2,4,5-Trimethylpyrrole-3-carboxylic Acid Esters of Various Alkaloids

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2,4,5-Trimethylpyrrole-3-carboxylic acid esters of various hydroxy alkaloids, such as codeine (**2b**), ephedrine (**3b**), jervine (**4b**), scopoline (**5b**), and methyl reserpate (**6b**), were synthesized with trifluoroacetic anhydride in a mixed anhydride procedure mild enough to leave intact the acid-labile pyrrolecarboxylic acid as well as the alkaloid moieties. The esters were evaluated for analgesic activity and norepinephrine release. The scopoline ester **5b** showed activity in two analgesic assay systems. In the hot plate assay, **5b** (ED_{50} 6.0) was slightly more active than codeine.

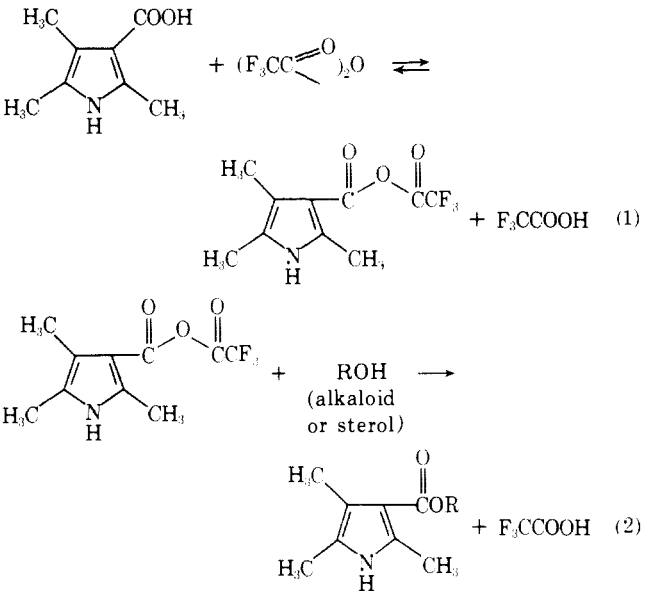
Batrachotoxin, a steroidal alkaloid obtained from the skin of the Colombian frog *Phyllobates aurotaenia*, is one of the most toxic substances known.[1,2] The venom selectively and irreversibly increases membrane permeability to sodium ions.[3,4] The toxicity of batrachotoxin is dependent upon the 2,4-dimethyl-3-carboxylate portion of the molecule, as shown by a 500-fold decrease in the activity of batrachotoxinin A in which this ester grouping is absent. A synthetic homolog of batrachotoxin containing a 2,4,5-trimethylpyrrole-3-carboxylate was found to be twice as active.[2] The effect of this trimethylpyrrolecarboxylic acid grouping upon esterification with various hydroxy alkaloids was of interest with regard to potentiation or modification of the activity of the parent alkaloids. In this preliminary study, some representative modified alkaloids were assayed for chemorelease of norepinephrine and analgesic activity (hot plate and Nilsen methods).

Results and Discussion

Chemistry. Several conventional esterification procedures were unsuccessful in providing the desired trimethylpyrrolecarboxylates of various hydroxy compounds. Attempts to convert pyrrolecarboxylic acids into acid chlorides with thionyl chloride or phosphorus pentachloride in chloroform gave dark-colored, intractable products in all cases. Reaction of the carboxylic acid with oxalyl chloride,[5,6] followed by addition of the hydroxy alkaloid or sterol to the acid chloride, gave no isolable esters. Also, the yields of the esters from the mixed anhydride derived from the pyrrolecarboxylic acid and ethyl chloroformate[2] were unsatisfactory for preparative purposes. Apparently, the success of this procedure depends on activation of the hydroxyl group by the β,γ unsaturation of the allylic hydroxyl as is present in batrachotoxinin A.

The preparation of the mixed anhydride of 2,4,5-trimethylpyrrole-3-carboxylic acid and trifluoroacetic anhydride was followed by infrared spectroscopy at various time intervals (see Experimental Section). The two strong ir bands of trifluoroacetic anhydride at 1890 and 1825 cm^{-1} disappeared immediately on mixing of the two reactants in carbon tetrachloride, with concomitant appearance of two bands of the mixed anhydride at 1785 and 1740 cm^{-1} (reaction 1). The slow decrease in the intensity of these latter carbonyl-stretching vibrations with time indicated the lability of this mixed anhydride. Furthermore, precipitation of authentic 2,4,5-trimethylpyrrole-3-carboxylic acid from solution after 12 min demonstrated the reversibility of the reaction.

Preliminary experiments with this mixed anhydride were carried out with cholesterol (1a). To the mixed anhydride generated *in situ* was added an equimolar amount of cholesterol (reaction 2). After a 15-min reaction period at room temperature, cholesterol 3-(2,4,5-trimethylpyrrole-3-carboxylate (**1b**) was formed in good yield in addition to a smaller amount of the trifluoroacetic acid ester of **1a**. No unreacted cholesterol was detected.



Next, pyrrole esters of various hydroxy alkaloids were synthesized (Table I). To illustrate the general reaction, 2,4,5-trimethylpyrrole-3-carboxylic acid reacts with an equimolar amount of trifluoroacetic anhydride in dry benzene for a period of 3 min at room temperature. To the mixed anhydride was then added an equimolar amount of, *e.g.*, codeine (**2a**), and the reaction mixture placed in a 50° bath for 1 hr. Evaporation of the solvent from the mixture, followed by column chromatography on silica gel and recrystallization, gave the desired codeine 6-(2,4.5-trimethylpyrrole-3-carboxylate) (**2b**) in 68% yield.

Similar reaction conditions (Table I) gave the 2,4,5-trimethylpyrrole-3-carboxylic acid esters of ephedrine (**3b**), jervine (**4b**), scopoline (**5b**), and methyl reserpate (**6b**) in moderate to excellent yields (Chart I).

Esterification of the low molecular weight amino alcohol, 2-diethylaminoethanol, with the mixed anhydride under the same mild reaction conditions gave numerous, dark-colored intractable products. Also, the reaction with veracevine, which is obtained by mild base hydrolysis of veratridine and which contains seven hydroxyl groups (three are normally acylable), was not selective, yielding a complex mixture of compounds which were not fully characterized.

The mild esterification of alcohols *via* the pyrrole-3-carboxylictrifluoroacetic acid anhydride represents a preparatively useful synthesis. Less gentle methods fail because pyrrolecarboxylic acids are notorious for their lability to oxygen and to acid-catalyzed polymerization reactions.[7] These mild esterification methods are suitable for sensitive alkaloids and other labile natural products.

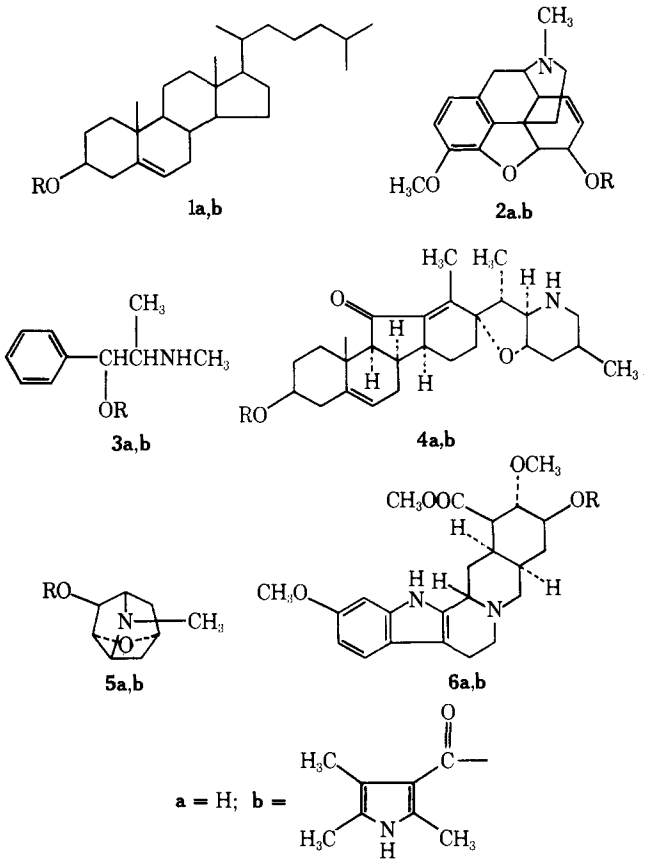
The use of trifluoroacetic anhydride in promoting esterifications has generally been limited to simple aliphatic and aromatic carboxylic acids.[8,9] However, the reagent

Table I. Esterifications with 2,4,5-Trimethylpyrrole-3-carboxylic Acid

Hydroxy compd No.	Hydroxy compd mmol	Pyrrole acid, mmol	Trifluoroacetic anhydride, mmol	Reaction 1,[a] time, min	Reaction 2 Time, min	Reaction 2 Temp, °C	Yield of ester, %
1a	1.0	1.0	2.0	15	15	25	
2a	1.5	1.5	1.5	3	30	46	68
3a	1.5	1.5	1.5	2	75	50	90
4a	1.0	1.0	2.0	7.5	90	50	88
5a	2.0	2.0	2.1	4	40	40	46
6a	1.0	1.0	2.0	15	15	25	70

[a] These reactions were all carried out at room temperature.

Chart I



has been used in the esterification of the antibiotic chloramphenicol with stearic acid[10] and more recently in the esterification of hindered aliphatic and aromatic carboxylic acids.[11]

The formation of the mixed anhydride (reaction 1) *in situ* with equimolar or 1 *M* excess trifluoroacetic anhydride proceeded rapidly (2–15 min) at room temperature (Table I). The kinetic study (ir) demonstrated the reaction to be reversible. Free 2,4,5-trimethylpyrrole-3-carboxylic acid could be precipitated from solution after 12 min. Due to the instability of the mixed anhydride, it was advantageous to add the hydroxy compound (reaction 2) to the mixed anhydride within a short time interval. The time for reaction 2 is not as critical (from 15 to 90 min) and the reaction proceeds adequately at room or slightly elevated temperatures. Pyrrole esters of jervine (**4b**), scopoline (**5b**), and methyl reserpate (**6b**) formed salts with trifluoroacetic acid (K_a = 0.58) generated *in situ* from reactions 1 and 2.

Table II. Chemorelease of Cardiac [^{3}H]Norepinephrine

Compd[a]	Dose, mg/kg	Release, % control[b]	ED_{50}, mg/kg[c]
2a	20	103.0 ± 3.6	
Codeine 6-acetate	20	107.8 ± 6.2	
2b	20	98.5 ± 5.9	
3a	20	61.0 ± 8.6	49.8
	40	56.0 ± 3.8	
3b	20	110.0 ± 10.2	>640
	80	95.0 ± 8.7	
	160	81.0 ± 12.8	
4a	20	103.0 ± 5.6	
4b	20	97.6 ± 8.6	
5a	20	101.0 ± 5.0	
5b	20	105.0 ± 2.6	
Reserpine	5	19.6 ± 4.5	0.19
6a	5	40.2 ± 8.6	2.5
6b	5	31.8 ± 4.6	1.1
2,4,5-Trimethylpyrrole-3-carboxylic acid	20	100.1 ± 2.8	
2,4,5-Trimethylpyrrole-3-carboxylic acid ethyl ester	20	97.0 ± 3.2	

[a] Compounds were administered subcutaneously as water-soluble salts or in 50% DMSO. [b] Control [^{3}H]norepinephrine was 23,000 cpm per heart ± S.E.M. of 980. Release is expressed as the mean ± S.E.M. of per cent control of 5–20 individual mice. [c] ED_{50} values were derived graphically from dose–response curves from 20 to 80% of control.

Table III. Analgesic Activity

Compd[a]	ED_{50} ± S.E.[b] Hot plate	ED_{50} ± S.E.[b] Nilsen
2a	7.5 ± 0.8	4.5 ± 3.1
2b	20	>40
4a	>50	
4b	>50	
5a	Inactive	Inactive
5b	6.0 ± 1.7	28.9 ± 9.4

[a] Administered subcutaneously as a water-soluble salt or in 50% DMSO. [b] ED_{50} were derived from dose–response curves by probit analysis and expressed the standard error limits of the dose.

Pharmacological Results. The 2,4,5-trimethylpyrrole-3-carboxylic acid esters and certain reference compounds, as shown in Table II, were tested as chemoreleasing agents of murine cardiac norepinephrine *in vivo*.[12] ED_{50} values were determined for those compounds (**3a**, **6a**, and **6b**) which gave positive results in this primary screen.[13] The introduction of a 2,4,5-trimethylpyrrole-3-carboxylic acid at position 18 in methyl reserpate (**6a**) did not block the potent chemoreleasing activity, as is characteristic of many esters of **6a** and reserpine.[14] The typical appearance of mice treated with reserpine[15] was indistinguishable from that resulting from administration of **6b**. No acute or long term toxicity (20 days) was observed with doses as high as 20 mg/kg.

Compound **3b** was virtually inactive with respect to the release of norepinephrine, with a potency 13 times less than that of L(−)-ephedrine (**3a**). The gross sympathomimetic responses elicited by L(−)-ephedrine (**3a**) were absent even at the highest dose of **3b** (300 mg/kg) suggesting that **3b** possesses no direct or indirect sympathomimetic activity and that **3b** does not undergo any appreciable hydrolysis to ephedrine *in vivo*. The remaining compounds were inactive. The derivatives shown in Table III and their corresponding parent compounds were tested for analgesic activity by the hot plate method[16] and the Nilsen

method.[17] The codeine derivative **2b** was approximately one-third as effective as codeine (**2a**) itself in the hot plate method and inactive in the more specific Nilsen test.[17] Compound **4b** and jervine (**4a**) both showed very little if any analgesic activity. In the hot plate assay, the scopoline derivative **5b** was 20% more active than codeine. The unesterified scopoline (**5a**) was inactive. This marked increase in analgesic activity conferred by the esterification of scopoline with 2,4,5-trimethylpyrrole-3-carboxylic acid is currently under investigation. Previous studies have shown scopoline benzilate, *p*-butoxybenzoate, and diphenylacetate esters (1% solutions) to possess surface anesthetic activity,[18] whereas the α,α-diphenylpropionate esters of scopoline and scopine have been useful as antispasmodic, antisecretory, anti-Parkinson, and tranquilizing agents.[19]

Experimental Section

Materials and Apparatus. L(−)-Ephedrine and scopoline were obtained from Sigma Chemical Co., jervine and veratridine from Aldrich Chemical Co., and methyl reserpate from Ciba Pharmaceuticals. Infrared spectra were obtained on a Perkin-Elmer spectrometer (Model 21 and Model 237B). Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Analyses indicated by element symbols agree with calculated values within ±0.4%.

Ethyl 2,4,5-Trimethylpyrrole-3-carboxylate. From 202 g (2 mol) of 2,3-butanedione monoxime, 260 g (2 mol) of ethyl acetoacetate, and 350 g of zinc dust in 1000 ml of glacial AcOH, there was obtained 133 g (37%) of ethyl 2,4,5-trimethylpyrrole-3-carboxylate as needles, mp 105–106° (lit.[20] mp 104–105°).

Saponification of Ethyl 2,4,5-Trimethylpyrrole-3-carboxylate. A mixture of 4.0 g (0.022 mol) of ethyl 2,4,5-trimethylpyrrole-3-carboxylate in 56 ml of MeOH and 56 ml of 4 *N* KOH solution was refluxed under an N_2 atmosphere for 6 hr. Most of the solvent was then removed *in vacuo* and the residue dissolved in 100 ml of H_2O. The insoluble residue was removed by suction filtration and the filtrate acidified with 5% HCl to Congo Red (*ca.* 120 ml). The precipitated tan solid was removed by suction filtration, washed with H_2O, and air-dried. Recrystallization from acetone gave 2.5 g (74%) of the desired 2,4,5-trimethylpyrrole-3-carboxylic acid as tan needles, mp 206–207° (lit.[20] mp 198°). The acid was homogeneous by tlc.

Infrared Study of the Reaction of 2,4,5-Trimethylpyrrole-3-carboxylic Acid with Trifluoroacetic Anhydride. Equimolar amounts (0.5 mmol) of carboxylic acid and anhydride were mixed in 5 ml of CCl_4. The reaction was followed by ir. The two strong bands of trifluoroacetic anhydride at 1890 and 1825 cm^{-1} disappeared immediately on mixing the two reactants and two new bands formed at 1785 (strong, coalescence of the newly formed mixed anhydride and trifluoroacetic acid) and 1740 cm^{-1} (medium, mixed anhydride). Ir spectra were measured at the following times (min): 0 (initial mixture), 2, 5, 8, 12, 34, 75, 135, and 1080. The instability of the mixed anhydride in the reaction medium was indicated by the decrease in the intensity of its carbonyl-stretching vibrations with time and the precipitation of crystals of 2,4,5-trimethylpyrrole-3-carboxylic acid from solution, noted at the 12-min time period and thereafter. The acid was identical with an authentic sample by ir (KBr).

Preliminary Investigation of the Esterification of Cholesterol (1a) with 2,4,5-Trimethylpyrrole-3-carboxylic Acid in the Presence of Trifluoroacetic Anhydride. To a mixture of 153 mg (1 mmol) of 2,4,5-trimethylpyrrole-3-carboxylic acid in 2 ml of dry C_6H_6 was added 420 mg (0.28 ml, 2 mmol) of trifluoroacetic anhydride with swirling of the flask. Immediate solution of the carboxylic acid took place upon addition of the anhydride. The reaction was allowed to stand at room temperature for 15 min and then 386 mg (1 mmol) of cholesterol was added with swirling of the flask (reaction no. 1). The cholesterol went into solution immediately upon its addition to the reaction. The solution was allowed to stand at room temperature for 15 min and then concentrated *in vacuo* to remove the solvent.

A control reaction (no. 2) was carried out as described above with the exception that cholesterol was not added. Control reaction (no. 3) contained no trimethylpyrrolecarboxylic acid.

Tlc of the above three reactions (silica gel GF, hexane–acetone–ether, 8:1:1) gave the following results. Reaction no. 1 showed the presence of the desired short-wave uv-absorbing pyrrolecarboxylic acid ester of cholesterol (**1b**) at R_f 0.41 [R_f (cholesterol) 0.33], a lesser amount of the trifluoroacetic acid ester of cholesterol at R_f 0.82, and no starting material. Control reaction no. 2 showed the presence of a uv spot at R_f 0.08, apparently the mixed anhydride of the pyrrolecarboxylic acid and trifluoroacetic acid, and the pyrrolecarboxylic acid at the origin. Control reaction no. 3 showed a single spot at R_f 0.82, the trifluoroacetic acid ester of cholesterol.

Codeine 6-(2,4,5-Trimethylpyrrole-3-carboxylate) (2b). To a mixture of 230 mg (1.5 mmol) of 2,4,5-trimethylpyrrole-3-carboxylic acid in 6 ml of dry C_6H_6 was added 0.21 ml (1.5 mmol) of trifluoroacetic anhydride with swirling of the reaction vessel. After a 3-min reaction period, 450 mg (1.5 mmol) of codeine (**2a**) was added. The reaction was placed in a 46° bath for 1 hr with occasional swirling. The solvent was then removed *in vacuo*, followed by two evaporations with dry C_6H_6. The reaction mixture was column chromatographed on silica gel (30 g). Elution with 6 and 12% MeOH in $CHCl_3$ gave 597 mg of the desired pyrrole ester as a tan-colored solid (R_f 0.41, silica gel GF, $CHCl_3$–MeOH, 8:1). Recrystallization of the product from MeOH–H_2O gave 440 mg (68%) of codeine 6-(2,4,5-trimethylpyrrole-3-carboxylate) (**2b**) as tan-colored needles: mp 102°; homogeneous by tlc; ir ($CHCl_3$) 1690 cm^{-1} (ester), no hydroxyl band at 3600 cm^{-1}. *Anal.* ($C_{26}H_{30}N_2O_4$) C, H, N.

L(−)-Ephedrine 2,4,5-Trimethylpyrrole-3-carboxylate (3b). The reaction was carried out in a manner similar to that described for **2b** (see Table I). Column chromatography (22 g of silica gel) of the reaction mixture (elution with 6 and 12% MeOH in $CHCl_3$) gave 439 mg (*ca.* 90%) of the desired ester as a reddish-brown oil plus two minor impurities. This product was rechromatographed (18 g of silica gel, elution with 6% MeOH in $CHCl_3$) and gave a homogeneous (tlc, R_f 0.37) L(−)-ephedrine 2,4,5-trimethylpyrrole-3-carboxylate (**3b**) as a viscous oil, which tended to partially crystallize on standing for long periods: ir ($CHCl_3$) 1690 cm^{-1} (ester); mass spectrum M^+ 300, m/e 152 ($C_8H_{10}NO_2$, pyrrole carboxylate). Attempts to crystallize this compound from several solvents failed. *Anal.* ($C_{18}H_{24}N_2O_2$) N.

Jervine 3-(2,4,5-Trimethylpyrrole-3-carboxylate) (4b). **4b** was prepared in a manner similar to that described for **2b** (see Table I). The mixture was column chromatographed on 15 g of silica gel. Elution with 4% MeOH in $CHCl_3$ gave 376 mg of orange-tan solid, homogeneous by tlc. Elution with 8% MeOH gave an additional 216 mg (88% yield). Recrystallization of the former fraction from MeOH–acetone gave 267 mg of jervine 3-(2,4,5-trimethylpyrrole-3-carboxylate (**4b**) as the trifluoroacetic acid salt: tan colored; mp 252° dec; ir ($CHCl_3$) 3475 (carbonyl overtone), 1685 cm^{-1} (ester). *Anal.* ($C_{37}H_{49}F_3N_2O_6$) C, H, N.

Scopoline 7-(2,4,5-Trimethylpyrrole-3-carboxylate) (5b). To a mixture of 306 mg (2 mmol) of 2,4,5-trimethylpyrrole-3-carboxylic acid in 8 ml of CCl_4 was added 0.3 ml (0.21 mmol) of trifluoroacetic anhydride. Nearly complete solution of the carboxylic acid was obtained. After a reaction period of 4 min, 310 mg (2 mmol) of scopoline (3α,6α-epoxy-7β-hydroxytropane) (**5a**) was added (exothermic reaction). A brown oil immediately precipitated upon addition of the scopoline. The reaction mixture was placed in a 40° bath for 40 min. Evaporation under reduced pressure gave a viscous oil which was chromatographed on 25 g of silica gel. Elution with 6–25% MeOH in $CHCl_3$ gave 617 mg of product homogeneous by tlc. Recrystallization of a portion of this from acetone gave scopoline 7-(2,4,5-trimethylpyrrole-3-carboxylate) (**5b**) trifluoroacetic acid salt, as a tan solid: mp 203–208° (gas evolution) with transcrystallization to needles at 190°; ir (KBr) 1685 cm^{-1} (ester); mass spectrum M^+ 290 (free base), m/e 154 ($C_8H_{12}NO_2$, scopline portion of ester), 136 ($C_8H_{10}NO$, pyrrole acyl portion). *Anal.* ($C_{18}H_{23}F_3N_2O_5$) C, H, N.

Methyl Reserpate 18-(2,4,5-Trimethylpyrrole-3-carboxylate) (6b). The reaction was similar to that described for **2b** (see Table I). The reaction mixture was concentrated *in vacuo* and then column chromatographed on 20 g of silica gel. Elution with 5% MeOH in $CHCl_3$ gave 464 mg (70%) of methyl reserpate 18-(2,4,5-trimethylpyrrole-3-carboxylate)trifluoroacetic acid salt (**6b**) as a reddish brown solid, homogeneous by tlc. Recrystallization from $CHCl_3$–MeOH gave 367 mg of tan needles, mp 208–210° dec (with gas evolution). A second recrystallization from dilute MeOH raised the melting point to 210–212° dec: ir (KBr) 1730 (methyl reserpate ester), 1680 cm^{-1} (pyrrolecarboxylate ester); mass spectrum M^+ 549 (free base), m/e 152 and 136 (pyrrolecarboxylate and pyrroleacyl). *Anal.* ($C_{33}H_{40}F_3N_3O_8$) C, H, N; F: calcd, 8.59; found, 9.09.

Attempted Esterification of 2-Diethylaminoethanol. The procedure was similar to that of **2b**. Evaporation and column chromatography of the reaction mixture gave various fractions which contained at least five short-wave uv-absorbing products, which were dark brown intractable oils which could not be obtained crystalline upon further chromatography (column and preparative tlc).

Attempted Esterification of Veracevine. The esterification of veracevine† (which contains seven hydroxyl groups, three of which are normally acylable) in a manner similar to the procedures described above was not selective and gave a complex mixture of products, none of which were fully characterized.

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†Obtained from the mild hydrolysis of veratridine as described in ref 21.

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A New Nonsteroidal Antiinflammatory Agent. 3.[1] Analogs of 2-Substituted 5-Benzothiazoleacetic Acids and Their Derivatives

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Compounds of 5-benzothiazole-α-alkylacetic acid with substitutions at the 2 position and/or the alkyl function were synthesized and their pharmacological activities studied. Introduction of a methyl group α to the acetic acid function of 2-phenyl-5-benzothiazoleacetic acid lowered toxicity and enhanced antiinflammatory activity relative to that of phenylbutazone employed as a standard.

We previously reported the synthesis of a series of 2-substituted 5-benzothiazoleacetic acids and studied their antiinflammatory activities.[1] It was found that the most active and the least toxic compound among them was 2-phenyl-5-benzothiazoleacetic acid (**9**). We therefore further synthesized several compounds with varied substituents on the α carbon of the acetic acid function in order to investigate whether such modification affected the pharmacological activities. For the same purpose, some benzothiazolineacetic acids were also synthesized.

Chemistry. General schemes for the synthesis of 2-phenyl-5-benzothiazole-α-alkylacetic acid (**1a–j**, **2**, **3**) are shown in Schemes I and II.

The many synthetic routes could be classified into two general categories. In the first category (type I), the benzothiazole skeleton was synthesized previous to alkylating the active methylene of the acetic acid at the 5 position. The second category (type II) involved the initial alkylation of the carbon α to the nitrile function of *p*-chlorophenylacetonitrile (**16**) followed by subsequent condensation with an appropriate moiety to form the benzothiazole skeleton.

Routes A–F in Scheme I belonged to the type I synthesis. The α-alkylacetic acid moiety was achieved by alkylating the carbon α to any of three functional groups: nitrile, ester, and acid.

Synthesis from the nitrile was achieved by methylating 2-phenyl-5-benzothiazoleacetonitrile (**4**) with methyl iodide using sodium amide. The product, α-(2-phenyl-5-benzothiazolyl)-α-methylacetonitrile (**5**), could be hydrolyzed directly (route A) or by means of an initial conversion to its amide **6** followed by hydrolysis to yield the desired product **1a** (route B). Higher yields of **1a** were obtained if ethyl carbonate was used to obtain **7** followed by methylation and hydrolysis *via* the amide.

Ethyl 2-phenyl-5-benzothiazolemalonate (**12**), obtainable from the ester **11** by reaction with ethyl carbonate in sodium ethoxide, was alkylated with subsequent hydrolysis to yield either **1a** or **2** (route C). Compound **11** could also be methylated directly at room temperature and hydrolyzed to the product **1a** (route D) but the yield was only 25%. Furthermore, at reflux the disubstituted α-(2-phenyl-5-benzothiazolyl)-α-methylpropionic acid (**3**) was obtained in 50% yield when **11** was subjected to methylation (route E). Ethylation of **11** at elevated temperature yielded **2** in 80% yield (route D).

The acid **9**, when treated with *n*-butyllithium and methyl iodide in the presence of diisopropylamine, gave the lithium salt which was immediately suspended in water and acidified to afford **1a** in 45% yield (route F). Ethylation by this route proved to be difficult.

Type II synthesis included route G in Schemes I and II.