PATENTS-US--A340958

DE83 002361

NOVEL 7-SUBSTITUTED COUMARIN COMPOUNDS AND AN IMPROVED METHOD FOR THEIR SYNTHESIS

By: Eugene R. Bissell, USA
101 Via Lucia
Alamo, California 94507

DISCLAIMER

NOVEL 7-SUBSTITUTED COUMARIN COMPOUNDS AND AN IMPROVED METHOD FOR THEIR SYNTHESIS

The United States Government has rights in this invention pursuant to Contract No. W-7405-ENG-48 between the University of California and the U. S. Department of Energy.

This invention relates generally to novel coumarin compounds and to a method of their synthesis. More specifically, the invention relates to 7-substituted coumarins and related compounds and to a novel method for their preparation, under milder experimental conditions and in greater yields.

Background Of The Invention

Coumarins (benz α-pyrenes) and coumarin derivatives abound in nature. They occur in grasses, citrus peel, orchids, clover, legumes and in the leaves of many vegetables. They form the parent structure of many plant pigments and are widely used in perfumery and as flavoring agents. Dicoumarol, a coumarin derivative found in sweet clover, was found to have anticoagulant activity and led to the discovery of this property in other coumarin compounds. Such compounds now find wide use as rat poisons. Many of the naturally occurring coumarin compounds also exhibit useful and diverse biological activity as antifungal, antispasmodic, anticholerostatic, and molluscacide agents. In addition,

coumarin compounds and their derivatives are being used as emission sources for dye laser applications, as fabric dyes, flourescence markers, flourescent whiteners, photographic sensitizers and as synthetic substrates for some proteolytic enzymes.

As a result, there has been a great deal of interest and activity for many decades, not only in isolating and purifying the naturally occurring coumarins, but also in the laboratory synthesis of these compounds by various methods. One of the earliest methods of preparing coumarin was by the condensation of salicylaldehyde with acetic anhydride. Since then, various precursors and methods of synthesis of many substituted coumarins have been reported.

3-carbethoxycoumarins are readily synthesized by the Knoevenagel reaction from salicylaldehydes (S. Wawzonek, "Heterocyclic Compounds", Vol.2, 174-6, (1951); L. L. Woods and J. Sapp, J. Org. Chem., 30, 312-3 (1965). However, the precursor aldehydes are not readily available and are not always simple or easy to prepare. Synthesis from the more readily available substituted phenols, which involves addition to dialkyl alkoxymethylenemalonates, gives substituted coumarins in low yields. G.A. Kraus and J.O.Pezzanite, J. Org. Chem., 44, 2480 (1979) reported the synthesis of 6-hydroxy coumarins by the addition of lithium salts of substitued phenol derivatives to dialkyl-alkoxy-methylene-malonates; and M.C. Gerphagnon et al., Comp. rend. 246, 1701 (1958) obtained in low yields, 7-hydroxy-3-carbethoxy coumarins by the thermal addition of polyhydroxy benzenes to diethyl ethoxy methylenemalonate.

The 3-carbethoxycoumarins serve as key intermediates in the synthesis of the more interesting and useful derivatives. The 7-substituted coumarins are of

particular interest not only from a synthesis point of view but also on account of their extensive use as laser dyes, flourescent markers, and as substrates for some proteolytic enzymes.

It would be desirable, therefore, to devise improved methods of preparing various novel 7-substituted derivatives of coumarin, in greater yields.

Summary Of The Invention

Accordingly, it is a general object of this invention to provide an improved method for the synthesis of substituted coumarins using milder experimental conditions and in better yields.

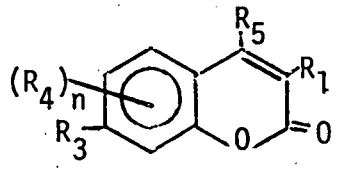
A further object is to provide an improved method for the synthesis of substituted coumarins, in the presence of Lewis acid catalysts.

Another object of the invention is to provide novel, 7-substituted coumarins and related compounds, which may be useful as laser dyes, as fluorescent markers or as synthetic substrates for some proteinases .

Additional objects and advantages and novel features of the invention are set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon an examination of the following or may be learned by the practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations pointed out in the appended claims.

The present invention accomplishes the foregoing and other objects in accordance with the purpose

of the present invention as embodied and broadly described herein, by providing an improved method for the preparation of 7-substituted coumarins of the general formula



where R_1 is cyano or $-COOR_2$;

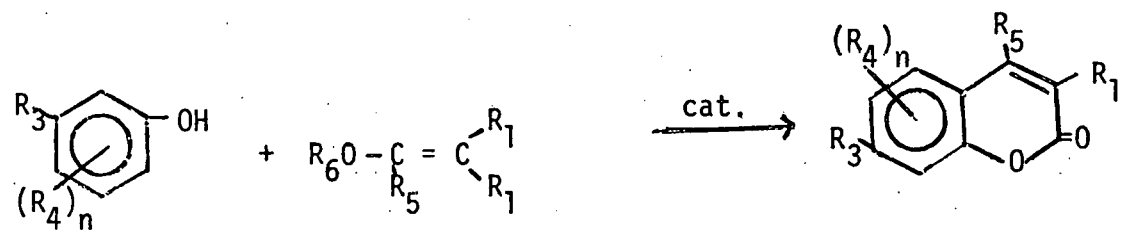
R_2 may be alkyl, preferably of from 1-8 carbons, and more preferably from 1-4 carbons, substituted alkyl, alkenyl, aryl, aralkyl, substituted aryl, heterocyclic radical and the like;

R_3 may be hydroxyl, alkoxyl, substituted amino, amido, substituted amido, carbamido moieties and the like;

R_4 may be hydrogen, alkyl, preferably of from 1-8 carbons, more preferably from 1-4 carbons, alkenyl, aryl, aralkyl, hydroxyl, alkoxyl, substituted amino, amido, substituted amido, carbamido and the like; and n is an integer from 0 to 3;

R_5 may be hydrogen, alkyl, preferably of from 1-8 carbons, and more preferably from 1-4 carbons, haloalkyl or may be the same as R_2 or different.

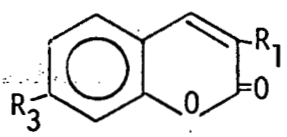
The method of the present invention proceeds by the reaction of a substituted phenol or a polyhydroxy benzene with a substituted or unsubstituted β-alkoxy acrylic acid or nitrile in the presence of a Lewis acid catalyst according to the scheme



where R_1, R_2, R_3, R_4, R_5 and n have the same meaning as before; R_6 may be any group defined as for R_2 and may be the same as or different from R_2.

The substituent R_3 on the phenol must be an electron donating group at the 3-position. Exemplary electron donating groups are hydroxyl, alkoxyl, amido, substituted amino, and the like.

The compounds prepared according to the method of this invention comprise novel, substituted coumarin compounds substituted at the 7-position which may also be optionally substituted at other positions. The novel compounds synthesized by the subject method are of the general formula



where R_1 is cyano or $COOR_2$; R_3 may be -OH, $-OR_2$, $-NHR_2$, $-N(R_2)_2$, $-NHC(=O)R_2$, and $-NHC(=O)OR_2$;
and R_2 may be alkyl, alkenyl, substituted alkenyl, substituted alkyl, aryl, substituted aryl, aralkyl, haloalkyl, heterocyclic and the like;

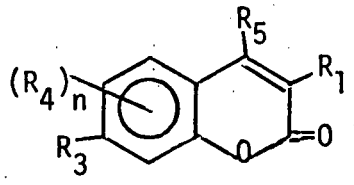
In one preferred embodiment, the synthesis of 7-ethylamino-6-methyl-3-carbethoxycoumarin from the reaction of 3-ethylamino-4-cresol with diethyl ethoxy-methylenemalonate in the presence of various Lewis acid catalysts is presented.

The subject method involving the use of Lewis acid catalysts enables the preparation of 7-substituted coumarins under milder experimental conditions, at lower temperatures than previously employed for such reactions and in very good yields. The novel compounds prepared

by the subject method are useful as laser dyes, fluorescence markers and brighteneres, as precursors for synthetic substrates or as synthetic substrates for some proteolytic enzymes.

Detailed Description Of The Invention

The present invention is directed to an improved method for the preparation of substituted coumarins, more specifically to the preparation of 7-substituted coumarins which may also be optionally substituted at other positions. The compounds prepared according to the method of the subject invention are of the general formula



where R_1 is cyano or $COOR_2$;

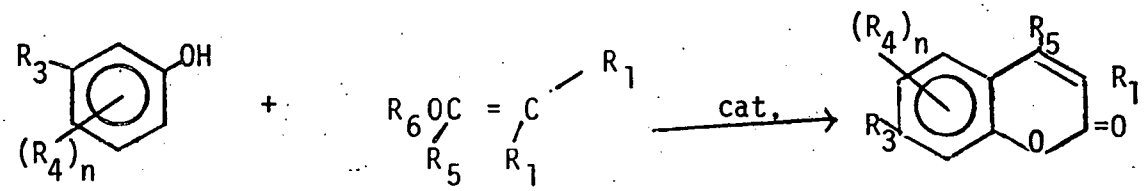
R_2 may be alkyl, preferably of from 1-8 carbons, and more preferably from 1-4 carbons, substituted alkyl, alkenyl, aryl, aralkyl, substituted aryl, heterocyclic radical and the like;

R_3 may be hydroxyl, alkoxyl, substituted amino, amido, substituted amido, carbamido moieties and the like;

R_4 may be hydrogen, alkyl, preferably of from 1-8 carbons, more preferably from 1-4 carbons, alkenyl, aryl, aralkyl, substituted amino, amido, substituted amido, carbamido and the like; and n is an integer from 0 to 3;

R_5 may be hydrogen, alkyl, preferably of from 1-8 carbons, and more preferably from 1-4 carbons, haloalkyl or may be the same as R_2 or different.

The subject method involves a thermal condensation of a polyhydroxy benzene or substituted phenol with a β-alkoxy acrylic acid or acrylonitrile, in the presence of a Lewis acid catalyst, according to the reaction scheme



where R_1, R_2, R_3, R_4, R_5 and n have the same meaning as before; R_6 may be any group defined as for R_2 and may be the same as or different from R_2.

The substituent at the 3-position on the phenols appears at the 7-position on the resulting coumarins. Substituents at the 3-position on the phenol are electron donating groups, exemplary groups including but not limited to hydroxyl, alkoxyl preferably of from 1 to 8 carbons, and more preferably from 1-4 carbon atoms, alkylamino and the like.

While any conventional Lewis acid catalyst may be used in the method of the subject invention, organometallic and inorganic halides, more specifically, the halides of groups II, III and IVB elements give good results. Preferred catalysts are $AlCl_3$, $FeCl_3$, $ZnCl_2$, $TiCl_4$, bis(acetylacetonato)-titaniumdichloride ($Ti(AA)_2Cl_2$) and the like, $TiCl_4$ and $ZnCl_2$ being the most preferred.

The reaction may be carried out in any suitable organic or inorganic solvent system. Suitable solvents are aliphatic alcohols, particularly, the lower

alcohols, including but not limited to methanol, ethanol, propanol and butanol, dimethylsulfoxide, tetrahydrofuran, dimethylformamide, 1,2-dimethoxyethane, and/or mixtures thereof. A nonprotonic solvent is preferred when $TiCl_4$ is the catalyst of choice.

The following examples are offered by way of illustration only and not by way of any limitation.

All temperatures not otherwise indicated are degrees Celsius.

All percentages not indicated otherwise are by weight.

The following abbreviations are employed.

NMR	-	nuclear magnetic resonance
DMSO	-	dimethylsulfoxide
$(CH_3)_4Si$	-	tetramethylsilane
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
ppm	-	parts per million
Hz	-	hertz
IR	-	infra-red

Experimental

Melting points, taken on a Mettler FP 1 apparatus at 2°C/min, are corrected. NMR measurements, in deuterated DMSO except as noted, were made on a Varian EM360 NMR Spectrometer; shifts (δ) are given in ppm relative to internal $(CH_3)_4Si$ with S=singlet, D=doublet, T=triplet, Q=quartet, M=complex multiplet; the value in parentheses is the relative area. Coupling constants (J) are given in Hz. Elemental analyses on all new compounds were within $\pm$ 0.44% of the expected values. IR spectra were measured in potassium bromide

pellets on a Perkin-Elmer Model 597 spectrometer. TLC was carried out either on 5 x 10 cm plastic-backed silica gel N-HR plates for analyses or on 20 x 20 x 0.5 cm glass-backed silica gel 60 plates for preparative scale experiments. Solvent systems were those noted in Table 2.

Diethyl ethoxymethylenemalonate, all solvents used, and the starting phenols, except where noted, were commercial reagent grade and were used without further purification.

The Lewis acid catalysts were anhydrous reagent grade and were used without further purification except for cadmium chloride and ferric chloride, which were commercial hydrates fused over an open flame and then held at 1 Pa for 1-3 days at room temperature. Sulfuric acid was 98% reagent-grade.

[Caution: Titanium chloride, one of the Lewis acid catalysts used, is highly corrosive and reacts vigorously with water and hydroxyl containing compounds. It should be handled only in a hood with adequate ventilation. Addition of titanium tetrachloride to ether solvents such as tetrahydrofuran and dimethoxyethane results in evolution of large amounts of heat.]

GENERAL PROCEDURE

Method A: The phenol (50 mmol), diethyl ethoxymethylenemalonate (55 mmol), the Lewis acid catalyst (63 mmol), and absolute ethanol (40 ml) were refluxed for 22-24 hrs. The cooled reaction mixture was poured with stirring, into 500 ml of water containing 2 ml of concentrated aqueous hydrochloric acid. The water-insoluble product was separated by filtration,

decantation or centrifugation, depending on its consistency, washed with water and dried over night at room temperature and 1-3 Pa. Except as noted below, purification was effected by preparative TLC. The appropriate zone was eluted with 9/1 methylene chloride/methanol, weighed and recrystallized, usually from ethanol.

Method B: The phenol (43 mmol), diethyl ethoxymethylenemalonate (47 mmol) and tetrahydrofuran (35 ml) were placed in a 100 ml round-bottom flask. Titanium tetrachloride (6 ml) was added from a pipet as rapidly as possible to avoid a violent reaction. The mixture darkens rapidly and the THF starts to boil. If addition is carried out too slowly, hydrolysis of the titanium tetrachloride by the moisture in the air, plugs the pipet. As soon as addition was complete, the joint on the flask was quickly wiped free of solids and a condenser attached. The reaction mixture was refluxed and then the procedure outlined in Method A above, was followed for the remainder of the experiment.

Table I shows the yield of a representative compound prepared according to the method of the present invention, 7-ethylamino-6-methyl-3-carbethoxy coumarin, synthesized from the reaction of 3-ethylamino-4-cresol with diethyl-ethoxy methylene malonate in the presence of various Lewis acid catalysts.

Table I.

Lewis Acid	Crude Yield (%)	Recovery[a] (%)	Purified Yield (%)
$AlCl_3$	33.8	41.7	14.1
BF_3Et_2O	nil	nil	nil
$CdCl_2$	84.5	8.3	7.0
$FeCl_3$	10.0	62.3	6.2
$HgBr_2$	258.4[b]	2 est	5 est
H_2SO_4	nil	nil	nil
P_2O_5	nil	nil	nil
$SnCl_4$	46.4	23.5	10.9
$Ti(AA)_2Cl_2$[c]	28.8	1.9	0.5
$TiCl_4$[d]	80.9	69.8	56.5
$ZnCl_2$	61.8	40.9	25.3
$ZnCl_2/Zn$	51.6	16.5	8.5

[a] On preparative layer chromatography on SiO_2, eluting with 1% $MeOH/CH_2Cl_2$.

[b] Contaminated with $HgBr_2$

[c] Bis(acetylacetonato)titanium dichloride

[d] Tetrahydrofuran solvent

The solvent used was ethanol (except as noted) but other solvents and/or mixtures thereof are equally suitable. Even though $TiCl_4$, $ZnCl_2$, $FeCl_3$, $AlCl_3$, $SnCl_4$ were found to be effective, $TiCl_4$ and $ZnCl_2$ were found to be the most effective under the chosen experimental conditions.

A series of 7-substituted coumarins were prepared according to the subject method, starting with a variety of precursor phenols, and using $TiCl_4$ and $ZnCl_4$ as the catalysts. The results obtained are tabulated and shown in Table 2. The solvent used for the TLC elution was methanol in methylene dichloride in various proportions. These proportions are shown in the last column of Table 2 and are given as percentages of MeOH in methylene dichloride.

Table 2.

7-Substituent	Other Subst.	Yield (%)				M.P.(°C)		TLC	
		$ZnCl_2$		$TiCl_4$		Found	Lit.	R_f	Solvent[b]
		Crude	Pure[a]	Crude	Pure[a]				
-OH	-	55.3	18.0	70.5	30.3	167	168	0.17	2
-OH	6-CH_2CH_3	76.9	21.4	-	-	194	192	0.53	5
-OCH_3	-	62.0	25.2	103.2	28.8	117	134	0.74	2
-$N(CH_3)_2$	-	41.2	21.3	86.8	64.3	170	–	0.42[c]	1
-$N(CH_2CH_3)_2$	-	39.3	18.4	45.8	33.0	-	-	0.49	1
-$NH(CH_2CH_3)$	6-CH_3	61.8	25.3	80.9	56.5	176	-	0.47	1
-$NH(CH_2)(CF_2)_6CF_3$	-	48.0	11.0	-	-	217	-	0.35	1
-$NH(CH_2CH_2CN)$	-	39.6	20.3	89.9	37.5[d]	204	-	0.15	1
-$NHCOCH_3$	-	35.2	3.3	85.9	11.1	220	236	0.20	2
-$NHOCOCH_2CH_3$	-	87.7	39.5	-	-	219	-	0.81	0
-$NHOCOCH_2C_6H_4NO_2$	-	17.3	12.6	-	-	174	-	0.22	2

a By preparative layer chromatography on SiO_2 eluting with the same solvent used for TLC.
b % Methanol in methylene dichloride.
c Identical to that of an authentic sample.
d Mixture of nitrile and amide.

Preparation Of Some Of The Individual Compounds:

7-Ethylamino-6-methyl-3-carbethoxycoumarin

3-Ethylamino-4-cresol by method A, with $ZnCl_2$ catalyst, gave 25.3% and by Method B 56.5% of purified (by preparative layer chromatography) 7-ethylamino-6-methyl-3-carbethoxycoumarin. The analytical sample, mp 176°C, was recrystallized from absolute ethanol; NMR, 1.28 two overlapping T(6) (ethyl CH_3), 2.14 S(3) (aromatic CH_3), 3.34 Q(2) J = 7 (CH_2N), 4.25 Q(2) J = 7 (CH_2O), 6.45 S(2*) (ArH + NH), 7.45 S(1) and 7.52 S(1) (ArH); IR, 1740 cm^{-1} (C=O). [*In the presence of CF_3COOD, this was reduced to 1.]

7-(Pentadecafluorooctylamino)-3-carbethoxycoumarin

3-(Pentadecafluorooctylamino)phenol (10 mmol) treated by Method A, with $ZnCl_2$ catalyst, yielded 2.95g (48%) of crude coumarin, which was extracted with 900 ml hot methylene dichloride. The solution was decanted from a small amount of insoluble material, extracted with 300 ml of 1 N aqueous sodium hydroxide, washed with 300 ml of water, dried over anhydrous magnesium sulfate, filtered and evaporated to leave 0.7g of a light yellow waxy solid. After three recrystallizations from absolute ethanol, the product melted at 217°C; IR 1740 cm^{-1} (C=O), 1130, 1210 and 1240 cm^{-1} (CF).

7-(Cyanoethylamino)-3-carbethoxycoumarin

3-Cyanoethylaminophenol treated by Method A, with $ZnCl_2$ catalyst, gave 40% of crude coumarin, which was purified by preparative layer chromatography and recrystallized from acetonitrile; mp 204°C; NMR 1.23 T(3) J = 7 (ethyl CH_3), 2.75 T(2) J = 6 (CH_2CN),

NOVEL 7-SUBSTITUTED COUMARIN COMPOUNDS AND AN IMPROVED METHOD FOR THEIR SYNTHESIS

Abstract Of The Disclosure

Novel substituted coumarin compounds and an improved method for their synthesis are disclosed. The preferred class of compounds are substituted at the 7-position. The method of synthesis comprises reacting a polyhydroxy benzene or a substituted phenol, with a β-alkoxy acrylic acid or nitrile, in the presence of a Lewis acid catalyst. By the inclusion of the catalyst in the reaction mixture, the reaction can be carried out under much milder experimental conditions and in increased yields. The method is also applicable to the preparation of substituted amino phenols.

3.43 T(**) J = 6 (CH_2N), 3.32 S(**) (NH), 4.20 Q(2) J = 7 (CH_2O), 7.1 M(3) (ArH), 8.59 S(1) (H_5); IR, 1755 cm^{-1} (C=O). Recrystallization from ethanol resulted in some hydrolysis of the nitrile to the amide. Method B produced a mixture of the nitrile and the amide. [** These two together gave an area equal to 3. In the presence of CF_3COOD, the NH resonance shifted to 7.4, and the area of the remaining CH_2 resonance was 2.]

7-(Ethoxycarbonylamido)-3-carbethoxycoumarin

3-Hydroxycarbanilic acid ethyl ester (25 mmol) by method A, with $ZnCl_2$ catalyst, yielded 6.64 g (87.7%) of the crude coumarin, which was purified by four crystallizations from absolute ethanol (45% recovery), mp 219°C; NMR 1.30 T(6) J = 8 (2 ethyl CH_3s), 4.30 two Q (4) J = 8 (2 ethyl CH_2s), 7.62 M(4) (ArH), 8.72 S(1) (NH); IR, 1715 cm^{-1} (C=O).

7-[(p-Nitrobenzyl)oxycarbonylamido]-3-carbethoxycoumarin

3-Hydroxycarbanilic acid p-nitrobenzyl ester (11 mmol) gave by Method A, with $ZnCl_2$ catalyst, 3.57g (17%) of crude coumarin, which was purified by preparative layer chromatography followed by recrystallization from aqueous ethanol, mp 174°C; NMR (acetone-d_6) 1.30 T(3) J = 7 (ethyl CH_3), 4.20 Q(2) J = 7 (ethyl CH_2), 5.35 S(2) (urethane CH_2), 7.0 M(5) (m-ArH + NH), 8.50 Q(4) (p-ArH); IR, 1705 cm^{-1} (C=O), 1520 (NO_2 asym. str.), 1350 (NO_2 sym. str.).

The precursor 3-Hydroxycarbanilic acid p-nitrobenzyl ester may be prepared by known methods as follows:

3-Hydroxycarbanilic Acid p-Nitrobenzyl Ester

p-Nitrobenzyl chloroformate (7.55 g, 35 mmol) was added to a stirred solution of 7.65 g (70 mmol) of 3-aminophenol in 500 ml of ether, and the mixture was kept stirred at room temperature for about 18 hrs. The precipitated salt was filtered and washed with ether. The combined ether fractions were evaporated, and the residue was dried overnight at room temperature and at 16 kPa leaving 3.48g (34.5%) of a yellow solid melting at 168°C.

Three recrystallizations raised the m.p. to 175°C; NMR (4/1 $CDCl_3/CD_3OD$) 4.12 S(2) (NH + OH), 5.30 S(2) (CH_2O), 7.1 M(4) (m-ArH), 7.92 Q(4) (p-ArH); IR, 1715 cm^{-1} (C=O), 1520 (NO_2 asym.str.), 1350 (NO_2 sym.str.).

If aminophenol was used as the precursor, a different set of products were obtained as demonstrated in the following experiment.

1,1-Dicarbethoxy-2-(3-hydroxyphenylamino)-ethylene

3-Aminophenol treated by Method A, with $ZnCl_2$ catalyst, gave 88.5% of 1,1-dicarbethoxy 2-(3-hydroxyphenylamino)ethylene, mp 154°C. After two recrystallizations from aqueous ethanol, it melted at 155°C; NMR 0.93 and 0.95 T(6) J = 7 (CH_3), 3.87 and 3.98 Q(4) J = 7 (CH_2), 6.6 M(4) (ArH + NH), 8.22 D(1) (=CH), 9.55 S(1); IR, 1690 cm^{-1} (C=O). Method B gave the same product in about 75% yield.

It has thus been shown that the method of the subject invention enables the synthesis of substituted coumarins, especially 7-substituted coumarins and their derivatives or precursors, under milder experimental

conditions and in greater yields. The instant invention thus overcomes the problems of the prior known methods for the synthesis of substituted coumarins. Although the foregoing invention has been described in some detail by way of illustration and example, only for purposes of clarity and of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.