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(54) KETENE DERIVATIVES AND THEIR PREPARATION

(71) We, PFIZER INC., formerly known as Chas. Pfizer & Co., Inc., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a series of novel derivatives of arylcarboxy ketenes, to methods for their preparation, and to their use as intermediates for further synthesis. More particularly, it relates to a series of novel arylchlorocarbonyl ketenes and to the corresponding bromo analogs; to novel arylcarboxy- and arylcarbothiolic ketene esters derived therefrom, and to the use of the esters as novel acylating agents for the acylation of amines such as 6-aminopenicillanic acid.

The production of ketenes from malonic acid derivatives is described in the literature. Staudinger, *Helv. Chim. Acta* 8, 306 (1925), for example, prepared a series of low-molecular-weight dialkyl ketenes by the thermal decomposition of di(lower)alkyl substituted malonic anhydrides. In a modification of this method using mixed anhydrides prepared from disubstituted malonic acids and diphenyl ketene, Staudinger et al, *Ibid*, 6, 291 (1923) and *Ber.* 46, 3539 (1913) prepared various disubstituted ketenes by thermal decomposition. A still further method comprises the dehalogenation of α -halo acyl halides with zinc (Staudinger, *Ann.* 356, 71 (1907); 380, 298 (1911)). By extension of this reaction, Staudinger et al, *Ber.* 42, 4908 (1909) prepared ethyl carboxy ketene by the dehalogenation of diethyl- α -bromo- α -ethyl malonate.

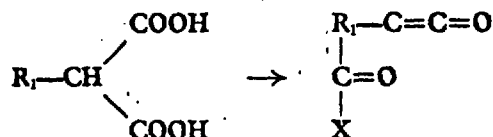
Another method, the decomposition of diazo ketones, has been used to prepare certain diaryl ketenes (Smith et al, Org. Syntheses 20, 47, 1940; Gilman et al, Rec. trav. chim., 48, 464, 1929). It is further known that certain disubstituted acetyl chlorides undergo dehydrohalogenation under the influence of tertiary amines to form keto ketenes. This method, however, appears to be limited to the preparation of certain aryl and high-molecular-weight keto ketenes, all of which are relatively resistant to dimerization (Staudinger et al, Ber. 41, 594, 1908).

The reaction of phenylmalonic acid with phosphorus pentachloride (1:2 molar ratio) in either solution is reported by Sorm et al (Collection Czechoslov. Chem. Commun. 20, 593—6, 1955) to produce phenylmalonyl chloride. The same authors report (loc. cit.) that when the reaction is conducted in the absence of a solvent at the reflux temperature, phenylchloromalonyl chloride is produced. Both products are isolated by vacuum distillation.

The preparation of lower alkyl esters of phenylcarboxy ketene by thermal decomposition of diazoketo esters has been described by Staudinger et al (Ber. 49, 2522, 1916). However, the method used by Staudinger is rather complex and results, on an overall basis, in rather poor yields. The process of the present invention for making such esters, on the other hand, is simple and productive of satisfactory yields.

The use of ketenes as acylating agents is well known in the art. The acylation of amino groups by means of simple or mixed acid anhydrides, acid halides, acid azides, β -thiolacetones, acylated enols and carboxylic acid with carbodiimides is also known in the art (Sheehan, U.S. Patent 3,159,617, December 1, 1964). However, the introduction of α -carboxy arylacetyl groups into 6-aminopenicillanic acid has, up until now, been limited to the use of a simple or mixed anhydride, an acid halide of an arylmalonic acid or an aryl malonic acid ester as acylating agent (U.S. Patent 3,142,673 British Patent 1,004,670).

It has now been unexpectedly found that a variety of aryl chlorocarbonyl ketenes, and the corresponding bromo analogs, can readily be prepared by the reaction of aryl malonic acids with a halogenating agent followed by vacuum distillation of the reaction product thus formed. The process and the compounds produced are summarized by the reaction:

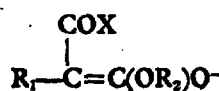


wherein R_1 , broadly referred to herein as an aryl group, is thienyl, furyl, pyridyl, phenyl, or substituted phenyl wherein the substituent is (lower)-alkyl, chloro, bromo, (lower)alkoxy, di(lower)alkylamino or trifluoromethyl, and X is chloro or bromo.

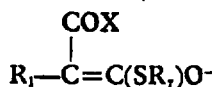
The process of this invention, in view of the teaching of Sorm et al (loc. cit.) that phenylmalonyl chloride and phenylchloromalonyl chloride are obtained by the action of phosphorous pentachloride on phenylmalonic acid in the presence of a solvent and the products recovered by vacuum distillation, is most surprising and unexpected. Repetition of the Sorm et al procedure for making phenylmalonyl chloride has been found to produce phenylchlorocarbonyl ketene rather than phenylmalonyl chloride. The existence of the ketene compound was completely unrecognized by Sorm et al.

The process, in general, comprises reacting an aryl substituted malonic acid with a halogenating agent selected from $\text{P}(\text{X})_3$, $\text{P}(\text{X})_5$, $\text{PO}(\text{X})_3$ and $\text{SO}(\text{X})_2$ wherein X is as defined above at a temperature of from 0°C . to 50°C . The dihalide thus produced is thermally decomposed at 80°C — 100°C . to provide the aryl halocarbonyl ketene.

The arylhalocarbonyl ketenes exhibit a dual functionality and react both as acid halides and ketenes. They are, therefore, valuable as intermediates for further synthesis. Alcohols (R_2-OH) and thiophenols (R_2SH) for example, react with the arylhalocarbonyl ketenes at low temperatures, e.g. from -70°C . to 30°C . to produce the corresponding esters of aryl carboxy and aryl-carbothiolic ketenes which are useful as acylating agents. Reaction appears to occur first with the ketene group to form a transient intermediate



or



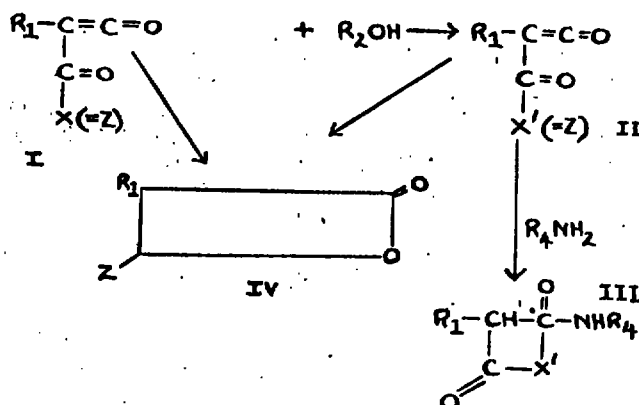
which rearranges with elimination of hydrogen halide to the arylcarboxy or arylcarbo-

thiolic ketene ester.

The novel arylcarboxy and arylcarbothiolic ketene esters of this invention are especially valuable as agents for the acylation of amines with production of esters of α -carbothiolic and α -carboxy- α -arylacetyl amines. They are particularly useful for the acylation of amines such as 6-aminopenicillanic acid for the production of known and novel antibacterial agents. Prior art methods for introducing α -carboxy arylacetyl groups into amino compounds such as 6-aminopenicillanic acid have made use of acid anhydrides, mixed or simple, or acid halides of aryl malonic acids. The use of the prior acylating agents requires extreme caution during reaction and recovery steps in order to obtain satisfactory yields and avoid decarboxylation of the carboxy group. The acylation agents of this invention on the other hand react smoothly and rapidly with amines at low temperatures and produce no undesirable by-products.

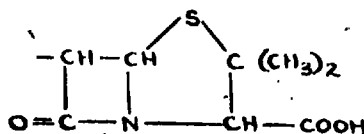
The acid halides and esters of the aryl carboxy ketenes form 3-aryl substituted 2-oxo-oxetenes (1,3-epoxypropenes) in solution. These compounds react in a manner analogous to that of the compounds from which they are derived.

The above reactions are summarized in the following sequence:

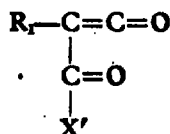


wherein Z in Formula IV is X or X' and R₁, R₂, X and X' are as hereinafter defined.

R₄ is



According to the present invention there are provided compounds of the formula:



... I or II

wherein R₁ is
thienyl
furyl
pyridyl
phenyl

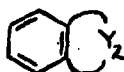
substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)-alkoxy, di(lower)alkylamino or trifluoromethyl;

and X' is X, —OR₂ or —SR,
wherein X is halogen;

wherein R₂ is

- 5 phenyl or substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, (lower)alkyl, (lower)alkoxy, lower alkanoyl, carbo(lower)alkoxy, nitro, or di-(lower)alkyl amino; 5
- 10 furyl quinolyl methyl substituted quinolyl phenazinyl 9,10-anthraquinonyl phenanthrenequinonyl anthracenyl phenanthryl (1,3-benzodioxolyl) 3-(2-methyl-4-pyronyl) 3-(4-pyronyl) or (N-methyl)pyridyl; 10
- 15 15

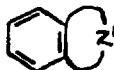
20



20

wherein Y₂ is

- 25 —CH=CH—O— —CH=CH—CH=CH—
—CH=CH—S— —C(O)—CH=CH—C(O)—
—CH₂—CH₂—S— —C(O)—C(O)—CH=CH—
or —CH=N—CH=CH—; 25



wherein Z' is —CH₂—, —CH₂—CH₂—, —CH₂—CH—, —(CH₂)₃— or —(CH₂)₄—,
CH₃

or substituted derivatives thereof wherein the substituent is methyl, chloro or bromo;

- 30 benzyl substituted benzyl 30
- wherein the substituent is
- 35 chloro bromo fluoro (lower)alkyl (lower)alkoxy (lower)alkanoyl carbo(lower)alkoxy nitro or di(lower)alkylamino; 35
- 40 phthalimidomethyl trityl benzohydryl cholesteryl alkenyl having up to 8 carbon atoms alkynyl having up to 8 carbon atoms cycloalkyl or (lower)alkyl-, substituted cycloalkyl having from 3 to 7 carbon atoms in the cycloalkyl moiety 40
- 45 bicyclo[4.4.0]decyl thujyl fenchyl isofenchyl 7-adamantanyl (2-pyrrolidino)methyl (4-imidazolyl)methyl 1-indanylmethyl 2-indanylmethyl furylmethyl pyridylmethyl 45
- 50 [2,2-di(lower)alkyl-1,3-dioxolon-4-yl]methyl 50

ac-indanyl or substituted derivatives thereof wherein the substituent is methyl, chloro or bromo;

ac-tetrahydronaphthyl N-substituted derivatives thereof wherein the substituent is methyl, chloro or bromo;

5 alkyl or substituted (lower)alkyl
wherein the substituent is at least one of:

chloro

bromo

10 fluoro

nitro

carbo(lower)-alkoxy

(lower)alkanoyl

(lower)alkoxy

15 cyano

(lower)alkylmercapto

(lower)alkylsulfinyl or

(lower)alkylsulfonyl;

—CH₂—CH₂—NR₅R₆

—CH₂—CH₂—CH₂—NR₅R₆

20 —CH₂—CH(CH₃)—NR₅R₆ or

—CH(CH₃)—CH₂—NR₅R₆ or —(lower alkylene)—Y₁

wherein —NR₅R₆ is —NH(lower)alkanoyl, —N $\begin{matrix} \text{(lower)alkyl} \\ \text{(lower)alkyl} \end{matrix}$

wherein the (lower)alkyl groups may be alike or different;

and —N(lower)alkyl anilino;

and Y₁ is

azetidino

aziridino

pyrrolidino

piperidino

30 morpholino

thiomorpholino

N-(lower)alkyl piperazino

pyrrolo

imidazolo

35 2-imidazolino

2,5-dimethylpyrrolidino

1,4,5,6-tetrahydropyrimidino

4-methylpiperidino or

2,6-dimethylpiperidino;

40 wherein each of (lower)alkoxy, (lower)alkyl and (lower)alkanoyl have from 1 to 4 carbon atoms, and (lower)alkylene contains from 1 to 3 carbon atoms; and R₁ is phenyl, mono-, di-, and tri-substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, (lower)alkyl, (lower)alkoxy or trifluoromethyl, with the proviso that only one of the positions, ortho to the thio group of the phenyl moiety be substituted; wherein each of (lower)alkyl and (lower)alkoxy contain from 1 to 4 carbon atoms.

Of the lower alkyl, lower alkoxy, lower alkanoyl and carbo(lower)alkoxy groups those having from one to four carbon atoms in the alkyl, alkoxy and alkanoyl moieties are preferred since the reactants bearing such groups are more readily available than are those required for such groups having a greater number of carbon atoms.

The production of arylchloro (and bromo) carbonyl ketenes comprises the reaction of an arylmalonic acid with a halogenating agent for example selected from P(X)₃, P(X)₃, PO(X)₃ and SO(X)₂ wherein X is as defined above at temperatures ranging from 0°C. to 50°C. for periods ranging from one hour to 10 hours. The reaction is conducted in the presence of a solvent system, preferably a reaction-inert solvent system. Suitable solvents are dialkyl ethers, e.g. diethyl ether, dipropyl ether, mono- and dimethyl ethers of ethylene glycol and propylene glycol, methylene chloride and chloroform.

The reaction period is, of course, dependent upon the reaction temperature and

the nature of the reactants. However, for a given combination of reactants, the lower temperatures require longer reaction periods than do higher temperatures.

The molar proportions of reactants, i.e. arylmalonic acid and halogenating agent, can vary widely, e.g. up to 1:10 or higher, but for satisfactory yields should be at least stoichiometric. In actual practice the stoichiometric ratio of reactants is preferred.

The reactants may be added all at once or separately. If separately, the order of addition is not critical. However, it appears that the reaction is smoother and subject to fewer side-reactions, as evidenced by the color of the reaction mixture, particularly upon distillation, when the arylmalonic acid is added to the halogenating agent. The reaction mixture, under such conditions, generally progresses from a yellow to a red color. The reaction mixture on reverse addition, i.e. the addition of halogenating agent to the arylmalonic acid, progresses from yellow to black.

The arylhalocarbonyl ketene products are isolated from the reaction by distillation *in vacuo*. Because of their great reactivity they are generally stored under a nitrogen atmosphere at low temperatures and in the absence of light.

Reaction of the aryl halocarbonyl ketenes with alcohols and thiophenols is conducted on a 1:1 molar ratio at a temperature of from -70°C . to 30°C . when conversion of the arylhalocarbonyl ketene to a ketene ester is desired. A reaction-inert solvent, such as ethyl ether, methyl ether, dioxane, methylene chloride, chloroform, is desirably used to permit better mixing and control of the reaction. The use of greater than a 1:1 molar ratio of arylhalocarbonyl ketene to alcohol or thiophenol or temperatures above 30°C . produces malonic acid diesters. For example, when two moles of alcohol is used per mole of arylhalocarbonyl ketene the corresponding diester of the arylmalonic acid is produced. Half-amides of arylmalonic acid esters are obtained by reacting the arylhalocarbonyl ketenes with an alcohol followed by reaction of the resulting arylcarboxy ketene ester with a primary or secondary amine as is described herein. Isolation of the intermediate ester is not necessary. A tertiary amine may be used as acid acceptor to remove the hydrogen halide produced during formation of the ester.

The arylcarboxy and aryl carbothiol ketene esters produced as described above are excellent acylating agents particularly suited for the acylation of amines to produce α -carbothiol- and α -carboxyarylacetyl amines. They are especially valuable as agents for the acylation of 6-aminopenicillanic acid.

EXAMPLE I

Phenylchlorocarbonyl Ketene

A. To phenylmalonic acid (20 g.) in ethyl ether (100 ml.) there is added phosphorous pentachloride (46 g.). A vigorous reaction occurs. The reaction mixture is refluxed for four hours then the ether partially removed by heating on a steam bath. The reaction mixture becomes black when about half the ether is removed and the remaining ether is removed under reduced pressure (at 100 mm.). The residue is distilled under vacuum and the fraction boiling at 75°C .— 90°C . at 1.5—4 mm. collected. The product, a yellow liquid, is redistilled at 74°C . and 1.5 mm. It shows a strong peak in the infra-red region of the spectrum at 4.69μ .

Repetition of this procedure but using 10 g. of phenylmalonic acid instead of 20 g. produces a less vigorous reaction on addition of the phosphorous pentachloride. The same product is obtained.

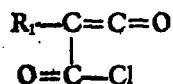
B. Phosphorous pentachloride (23 g.) is added over a 5-minute period to a stirred solution of phenylmalonic acid (10 g.) in ethyl ether (50 ml.) initially at a temperature of 0°C .— 5°C . The temperature rises to 13°C . during the addition. The mixture is then refluxed for five hours and allowed to stand overnight at room temperature. Removal of the ether at 20 mm. produces a dark concentrate which is vacuum distilled to give the desired product: b.p. 80°C .— 88°C . at 1.5—2.0 mm. and 74°C . at 0.2 mm.

C. To a stirred solution of phosphorous pentachloride (46 g.) in ethyl ether (100 ml.) there is added phenylmalonic acid (10 g.) over a two-minute period. The mixture is stirred at room temperature for four hours then refluxed for four hours and allowed to stand overnight at room temperature. The excess phosphorous pentachloride is filtered off and the ether boiled off at atmosphere pressure. The reaction mixture gradually progresses in color from dark yellow to red. The residue is distilled *in vacuo* to give the product: b.p. 83°C .— 86°C . at 1.5 mm. as a yellow liquid.

D. Repetition of this procedure but using an equivalent amount of phosphorous oxychloride as halogenating agent in place of phosphorous pentachloride produces the same product.

EXAMPLE II

The procedure of Example I-C is repeated but using the appropriate malonic acid derivative in place of phenylmalonic acid to produce the following compounds.



5	R ₁	R ₁	5
	2-thienyl	3-furyl	
	3-thienyl	2-pyridyl	
	2-furyl	3-pyridyl	
10	o-tolyl	4-pyridyl	10
	m-tolyl	o-bromophenyl	
	p-tolyl	m-bromophenyl	
	o-methoxyphenyl	o-chlorophenyl	
	m-methoxyphenyl	p-chlorophenyl	
15	p-methoxyphenyl	m-chlorophenyl	15
	o-trifluoromethylphenyl	o-butoxyphenyl	
	p-trifluoromethylphenyl	o-dimethylaminophenyl	
	m-trifluoromethylphenyl	o-diethylaminophenyl	
	o-isopropylphenyl	m-dimethylaminophenyl	
		p-dimethylaminophenyl	

EXAMPLE III

Repetition of the procedures of Examples I-C and II but using PBr₃ in place of PCl₅ produces the corresponding bromo compounds.

EXAMPLE IV

Methyl Ester of Phenylcarboxy Ketene

To a solution of phenylchlorocarbonyl ketene (0.5 g.) in dry chloroform (5 ml.) there is added anhydrous methanol (0.1 ml.) at room temperature. Hydrogen chloride is liberated. The mixture, maintained under a atmosphere of nitrogen, is stirred for 20 minutes and the product recovered by evaporation of the solvent.

EXAMPLE V

Dibenzyl Phenyl Malonate

Benzyl alcohol (0.6 ml.) is added to a solution of phenylchlorocarbonyl ketene (1.0 g.) in dry, ethanol-free, chloroform (12 ml.) at room temperature. Hydrogen chloride is evolved almost immediately upon addition of the benzyl alcohol. The mixture is stirred for five minutes, additional benzyl alcohol (0.6 ml.) added, and stirring continued for three hours. The chloroform solvent is evaporated off. The residue, upon standing, crystallizes. After two recrystallizations from hexane it melts at 69°—70°C.

Analysis

Calcd. for C₂₃H₂₀O₄: C, 76.65; H, 5.59%
Found: C, 76.92; H, 5.49%

EXAMPLE VI

Benzyl Phenyl-N-Benzylmalonamate

Benzyl alcohol (0.6 ml. in 2 ml. of methylene chloride) is added to a solution of phenylchlorocarbonyl ketene (1.0 g.) in methylene chloride (12 ml.) at -70°C. in a closed system filled with nitrogen gas. The mixture is stirred for three minutes then benzylamine (1.2 ml. in 2 ml. of methylene chloride) added. An immediate precipitate forms. The mixture is held at -70°C. for one hour with occasional shaking and then warmed to room temperature. The mixture is held at -70°C. for one hour with occasional shaking and then warmed to room temperature. The mixture is filtered and the filtrate evaporated to dryness. The residue, a somewhat gummy solid, is slurried in ether, filtered and then recrystallized twice from hexane, m.p. 143—143.5°C.

Analysis

Calcd. for C₂₃H₂₁NO₃: C, 76.85; H, 5.88; N, 3.89%
Found: C, 76.67; H, 5.86; N, 3.99%

Repetition of this example but using the compounds of Examples II and III in place of phenylchlorocarbonyl ketene produces the corresponding malonamates.

EXAMPLE VII

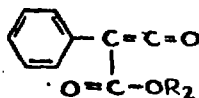
A mixture of phenylmalonic acid (5 g.) and thionyl chloride (30 ml.) is heated to reflux for six hours to give a clear yellow solution. Removal of the excess thionyl chloride by evaporation provides the crude phenylchlorocarbonyl ketene. The pure compound is obtained by distillation *in vacuo*.

EXAMPLE VIII

Esters of Arylocarboxy Ketenes — General Preparation Method

To a solution of the appropriate aryl halocarbonyl ketene (0.1 mole) in methylene chloride (sufficient to provide a clear solution and generally from 5 to 10 ml. per gram of ketene) there is added the proper alcohol R_2OH (0.1 mole). The reaction mixture is maintained under an atmosphere of nitrogen and stirred for a period of from 20 minutes to 3 hours, care being taken to exclude moisture. The temperature may range from $-70^{\circ}C.$ to $-20^{\circ}C.$

The compounds thus prepared are presented below.



R_2		R_2	
20	1-methyl-2-nitroethyl 4-nitrobutyl 1-methyl-2-nitropropyl 2,2-dinitroethyl 1-methyl-2-chloro-2-nitroethyl 1-trichloromethyl-2-nitroethyl	1-methyl-4-oxopentyl 1-methyl-3-oxobutyl 1-acetyl-1-methylpropyl 2-acetylbutyl 2-acetylpropyl 5-oxohexyl	20
25	1,1-dimethyl-2,2,2-trichloroethyl 2-methoxyethyl 2-ethoxyethyl 2-isobutoxyethyl 4-ethoxy-n-butyl	1-methoxy-2,2,2-trichloroethyl 1-methoxy-2,2,2-trifluoroethyl methyl ethyl n-propyl n-butyl sec-butyl t-butyl decyl	25
30	1,1-dimethyl-2-ethoxyethyl 1-cyanoethyl 4-cyanobutyl 2-cyano-1-methylethyl	1-methyl-2-chloroethyl 1-ethyl-2-chloroethyl 1-methyl-2-chloropropyl 1,1-dimethyl-2-chloroethyl 2-bromoethyl 2-bromo-1-butyl 1,3-dichloropropyl 1,1-dichloromethylethyl 2-bromo-3-chloropropyl 1-bromomethyl-2-chloroethyl 1,1-dichloromethylethyl 1,1-dimethyl-2,2-dichloroethyl 2,3,3-tribromopropyl 2,2,3,3-tetrabromopropyl 2,2,2-trifluoroethyl 2-nitroethyl 2,3-diacetoxypropyl 2,3-distearoyloxypropyl (1,2,3-tricarbomethoxy)-2-propyl 2-fluoroethyl 2,2,3,3,4,4,4-heptafluorobutyl	30
35	1-chloromethyl-2-cyanoethyl 1-cyano-2,2-dichloropropyl 1-cyano-2,2,2-trichloroethyl 1-methyl-1-(1'-cyano-1'-methyl-ethoxy)ethyl		35
40	2-acetoxyethyl 2-butyryloxyethyl 2-acetoxy-n-butyl carbomethoxymethyl 2-carbethoxyethyl 4-carbethoxybutyl 2-carbethoxypropyl 1-carbethoxyethyl 1-trichloromethyl-2-carbomethoxyethyl 1-chloromethyl-2-carbomethoxyethyl		40
45			45
50	1-carbethoxy-2,2-dichloropropyl 1-carbomethoxy-2,2,2-trichloroethyl 1-carbomethoxymethyl-2,2,2-trichloroethyl		50
55	acetonyl acetonylmethyl 4-oxopentyl		55

	R ₂		R ₂	
5	2-dimethylaminoethyl		phenyl	
	2-dibutylaminoethyl		o-chlorophenyl	
5	2-diisopropylaminoethyl		p-chlorophenyl	
	3-diisopropylaminopropyl		m-bromophenyl	5
	3-diethylaminopropyl		o-tolyl	
	2-diethylaminoethyl		p-tolyl	
	2-di-(n-propyl)aminoethyl		m-ethylphenyl	
10	3-di-methylaminopropyl		o-isopropylphenyl	
	3-di-(n-propyl)amino-2-propyl		p-t-butylphenyl	10
	2-(2,5-dimethylpyrrolidino)ethyl		o-methoxyphenyl	
	2-(4-methylpiperidino)ethyl		m-ethoxyphenyl	
	3-piperidinopropyl		p-butoxyphenyl	
15	3-pyrrolidino-2-propyl		o-fluorophenyl	
	3-piperidino-2-propyl		o-formylphenyl	15
	2-(2-imidazolino)ethyl		p-acetylphenyl	
	3-(2-imidazolino)propyl		p-butylphenyl	
	2-piperidinoethyl		o-nitrophenyl	
20	2-morpholinoethyl		m-nitrophenyl	
	3-morpholinopropyl		o-carbomethoxyphenyl	20
	3-thiomorpholinopropyl		p-carbomethoxyphenyl	
	2-pyrrolidinoethyl		m-carbomethoxyphenyl	
	2-pyrroloethyl		o-dimethylaminophenyl	
25	2-N-methylpiperazinoethyl		m-di-n-propylaminophenyl	
	3-N-butylpiperazinopropyl		p-methylethylaminophenyl	25
	2-(1,4,5,6-tetrahydropyrimidino)ethyl		2,3-dimethylphenyl	
	3-dimethylamino-2-propyl		3,5-dimethylphenyl	
	2-diethylamino-1-propyl		2,6-diethylphenyl	
30	2,3,4,6-tetramethylphenyl		5-ethyl-3-methylphenyl	
	2,6-dichlorophenyl		2,3,4-trimethylphenyl	30
	2,4,6-tribromophenyl		2,6-diethyl-4-methylphenyl	
	pentafluorophenyl		7-isoquinolyl	
	2,4-dinitrophenyl		4-benzofuryl	
35	2,3,6-trinitrophenyl		2-phenanthrenequinonyl	
	2,4-difluorophenyl		2-(1,4-anthraquinonyl)	35
	3-chloro-2-fluorophenyl		3-phenanthryl	
	2-chloro-6-methoxyphenyl		3-thionaphthenyl	
	3-methoxy-2-methylphenyl		cyclopropyl	
40	2-carbomethoxy-5-fluorophenyl		cyclobutyl	
	2-acetyl-4-fluorophenyl		cyclopentyl	40
	3-bromo-5-methylphenyl		cyclohexyl	
	4-chloro-2,6-dimethylphenyl		cycloheptyl	
	3-chloro-4-fluoro-6-nitrophenyl		1-methyl-1-cyclopentyl	
45	4-indanyl		3-methyl-1-cyclopentyl	
	8-quinolyl		2,2-dimethyl-1-cyclopentyl	45
	4-(6-methylquinolyl)		2-methyl-1-cyclohexyl	
	1-naphthyl		3,5-dimethyl-1-cyclohexyl	
	5-(1,2,3,4-tetrahydronaphthyl)		3-isopropyl-1-cyclopentyl	
50	2-phenaziny		1-methyl-1-cyclobutyl	
	3-(2-methyl-4-pyronyl)		1-indanyl	50
	2-(1,4-naphthoquinonyl)		7-adamantanyl	
	2-furyl		4-bicyclo[4.4.0]-decyl	
	2-methyl-1-indanyl		4-cyclohexyl-1-cyclohexyl	
55	2-(1,2,3,4-tetrahydronaphthyl)		1-methyl-1-cycloheptyl	
	thujyl		fenchyl	55
	2-chloro-1-indanyl			
	allyl		propargyl	
	crotyl		1-butyne-3-yl	
60	3-buten-1-yl		1-pentyl-3-yl	
	3-penten-1-yl		3-methyl-1-pentyl-3-yl	60
	3-penten-2-yl		2-hexyn-1-yl	
	2-methyl-3-buten-1-yl		2-heptyn-1-yl	
	4-hexen-1-yl		2-octyn-1-yl	
	1-hexen-3-yl		3,4,4-trimethyl-5-pentyn-1-yl	

	R ₂	R ₂	
	2,2-dimethyl-3-buten-1-yl	3-ethyl-1-pentyn-3-yl	
	2-hepten-1-yl	2-octen-1-yl	
	2-hepten-4-yl	1-octen-3-yl	
5	3-(N-methyl)pyridyl	4-(N-methyl)pyridyl	5
	benzyl	o-ethoxybenzyl	
	o-chlorobenzyl	m-acetylbenzyl	
	p-butyrylbenzyl	p-butyrylbenzyl	
	p-bromobenzyl	o-carbomethoxybenzyl	
10	m-methylbenzyl	p-(carbo-t-butoxy)benzyl	10
	o-fluorobenzyl	o-fluorobenzylbenzyl	
	p-methoxybenzyl	p-dimethylaminobenzyl	
	o-nitrobenzyl	benzohydryl	
	trityl	1-indanylmethyl	
15	cholesteryl	2-pyridylmethyl	15
	[2,2-dimethyl-1,3-dioxolan-4-yl-	2-furylmethyl	
	phthalimidomethyl	(2-pyrrolidino)methyl	

In like manner but using the appropriate thiophenol in place of R₂OH, the following compounds are prepared.

20	$\begin{array}{c} \text{C}_6\text{H}_5-\text{C}=\text{C}=\text{O} \\ \\ \text{O}=\text{C}-\text{SR}_7 \end{array}$	20
----	--	----

	R ₇	R ₇	
	phenyl	p-fluorophenyl	
	o-tolyl	2,4-dichlorophenyl	
	p-tolyl	2,4,5-trichlorophenyl	
25	m-ethylphenyl	p-methoxyphenyl	25
	o-n-propylphenyl	o-ethoxyphenyl	
	p-isopropylphenyl	3-methoxy-4-methylphenyl	
	p-t-butylphenyl	4-methoxy-2,5-dimethylphenyl	
	2,5-dimethylphenyl	6-chloro-3-isopropylphenyl	
30	2,5-diethylphenyl	4-bromo-3-methylphenyl	30
	2-methyl-5-isopropylphenyl	2-chloro-3,5-dimethylphenyl	
	m-chlorophenyl	4,6-dichloro-3-dimethylphenyl	
	o-bromophenyl	o-trifluoromethylphenyl	

	$\begin{array}{c} \text{C}_6\text{H}_5\text{C}=\text{C}=\text{O} \\ \\ \text{COOR}_2 \end{array}$																																							
35	<table><thead><tr><th>R₂</th><th>I.R.</th></tr></thead><tbody><tr><td>2-dimethylaminoethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-diethylaminoethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-di(n-propyl)aminoethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-di(isopropyl)aminoethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-di(n-butyl)aminoethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>3-dimethylaminopropyl</td><td>1474, 1640, 1730, 1850, 2130, 2960, 3035</td></tr><tr><td>3-di-(n-propyl)amino-2-propyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-pyrrolidinoethyl</td><td>1500, 1600, 1725, 1750, 2130, 2960, 3035</td></tr><tr><td>2-piperidinoethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-morpholinoethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-(2,5-dimethylpyrrolidino)ethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-(4-methylpiperidino)ethyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>3-(pyrrolidino)propyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>3-piperidinopropyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>3-morpholinopropyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>3-pyrrolidino-2-propyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>3-piperidino-2-propyl</td><td>1720, 1740, 2130, 2960, 3035</td></tr><tr><td>2-aziridinoethyl</td><td>3025, 2950, 2880, 2550, 2400, 2325, 2125, 1730</td></tr></tbody></table>	R ₂	I.R.	2-dimethylaminoethyl	1720, 1740, 2130, 2960, 3035	2-diethylaminoethyl	1720, 1740, 2130, 2960, 3035	2-di(n-propyl)aminoethyl	1720, 1740, 2130, 2960, 3035	2-di(isopropyl)aminoethyl	1720, 1740, 2130, 2960, 3035	2-di(n-butyl)aminoethyl	1720, 1740, 2130, 2960, 3035	3-dimethylaminopropyl	1474, 1640, 1730, 1850, 2130, 2960, 3035	3-di-(n-propyl)amino-2-propyl	1720, 1740, 2130, 2960, 3035	2-pyrrolidinoethyl	1500, 1600, 1725, 1750, 2130, 2960, 3035	2-piperidinoethyl	1720, 1740, 2130, 2960, 3035	2-morpholinoethyl	1720, 1740, 2130, 2960, 3035	2-(2,5-dimethylpyrrolidino)ethyl	1720, 1740, 2130, 2960, 3035	2-(4-methylpiperidino)ethyl	1720, 1740, 2130, 2960, 3035	3-(pyrrolidino)propyl	1720, 1740, 2130, 2960, 3035	3-piperidinopropyl	1720, 1740, 2130, 2960, 3035	3-morpholinopropyl	1720, 1740, 2130, 2960, 3035	3-pyrrolidino-2-propyl	1720, 1740, 2130, 2960, 3035	3-piperidino-2-propyl	1720, 1740, 2130, 2960, 3035	2-aziridinoethyl	3025, 2950, 2880, 2550, 2400, 2325, 2125, 1730	35
R ₂	I.R.																																							
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40		40																																						
45		45																																						
50		50																																						
55		55																																						

	R ₂	I.R.	
	2-pyrrolidino-1-propyl	3025, 2950, 2880, 2520, 2300(Br.), 2125, 1725	
5	2-azetidinoethyl	3012, 2941, 2703, 2315, 2119, 1748 1639, 1587, 1493, 1439	5
	2-piperidino-1-propyl	3025, 2950, 2860, 2600, 2420, 2300(B), 2120, 1725, 1480, 1440	
10	2-(2,6-dimethyl piperidino)ethyl	3020, 2940, 2860, 2525, 2300(B), 2120, 1725, 1480, 1440	10
	2-morpholino-1-propyl	3020, 2970, 2870, 2440, 2220(B) 2130, 1735, 1480, 1440	
	2-di(n-propylamino)-1-propyl	3020, 2970, 2940, 2870, 2550, 2300(B), 2120, 1725, 1480, 1450	
15	3-dimethylamino-2-propyl	3020, 2950(B), 2300(B), 2130, 1735	15
	3-morpholino-2-propyl	3025, 2940(B), 2300(B), 2120, 1735, 1480, 1440	

EXAMPLE IX

The following additional ketene esters are prepared by the general procedure of Example VIII from aryl-halo-carbonyl-ketenes of Examples II and III wherein R₁ is 2-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 4-pyridyl, p-tolyl, o-methoxyphenyl, p-methoxyphenyl, o-trifluoromethylphenyl, p-chlorophenyl, o-dimethylaminophenyl, and p-dimethylaminophenyl. For convenience only the R₂ values are listed.

	R ₂	R ₂	
25	methyl	2-cyanoethyl	25
	ethyl	3-cyanopropyl	
25	n-butyl	2-cyano-1-methylpropyl	
	t-butyl	1-cyano-2-chloropropyl	
	decyl	1-cyano-2,2-dichloropropyl	
30	tetradecyl	1-cyano-2,2,2-trichloroethyl	30
	2-chloroethyl	1-methyl-1-(1'-cyano-1'-methylethoxy)propyl	
0	2-chloropropyl	2-acetoxyethyl	
35	4-chloro-1-butyl	2-butyryloxyethyl	35
	1-methyl-3-chloropropyl	3-acetoxypentyl	
	2-bromoethyl	carbomethoxymethyl	
	1-ethyl-2-bromoethyl	2-carbethoxyethyl	
40	1,3-dichloropropyl	3-carbobutoxypropyl	40
	2-bromo-3-chloropropyl	2-carbethoxypropyl	
	3,4-dichloro-1-butyl	1-trichloromethyl-2-carbomethoxyethyl	
	2,2-dichloroethyl	1-carbethoxy-2,2-dichloropropyl	
45	1,1-dimethyl-2,2-dichloroethyl	1-carbomethoxy-2,2,2-trichloroethyl	45
	2,2,3-tribromopropyl	acetonyl	
	2,2,3-trichlorobutyl	2-oxopentyl	
	2,2,2-trichloroethyl	4-oxopentyl	
50	2,2,2-trifluoroethyl	2-acetylbutyl	50
	3-nitropropyl	1-methyl-3-oxohexyl	
	2-nitrobutyl	3-oxopentyl	
	2,2-dinitroethyl	4-oxohexyl	
	2-chloro-2-nitropropyl	1-ethoxy-2,2,2-trichloroethyl	
55	1-trichloromethyl-2-nitroethyl	1-methoxy-2,2,2-trifluoroethyl	55
	1-trifluoromethylethyl	2,3-diacetoxypentyl	
60	1,1-dimethyl-2,2,2-trifluoroethyl	2,3-distearoyloxypropyl	60
	1-ethyl-1-methyl-2,2,2-trichloroethyl	(1,2,3-tricarbomethoxy)-2-propyl	
	2-methoxyethyl	3-fluoropropyl	
	3-sec-butoxypropyl		

	R ₂	R ₂	
5	4-methoxy-n-butyl 1,1-dimethyl-2-methoxyethyl carbethoxy ethoxymethyl	4,4,4-trichlorobutyl chlorodicarbomethoxymethyl 1,1-dicarbethoxymethyl- 2-ethoxyethyl	5
10	1-methyl-3-chloropropyl 2-bromooethyl 1-ethyl-2-bromooethyl 1,3-dichloropropyl 2-bromo-3-chloropropyl 3,4-dichloro-1-butyl 2,2-dichloroethyl	2-butyryloxyethyl 3-acetoxypentyl carbomethoxymethyl 2-carbethoxyethyl 3-carbobutoxypropyl 2-carbethoxypropyl 1-trichloromethyl-2- carbomethoxyethyl 1-carbethoxy-2,2-dichloro- propyl 1-carbomethoxy-2,2,2-tri- chloroethyl	10
15	1,1-dimethyl-2,2-dichloroethyl 2,2,3-tribromopropyl	acetonyl 2-oxopentyl 4-oxopentyl 2-acetylbutyl 1-methyl-3-oxohexyl 3-oxopentyl 4-oxohexyl	15
20	2,2,3-trichlorobutyl 2,2,2-trichloroethyl 2,2,2-trifluoroethyl 3-nitropropyl 2-nitrobutyl 2,2-dinitroethyl 2-chloro-2-nitropropyl 1-trichloromethyl-2-nitroethyl	1-ethoxy-2,2,2-trichloro- ethyl 1-methoxy-2,2,2-trifluoro- ethyl 2,3-diacetoxypentyl 2,3-distearoyloxypropyl	20
25	1-trifluoromethylethyl	(1,2,3-tricarbomethoxy)- 2-propyl 3-fluoropropyl 4,4,4-trichlorobutyl chlorodicarbomethoxymethyl 1,1-dicarbethoxymethyl- 2-ethoxyethyl	25
30	1,1-dimethyl-2,2,2-trifluoroethyl 1-ethyl-1-methyl-2,2,2-trichloro- ethyl 2-methoxyethyl	2,6-dichlorophenyl 2-chloro-4-fluorophenyl 2,3,5,6-tetrabromophenyl 2,4-dinitrophenyl 5-fluoro-2-nitrophenyl 6-methoxy-2-methylphenyl 2-acetyl-4-fluorophenyl 3-dimethylamino-4-methyl- phenyl 3-chloro-4-fluoro-6- nitrophenyl 3-carbomethoxy-4-chloro- phenyl 2-carbomethoxy-4-chloro- 5-methylphenyl 1-naphthyl 2-naphthyl 4-indanyl 6-(1,2,3,4-tetrahydro- naphthyl) 3-quinolyl 7-quinolyl 5-(1,3-benzodioxolyl) 7-(1,2-naphthoquinonyl) 1-chloro-2-indanyl cyclopropyl cyclohexyl	30
35	3-sec-butoxypropyl 4-methoxy-n-butyl 1,1-dimethyl-2-methoxyethyl carbethoxy ethoxymethyl		35
40	phenyl o-chlorophenyl m-chlorophenyl p-bromophenyl m-tolyl o-ethylphenyl p-t-butylphenyl o-methoxyphenyl		40
45	m-isopropoxyphenyl		45
50	p-butoxyphenyl p-acetylphenyl		50
55	m-butyrylphenyl o-nitrophenyl p-carbomethoxyphenyl o-dimethylaminophenyl		55
60	2,3-dimethylphenyl 3-methyl-6-propylphenyl 2,4-dimethyl-3-ethylphenyl 3,4-dimethyl-2,6-diethylphenyl 2-dimethylaminoethyl 2-diisopropylaminoethyl 3-diethylaminopropyl		60
65			65

	R ₂	R ₂	
5	5	1-indanyl	
		7-adamantanyl	
		2-methyl-1-cyclopentyl	5
		4-methyl-1-cyclohexyl	
		3,3-dimethyl-1-cyclohexyl	
		4- <i>t</i> -butyl-1-cyclohexyl	
		1,2,4-trimethyl-1-cyclopentyl	
10	10	3,3,5-trimethyl-5-cyclohexyl	10
		1-methyl-1-cycloheptyl	
		3-bicyclo-[4.4.0]-decyl	
15	15	isofenchyl	15
		1-ethyl-1-indanyl	
		<i>o</i> -chlorobenzyl	
		<i>m</i> -bromobenzyl	
		<i>p</i> -butylbenzyl	
20	20	<i>o</i> -methylbenzyl	20
		<i>m</i> -nitrobenzyl	
		<i>o</i> -fluorobenzyl	
		<i>p</i> -methoxybenzyl	
		(4-imidazolyl)methyl	
5	25	<i>o</i> -acetylbenzyl	25
		<i>p</i> -carbethoxybenzyl	
		<i>o</i> -dimethylaminobenzyl	
		benzohydroxyl	
		trityl	
0	30	cholesteryl	30
		2-indanylmethyl	
		3-furylmethyl	
		3-pyridylmethyl	
		benzyl	
5	35	4-(<i>N</i> -methyl)pyridyl	35

Repetition of this procedure but using the appropriate thiophenol in place of R₂OH produces the compounds:

	R ₁	R ₁	
40	phenyl	2,3,4-trichlorophenyl	
	<i>o</i> -tolyl	<i>m</i> -methoxyphenyl	40
	<i>p</i> -ethylphenyl	3-methoxy-2-methylphenyl	
	<i>m</i> -tolyl	<i>o</i> -ethoxyphenyl	
	<i>p</i> -butylphenyl	6-methoxy-2-methylphenyl	
45	3,5-dimethylphenyl	4-methoxy-3,5-dimethylphenyl	45
	2,5-diethylphenyl	5-chloro-2-methylphenyl	
	2-methyl-5-isopropylphenyl	5-bromo-2-methylphenyl	
	<i>o</i> -chlorophenyl	4-chloro-3,5-dimethylphenyl	
	<i>m</i> -bromophenyl	2,4-dichloro-3-methylphenyl	
50	<i>p</i> -fluorophenyl	<i>p</i> -trifluoromethylphenyl	50
	2,5-dichlorophenyl		

EXAMPLE X

Again following the procedure of Example VIII, the arylcarboxyketene esters listed below are prepared. The aryl group, R₁, for each of the R₂ values is 3-furyl, *m*-tolyl, *m*-methoxyphenyl, *p*-trifluoromethylphenyl, 3-pyridyl, *o*-isopropylphenyl, *o*-chlorophenyl, *o*-bromophenyl, *m*-bromophenyl, *m*-chlorophenyl, *o*-butoxyphenyl, *o*-butylphenyl, *o*-diethylaminophenyl and *m*-dimethylaminophenyl.

	R ₂	R ₂	
60	methyl	2-cyanoethyl	60
	<i>n</i> -propyl	3-cyanopropyl	
	<i>t</i> -butyl		

	R ₂		R ₂		
	dodecyl		1-cyano-2-chloropropyl		
	octadecyl		1-cyano-2,2,2-trichloroethyl		
5	3-chloropropyl		1-methyl-1-(1'-cyano-1'-methylethoxy)propyl	5	5
	3-chloro-1-butyl		2-propionyloxyethyl		
	1-methyl-2-chloropropyl		2-acetoxy-n-butyl		
10	1,1-dimethyl-2-chloroethyl		4-propionyloxy-n-butyl	10	10
	2-bromopropyl		carbomethoxymethyl		
	4-bromo-1-butyl		2-carbethoxyethyl		
	1,3-dichloropropyl		3-carbomethoxypropyl		
	1,4-dibromo-2-butyl		1-carbethoxyethyl		
15	2,2-dichloroethyl		1-trichloromethyl-2-carbomethoxyethyl	15	15
	2,2,3-trichlorobutyl		1-carbethoxy-2-chloropropyl		
	2,2,2-trichloroethyl		1-carbomethoxy-2,2,2-trichloroethyl		
20	2-(2-trifluoromethyl)propyl		1-carbomethoxymethyl-2,2,2-trichloroethyl	20	20
	2-nitroethyl		acetonyl		
	2-nitrobutyl		2-oxopentyl		
	4-nitrobutyl		2-acetylbutyl		
25	1-methyl-2-nitropropyl		3-oxopentyl	25	
	2-chloro-2-nitropropyl		4-oxohexyl		
	1-trifluoromethylethyl		1-methoxy-2,2,2-trichloroethyl		
	2-methoxyethyl		2,3-diacetoxypropyl		
30	2-isobutoxyethyl		2-fluoroethyl	30	
	3-methoxypropyl		1-trifluoromethyl-2-nitroethyl		
	4-ethoxy-n-butyl		carbethoxyethoxymethyl		
35	phenyl		2,4-dibromophenyl	35	
	o-tolyl		pentachlorophenyl		
	m-ethylphenyl		2-bromo-4-fluorophenyl		
	o-n-propylphenyl		5-bromo-2-methoxyphenyl		
	p-chlorophenyl		3-methoxy-2-methylphenyl		
40	m-bromophenyl		2-acetyl-4-fluorophenyl	40	
	p-methoxyphenyl		2-dimethylamino-3,5-dimethylphenyl		
	o-ethoxyphenyl		4-carbethoxy-2-chlorophenyl		
	o-fluorophenyl		p-(carbo-t-butoxy)phenyl		
45	m-nitrophenyl		2,3-dimethoxyphenyl	45	
	o-carboisopropoxyphenyl		5-indanyl		
	p-dimethylaminophenyl		5-(1,2,3,4-tetrahydronaphthyl)		
50	2,5-dimethylphenyl		4-quinolyl	50	
	4-isopropyl-3-methylphenyl		2-(1-methylimidazolyl)		
	o-formylphenyl		1-naphthyl		
	cyclopropyl		2-dimethylaminoethyl		
	cyclohexyl		3-diethylaminopropyl		
55	1-methyl-1-cyclohexyl		2-piperidinoethyl	55	
	1-indanyl		3-morpholino-2-propyl		
	2-methyl-1-indanyl		2-(4-methylpiperidino)ethyl		
	7-adamantanyl		3-piperidino-2-propyl		
60	1-isopropyl-1-cyclohexyl		2-diethylamino-1-propyl	60	
	2-methyl-6-ethyl-1-cyclohexyl		3-diethylamino-2-propyl		
	bicyclo-[4.4.0]-3-decyl		2-morpholinoethyl		
	1-methyl-2-cycloheptyl		3-thiomorpholinopropyl		
	1,2,5-trimethyl-1-cyclopentyl		2-pyrrolidinoethyl		
	thujyl		3-pyrrolpropyl		
65	4-chloro-1-indanyl		2-diisopropylaminoethyl	65	

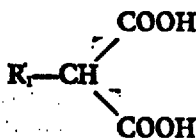
	R_2	R_2	
	3-bromo-1-indanyl	2-(1,4,5,6-tetrahydro- pyrimidino)ethyl	
5	5		5
	1-(2-chloro-1,2,3,4-tetrahydro- naphthyl)		
	allyl	benzyl	
	3-buten-1-yl	o-bromobenzyl	
	3-penten-2-yl	p-chlorobenzyl	
10	10	p-fluorobenzyl	10
	1-penten-5-yl	o-nitrobenzyl	
	2-methyl-3-buten-1-yl	o-dimethylaminobenzyl	
	4-hexen-1-yl	m-methylbenzyl	
	4-methyl-3-penten-2-yl	o-acetylbenzyl	
	propargyl	p-ethoxybenzyl	
15	15	benzohydryl	15
	2-butyne-1-yl	trityl	
	1-pentyne-3-yl	cholesteryl	
	1-hexyne-3-yl	(1-indanyl)methyl	
	2-heptyne-1-yl	(2-pyrrolidono)methyl	
	3-ethyl-1-pentyne-3-yl		
20	20		20
	4-octyne-1-yl		
	3-N-(methyl)pyridyl		

Replacement of R_2OH in the above procedure by R_2SH produces the following compounds:

	R_1	R_1	
25	phenyl	2,4,5-trichlorophenyl	25
30	o-tolyl	p-methoxyphenyl	
	p-ethylphenyl	m-methoxyphenyl	
	o-isopropylphenyl	2-methoxy-4-methylphenyl	
	2,5-diethylphenyl	4-methoxy-2,5-dimethyl- phenyl	
35	30	4-chloro-2-methylphenyl	30
	3-methyl-5-ethylphenyl	4-bromo-3-methylphenyl	
	p-chlorophenyl	5-chloro-2,4-dimethyl- phenyl	
	o-bromophenyl	4,6-dichloro-3-methyl- phenyl	
	p-fluorophenyl		35
40	35		
	p-trifluoromethylphenyl		

Preparation A Malonic Acids

The following aryl malonic acids not previously described in the literature are prepared by the method of Wallingford et al, J. Am. Chem. Soc. 63, 2056—2059 (1964) which comprises condensing an alkyl carbonate, usually diethyl carbonate, with an equimolar proportion of the desired ethyl aryl acetate in the presence of an excess (4—8 times) of sodium ethylate with continuous removal of by-product alcohol from the reaction mixture. The esters thus produced are hydrolyzed to the acid by known methods.



R_1
o-methoxyphenyl
m-methoxyphenyl
p-methoxyphenyl

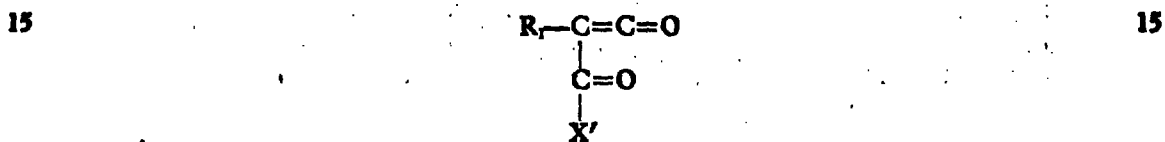
R_1
3-pyridyl
4-pyridyl
o-butoxyphenyl

	R_1	R_1	
	o-trifluoromethylphenyl*	o-dimethylaminophenyl	
	m-trifluoromethylphenyl	o-diethylaminophenyl	
5	p-trifluoromethylphenyl	m-dimethylaminophenyl	5
	o-isopropylphenyl	p-dimethylaminophenyl	
	3-furyl		

*The necessary o-trifluorophenylacetic acid is prepared from o-trifluorobenzonitrile by the procedure of Corse et al, J. Am. Chem. Soc. 70, 2841 (1948) which comprises: (a) conversion of the nitrile to o-trifluoromethylacetophenone by a Grignard reaction with methylmagnesium iodide followed by hydrolysis; (b) reaction of the acetophenone with sulfur and morpholine at 135°C. for 16 hours followed by treatment with glacial acetic acid and hydrochloric acid.

WHAT WE CLAIM IS:—

1. Compounds of the formula:



wherein R_1 is
thienyl
furyl
pyridyl
phenyl

substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)alkoxy, di(lower)alkylamino or trifluoromethyl;

and X' is X, $-OR_2$ or $-SR_2$,

wherein X is halogen;

wherein R_2 is

phenyl

substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, (lower)alkyl, (lower)alkoxy, (lower)alkanoyl, carbo(lower)alkoxy, nitro, or di(lower)alkyl amino;

furyl

quinolyl

methyl substituted quinolyl

phenazinyl

9,10-anthraquinonyl

phenanthrenequinonyl

anthracenyl

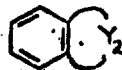
phenanthryl

(1,3-benzodioxolyl)

3-(2-methyl-4-pyronyl)

3-(4-pyronyl)

(N-methyl)pyridyl



wherein Y_2 is

$-CH=CH-O-$

$-CH=CH-S-$

$-CH_2-CH_2-S-$

or $-CH=N-CH=CH-$;

$-CH=CH-CH=CH-$

$-C(O)-CH=CH-C(O)-$

$-C(O)-C(O)-CH=CH-$





16

1,243,209

16

5 R_1
o-trifluoromethylphenyl*
m-trifluoromethylphenyl
p-trifluoromethylphenyl
o-isopropylphenyl
3-furyl

R_1
o-dimethylaminophenyl
o-diethylaminophenyl
m-dimethylaminophenyl
p-dimethylaminophenyl

5

10

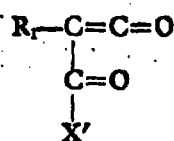
*The necessary o-trifluorophenylacetic acid is prepared from o-trifluorobenzonitrile by the procedure of Corse et al, J. Am. Chem. Soc. 70, 2841 (1948) which comprises: (a) conversion of the nitrile to o-trifluoromethylacetophenone by a Grignard reaction with methylmagnesium iodide followed by hydrolysis; (b) reaction of the acetophenone with sulfur and morpholine at 135°C. for 16 hours followed by treatment with glacial acetic acid and hydrochloric acid.

10

WHAT WE CLAIM IS:—

1. Compounds of the formula:

15



15

.... I or II

wherein R_1 is
thienyl
furyl
pyridyl
phenyl

20

substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)alkoxy, di(lower)alkylamino or trifluoromethyl;

20

and X' is X, $-OR_2$ or $-SR_2$,

wherein X is halogen;

25

wherein R_2 is

25

phenyl

substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, (lower)alkyl, (lower)alkoxy, (lower)alkanoyl, carbo(lower)alkoxy, nitro, or di(lower)alkyl amino;

30

furyl

30

quinolyl

methyl substituted quinolyl

phenazinyl

35

9,10-anthraquinonyl

35

phenanthrenequinonyl

anthracenyl

phenanthryl

(1,3-benzodioxolyl)

40

3-(2-methyl-4-pyronyl)

40

3-(4-pyronyl)

(N-methyl)pyridyl



wherein Y_2 is

45

$-CH=CH-O-$

$-CH=CH-S-$

$-CH_2-CH_2-S-$

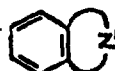
or $-CH=N-CH=CH-$;

$-CH=CH-CH=CH-$

$-C(O)-CH=CH-C(O)-$

$-C(O)-C(O)-CH=CH-$

45



wherein Z' is $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-$, $-(\text{CH}_2)_4-$ or $-(\text{CH}_2)_6-$,

or substituted derivatives thereof wherein the substituent is methyl, chloro or bromo;

benzyl
substituted benzyl

wherein the substituent is

chloro

bromo

fluoro

(lower)alkyl

(lower)alkoxy

(lower)alkanoyl

carbo(lower)alkoxy

nitro or

di(lower)alkylamino;

phthalimidomethyl

trityl

benzohydryl

cholesteryl

alkenyl having up to 8 carbon atoms

alkynyl having up to 8 carbon atoms

cycloalkyl

(lower)alkyl substituted cycloalkyl
having from 3 to 7 carbon atoms in
the cycloalkyl moiety

[2,2-di,(lower)alkyl-1,3-dioxolon-4-yl]methyl

ac-indanyl or substituted derivatives thereof wherein the substituent is methyl,
chloro or bromo;

ac-tetrahydronaphthyl or substituted derivatives thereof wherein the substituent
is methyl, chloro or bromo;

alkyl or substituted (lower)alkyl wherein the substituent is at least one of:

chloro

bromo

fluoro

nitro

carbo(lower)alkoxy

(lower)alkanoyl

(lower)alkoxy

cyano

(lower)alkylmercapto

(lower)alkylsulfinyl or

(lower)alkylsulfonyl;

$-\text{CH}_2-\text{CH}_2-\text{NR}_5\text{R}_6$

$-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NR}_5\text{R}_6$

$-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{NR}_5\text{R}_6$

$-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{NR}_5\text{R}_6$

bicyclo[4.4.0]decyl

thujyl

fenchyl

isofenchyl

7-adamantanyl

(2-pyrrolidino)methyl

(4-imidazolyl)methyl

(1-indanyl)methyl

(2-indanyl)methyl

furylmethyl

pyridylmethyl;

wherein $-\text{NR}_5\text{R}_6$ is $-\text{NH}(\text{lower})\text{alkanoyl}$, $-\text{N}$ (lower)alkyl wherein the (lower)-

alkyl groups may be alike or different; or $-\text{N}(\text{lower})\text{alkyl}$ anilino; or $-(\text{lower})$ -

alkylene- Y_1 ; wherein Y_1 is

azetidino

aziridino

pyrrolidino

piperidino

morpholino

thiomorpholino

N-(lower)alkyl piperazino

pyrrolo

imidazolo



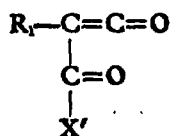
2-imidazolino
2,5-dimethylpyrrolidino
1,4,5,6-tetrahydropyrimidino
4-methylpiperidino or
2,6-dimethylpiperidino;

5

10

wherein each of (lower)alkoxy, (lower)alkyl and (lower)alkanoyl have from 1 to 4 carbon atoms, and (lower)alkylene contains from 1 to 3 carbon atoms; and R, is phenyl, mono-, di-, or tri-substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, (lower)alkyl, (lower)alkoxy or trifluoromethyl, with the proviso that only one of the positions, ortho to the thio group of the phenyl moiety be substituted; wherein each of (lower)alkyl and (lower)alkoxy contain from 1 to 4 carbon atoms.

2. A process for the preparation of compounds of the formula:

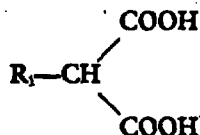


... I or II

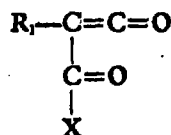
15

wherein R₁ and X' are as defined in claim 1 by reacting malonic acids of the formula:

15



or their functional derivatives, with a halogenating agent to provide compounds of the formula:



... I

20

wherein X is halogen, and, when required, reacting said compounds with compounds of the formula:

20



25

in a 1:1 molar ratio at a temperature of from -70°C. to +30°C., to give compounds of the formula II wherein X' is -OR₂, or -SR₂, and R₁, R₂ and R₃ are as defined in claim 1, and wherein said halogenating agent is P(X)₃, P(X)₃, PO(X)₃ or SO(X)₂, wherein X is halogen and the reaction is at a temperature of from 0°C. to 50°C. and the dihalide thus produced is thermally decomposed at 80°-100°C. to produce the aryl halocarbonyl ketene of Formula I.

25

30

3. The compounds of Formula I or II prepared by the process substantially as described herein.

30

4. The process of preparing the compounds of Formula I or II substantially as herein described.

STEVENS, HEWLETT & PERKINS,
Chartered Patent Agents,
5, Quality Court,
Chancery Lane,
London, W.C.2.
Tel. 01-405 8393

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