was added in portions to the resulting brown mixture. The reaction mixture was stirred for 0.5 hr at room temperature and filtered, and the residue was washed with 500 ml of hot water. The chilled filtrate was acidified to pH 2 with concentrated hydrochloric acid. The product was collected by filtration, washed with water, and recrystallized. Compound II*m* was described previously as an oil, bp 120–122°/30 mm (9).

Compounds II*i*–II*l* were prepared similarly from the appropriately substituted 5-phenyl-2-furancarboxaldehydes.

The IR spectra of II showed broad carbonyl absorption (COOH) at 5.85–6.0 μm. Other pertinent data are summarized in Table II.

Procedure for 5-Substituted Phenyl-2-furancarboxaldehydes (IV)—Thirty minutes after the formation of the diazonium salt from the appropriately substituted aniline (1.0 mole), the mixture was gravity filtered; the filtrate was added to a mixture of 2-furancarboxaldehyde (123 g, 1.28 moles) in 200 ml of water. A solution of cupric chloride (46 g) in 200 ml of water was added. The resulting mixture was heated with stirring at 56° for 4 hr and then stirred overnight at room temperature.

The product was extracted with 1 liter of chloroform in portions. After the extracts were dried over anhydrous magnesium sulfate and charcoal, the product was isolated by filtration and evaporation under reduced pressure. The crude aldehydes were obtained in 9–40% yields and were used for Method B without further purification.

5-(4-Trifluoromethyl)phenyl-, 3,4-difluorophenyl-, 4-methoxyphenyl- (10), and 3-methoxyphenyl-2-furancarboxaldehydes were prepared in this manner.

3-Diethylamino-2,2-(dimethyl)propyl-5-(4-nitrophenyl) -2- furancarboxylate Hydrochloride (I*f*)—Acid II*f* (55 g, 0.24 mole) was added with rapid stirring at room temperature to 84 ml of thionyl chloride. The resulting mixture was heated until dissolution occurred (~45 min), refluxed for an additional 0.5 hr, and cooled. Excess thionyl chloride was evaporated under reduced pressure. The residue was taken up in 1.3 liters of dry benzene, and III (11) (38.5 g, 0.24 mole) was added. The resulting solution was heated under reflux for 3 hr, cooled, diluted with 750 ml of petroleum ether, and allowed to stand overnight.

After removal of the benzene–petroleum ether by decantation, the residue was suspended in 2 liters of water containing 4 ml of concentrated hydrochloric acid. The mixture was stirred for 0.5 hr, and the pH was adjusted to ~8 by the cautious addition of 200 ml of saturated aqueous sodium carbonate solution. The mixture was extracted with 2.1 liters of benzene in portions, and the extracts were dried over anhydrous magnesium sulfate. The benzene extracts were treated with an ethereal hydrogen chloride solution to pH 3, diluted with 800 ml of petroleum ether, and allowed to stand for 1 hr. After filtration and recrystallization of the residue, I*f* was obtained as colorless needles.

The remaining I esters were prepared similarly from the appropriately substituted II acids. Ester I*k* was isolated as the fumarate salt rather than as the hydrochloride salt as follows. The benzene extracts, containing the free base of I*k*, were evaporated to dryness under reduced pressure. The residue was dissolved in 2-propanol and treated with a 2-propanol solution of fumaric acid. After cooling, the precipitated I*f* was isolated by filtration; IR: 6.8 (I*a*–I*d* and I*f*–I*m*) and 6.9 (I*e*) (ester carbonyl) μm; NMR (dimethyl sulfoxide-d_6): I*f*: δ 0.78 [s, 6, $C(CH_3)_2$], 0.89 (t, 6, J = 7

[1] All melting points were determined using a hot-stage apparatus and are uncorrected.

Hz, CH_2CH_3), 2.74 [m, 6, $N(CH_2)_3$], 3.9 (s, 2, OCH_2), 7.06, 7.18 (doublets, J = 3.5 Hz, 2, 3,4-furan CH), 7.61, 7.89 (doublets, J = 9.0 Hz, 4, phenyl CH), and 10.8 (b, 1, HCl)

Other I esters had similar NMR spectra except for expected variations due to various phenyl substitutents. Other pertinent data are summarized in Table I.

The I esters were evaluated initially *in vitro* on the rabbit ileum as described previously (7). Each drug was dissolved in distilled water for administration.

REFERENCES

(1) H. R. Snyder, Jr., C. S. Davis, R. K. Bickerton, and R. P. Halliday, *J. Med. Chem.*, **10**, 807 (1967).

(2) T. J. Schwan and K. O. Ellis, *J. Pharm. Sci.*, **64**, 1047 (1975).

(3) R. L. White and T. J. Schwan, *ibid.*, **65**, 135 (1976).

(4) G. C. Wright, H. A. Burch, and M. M. Goldenberg, U.S. pat. 3,856,825 (Dec. 1974).

(5) C. M. Suter, "Medicinal Chemistry," vol. I, Wiley, New York, N.Y., pp. 151–220.

(6) C. S. Davis and G. S. Lougheed, *J. Heterocycl. Chem.*, **4**, 153 (1967).

(7) M. M. Goldenberg, *Arzneim.-Forsch.*, **26**, 341 (1976).

(8) M. M. Goldenberg, *Arch. Int. Pharmacodyn. Ther.*, **222**, 27 (1976).

(9) H. Akashi and R. Oda, *J. Chem. Soc. Jpn., Ind. Sect.*, **55**, 271 (1952); through *Chem. Abstr.*, **48**, 3953f (1954).

(10) *Ibid.*, **53**, 202 (1950); through *Chem. Abstr.*, **46**, 9312i (1952).

(11) K. Hayes and G. Drake, *J. Org. Chem.*, **15**, 873 (1950).

ACKNOWLEDGMENTS

F. Abbott, R. Burns, J. Clark, J. Curtis, P. Curtis, R. Finch, D. George, G. Gustin, C. Jeffrey, G. Lougheed, N. Miles, W. Smith, B. Stevenson, M. Tefft, and A. Winterstein are acknowledged for their technical assistance in the preparation, analysis, and biological evaluation of the compounds.

Simultaneous Quantitation of Acetaminophen, Aspirin, Caffeine, Codeine Phosphate, Phenacetin, and Salicylamide by High-Pressure Liquid Chromatography

V. DAS GUPTA

Received May 7, 1979, from the *Department of Pharmaceutics, College of Pharmacy, University of Houston, Houston, TX 77004.* Accepted for publication July 31, 1979.

Abstract □ A method for the simultaneous quantitation of acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide was developed. The method is based on reversed-phase high-pressure liquid chromatography with a mobile phase buffered with phosphate (pH 2.3). The procedure not only separated these six active ingredients but also salicylic acid, the major decomposition product of aspirin. The method gave excellent results for three commercial products and a synthetic mixture containing four active ingredients. Lowering the pH increased the retention time of some weak acids and decreased that of some weak bases. Only these changes in the retention times made the separation possible.

Keyphrases □ High-pressure liquid chromatography—simultaneous quantitation of acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide □ Acetaminophen—simultaneous quantitation with aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide, high-pressure liquid chromatography □ Aspirin—simultaneous quantitation with acetaminophen, caffeine, codeine phosphate, phenacetin, and salicylamide, high-pressure liquid chromatography □ Caffeine—simultaneous quantitation with acetaminophen, aspirin, codeine phosphate, phenacetin, and salicylamide, high-pressure liquid chromatography □ Codeine phosphate—simultaneous quantitation with acetaminophen, aspirin, caffeine, phenacetin, and salicylamide, high-pressure liquid chromatography □ Phenacetin—simultaneous quantitation with acetaminophen, aspirin, caffeine, codeine phosphate, and salicylamide, high-pressure liquid chromatography □ Salicylamide—simultaneous quantitation with acetaminophen, aspirin, caffeine, codeine phosphate, and phenacetin, high-pressure liquid chromatography

About 80 commercially available nonprescription drugs (1) contain one or more pain relievers such as acetaminophen, aspirin, phenacetin, and salicylamide. Many of them also contain caffeine and buffering agents such as aluminum hydroxide and magnesium hydroxide (1). At least two commercial products contain a combination of acetaminophen, aspirin, caffeine, and salicylamide (1). Other products contain a combination of acetaminophen or aspirin, caffeine, phenacetin, and salicylamide (1). Many prescription drugs contain codeine phosphate, usually combined with aspirin, caffeine, and phenacetin.

BACKGROUND

The simultaneous quantitation of these ingredients is difficult. The NF methods (2) for the quantitation of aspirin, caffeine, codeine phosphate, and phenacetin in combination are tedious and time consuming. The colorimetric (3) and fluorometric (4) methods for aspirin quantitation are based on its hydrolysis to salicylic acid. Since salicylic acid is the principal decomposition product of aspirin, these methods are not specific. The GLC method (5) for aspirin quantitation is more specific but requires derivatization, which takes ~1 hr and can be complicated by the hydrolysis of aspirin to salicylic acid.

Previous investigators (6) reported that aspirin-containing combinations were difficult to chromatograph using nonpolar solvents and normal-phase chromatography. They preferred (7) paired-ion chromatography using the tetrabutylammonium ion to separate aspirin from muscle relaxants. They did not apply this method to separate combinations of the various pain relievers mentioned.

An automated high-pressure liquid chromatographic (HPLC) method (8) for the quantitation of aspirin, caffeine, and phenacetin was reported. The investigators used a controlled pore glass support as the stationary column and 8% acetic acid in chloroform as the mobile phase. This method was not tried on other pain relievers or in the presence of codeine phosphate.

Another HPLC method (9) analyzed small aspirin quantities in plasma in the presence of large salicylic acid quantities. However, the salicylic acid quantity is very small and the aspirin quantity is high in the dosage forms.

One study (10) used macroporous poly(methyl methylacrylate) resin to assay aspirin. This method was tedious and complicated. Two columns and two solvents were used to analyze some pain reliever combinations.

The purposes of the present investigations were to: (*a*) develop a rapid

0022-3549/80/0100-0108$01.00/0