United States Patent Office 3,254,082 Patented May 31, 1966

3,254,082
PROCESS FOR PREPARING SUBSTITUTED URACILS

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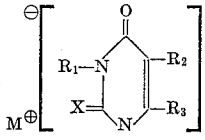
No Drawing. Filed June 3, 1963, Ser. No. 284,835
9 Claims. (Cl. 260—260)

This application is a continuation-in-part of abandoned application Serial No. 12,957, filed March 7, 1960, and copending application Serial No. 123,636, filed July 13, 1961, now abandoned.

This invention relates to processes for the preparation of substituted uracils and their salts.

The compounds made according to this invention are of the formula

(1)



where:

R_1 is alkyl of 1 through 10 carbon atoms, substituted alkyl of 1 through 8 carbon atoms, aryl of 5 through 10 carbon atoms, substituted phenyl, aralkyl of 5 through 13 carbon atoms, substituted aralkyl of 5 through 13 carbon atoms, alkenyl of 3 through 8 carbon atoms, alkynyl of 3 through 8 carbon atoms, cycloalkyl of 3 through 12 carbon atoms, cycloalkenyl of 4 through 12 carbon atoms, cycloalkyl alkyl of 4 through 13 carbon atoms, cycloalkenyl alkyl of 5 through 13 carbon atoms, (substituted cycloalkyl)alkyl of 5 through 14 carbon atoms, or (substituted cycloalkenyl) alkyl of 5 through 14 carbon atoms;

R_2 is hydrogen, chlorine, fluorine, bromine, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, butoxy, alkenyl of 3 through 6 carbon atoms, cyano, alkylthio of 1 through 4 carbon atoms or 2-hydroxy alkyl of 2 through 6 carbon atoms;

R_3 is alkyl of 1 through 5 carbon atoms;

X is oxygen or sulfur; and

M is hydrogen, sodium, potassium, or lithium.

In the above formula, R_2 and R_3 can be taken together by way of a methylene bridge to form a ring. This methylene bridge can be represented by the formula $—(CH_2)_n—$, where n is 3, 4 or 5.

When M is sodium, potassium, or lithium, the negative charge of the molecule in Formula 1 is distributed throughout the ring because of electron shifts. For convenience, however, it is represented as in Formula 1.

In Formula 1, the term "substituted alkyl" is intended to include such radicals as

Bromoalkyl of 1 through 10 carbon atoms,
Chloroalkyl of 1 through 10 carbon atoms,
Hydroxyalkyl of 1 through 8 carbon atoms,
Alkoxyalkyl of 2 through 8 carbon atoms,
Alkoxy carbonyl alkyl of 3 through 8 carbon atoms, and
Cyanoalkyl of 2 through 8 carbon atoms.

Similarly, the term "substituted phenyl" embraces radicals such as

Phenyl,
Furfuryl,
Naphthyl,
o-Biphenyl,
Pyridyl,
Chlorophenyl,

Bromophenyl,
Alkoxyphenyl,
Dibromophenyl,
Fluorophenyl,
Trichlorophenyl,
Alkylphenyl of 7 through 11 carbon atoms,
Dialkylphenyl of 8 through 12 carbon atoms,
Chloroalkylphenyl of 7 through 10 carbon atoms,
Nitrochlorophenyl,
Nitrophenyl,
Dichloronitrophenyl,
Chloroalkoxyphenyl of 7 through 11 carbon atoms,
Trifluoromethylphenyl,
Tetrahydronaphthyl, and
Indenyl.

The term "substituted aralkyl" is intended to include such radicals as

Furfuryl,
Benzyl,
Phenylalkyl of 8 through 11 carbon atoms (total),
Chlorobenzyl,
Dichlorobenzyl,
Alkylbenzyl of 8 through 11 carbon atoms (total),
Dialkylbenzyl of 9 through 13 carbon atoms (total),
Nitrobenzyl,
Alkoxybenzyl of 8 through 11 carbon atoms (total), and
Naphthylmethyl.

The terms "cycloalkyl," "cycloalkenyl," "cycloalkyl alkyl," and "cycloalkenyl alkyl" will include

Cyclohexyl,
Cyclohexenyl,
Cyclohexylalkyl,
Cyclohexenylalkyl,
Cyclopentyl,
Cyclopentenyl,
Cyclopentylalkyl,
Cyclopentenylalkyl,
Norbornyl,
Norbornenyl,
Norbornylalkyl,
Norbornenylalkyl,
Bicyclo (2,2,2) octyl,
Bicyclo (2,2,2) octenyl,
Bicyclo (2,2,2) octylalkyl,
Bicyclo (2,2,2) octenylalkyl,
Cyclopropyl,
Cyclobutyl,
Cyclobutylalkyl,
Cyclobutenyl,
Cyclobutenylalkyl,
Hexahydroindanyl,
Tetrahydroindanyl,
Hexahydroindenyl,
Hexahydroindenyl alkyl,
Tetrahydroindanyl alkyl,
Hexahydroindanyl alkyl,
Hexahydro-4,7-methanoindenyl,
Tetrahydro-4,7-methanoindanyl,
Hexahydro-4,7-methanoindanyl,
Hexahydro-4,7-methanoindenyl alkyl,
Tetrahydro-4,7-methanoindanyl alkyl,
Hexahydro-4,7-methanoindanyl alkyl,
Decahydronaphthyl,
Decahydronaphthyl alkyl,
Tetrahydronaphthyl,
Tetrahydronaphthyl alkyl,
Decahydro-1,4-methanonaphthyl,
Decahydro-1,4-methanonaphthyl alkyl,
Octahydro-1,4-methanonaphthyl,

Octahydro-1,4-methanonaphthyl alkyl,
Decahydro-1,4-5,8-dimethanonaphthyl,
Decahydro-1,4-5,8-dimethanonaphthyl alkyl,
Octahydro-1,4-5,8-dimethanonaphthyl, and
Octahydro-1,4-5,8-dimethanonaphthyl alkyl.

These cyclic substituents can be further substituted with alkyl groups of 1 through 4 carbon atoms, methoxy, chlorine or bromine.

The compounds produced according to the processes of this invention are herbicidally active and can be formulated with suitable inert carriers to give compositions which can be used to control undesired vegetation.

Those compounds produced according to these processes which are not substituted in the 5-position are also useful as intermediates, which can react with typical electrophilic reagents such as halogens, nitric acid, formaldehyde, and thiocyanogen to form other herbicidal 3,5,6-trisubstituted uracils. Details regarding these phenomena can be found in copending application Serial No. 217,521, filed August 28, 1962.

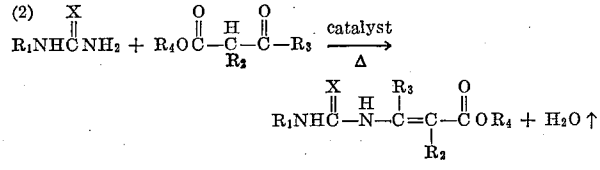
All the steps involved in practicing the processes of this invention can be carried out in one reaction vessel. Intermediate compounds need not be isolated and purified.

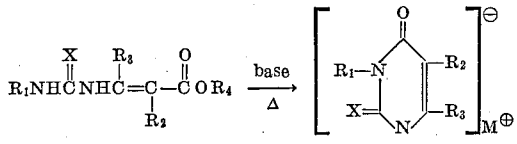
The processes of this invention give substantially higher yields of the compounds of Formula 1 than was previously possible. These higher yields are obtained without the production of undesirable by-products.

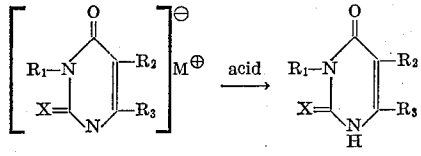
It should be noted that the compounds produced according to the processes of this invention can be used directly as herbicides without recrystallization.

The compounds of Formula 1 are prepared by a sequence of three reactions. The first reaction comprises heating a mono-substituted urea or thiourea with a β-keto ester in the presence of a catalyst to form a 3-(3-substituted ureido)-2,3-unsaturated ester. The second reaction comprises heating this unsaturated ester with a strong base. This effects ring closure and produces the corresponding 3,6-substituted uracil salt. If desired, this salt can then be converted to the 3,6-substituted uracil by reacting it with an acid.

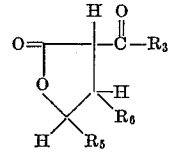
This three-step reaction sequence is illustrated by the following equations:

(2) 

(3) 

(4) 

The β-keto ester starting material in Equation 2 can be replaced by a γ-lactone having the following formula:

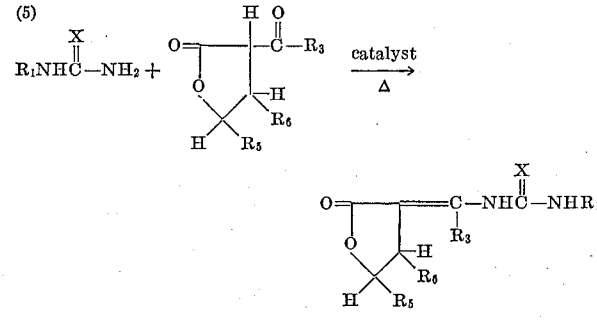


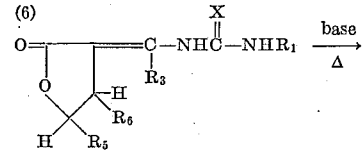
where

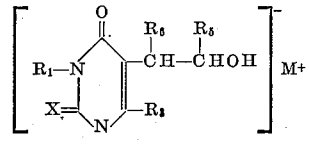
R_5 is hydrogen or an alkyl group of 1 to 4 carbon atoms, and

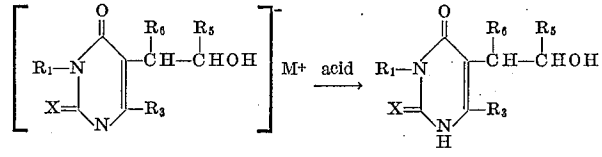
R_6 can be hydrogen or an alkyl group of 1 to 4 carbon atoms.

If this replacement is made, the process proceeds according to the following squence:

(5) 

(6) 



(7) 

In the foregoing equations, R_1, R_3, X, and M have the same meaning as in Formula 1. R_4 is an alkyl radical containing from 1 to 6 carbon atoms.

The reactions illustrated by the foregoing equations can be carried out in one vessel. For illustrative purposes, however, the reaction conditions for each equation will be discussed separately.

PROCEDURE AND PROCESS VARIABLES FOR STEP 1

A mixture of β-keto ester or γ-lactone, catalyst, and mono-substituted urea or thiourea stirred and distilled to remove evolved water. For maximum yields, the reaction temperature should be kept low and water should be removed as rapidly as possible.

In order to obtain maximum theoretical conversion, the mole ratio of the β-keto ester or γ-lactone to the mono-substituted urea or thiourea should be about 1 to 1. In practice, the ester-lactone/urea mole ratio can vary from 0.7 to 1.30 moles of ester or lactone for each mole of urea.

Although the reaction proceeds satisfactorily in the absence of a liquid medium, it is facilitated if it is carried out in such a medium. This liquid must be a substance which does not react with the reagents or products involved in the entire process under the described reaction conditions, and preferably boils in the temperature range of 50° C. to 140° C. at pressures of 25–1500 mm. of mercury. Inert liquids which can be used for this reaction include cyclohexane, hexane, heptane, octane, o-dichlorobenzene, benzene, toluene, xylene, chlorobenzene, diisobutylene, or mixtures of these liquids with a water-miscible liquid such as dioxane. Xylene is preferred. Preferably about 0.3 to 3 parts by weight of the inert liquid are used for each part of reactants.

When the reaction is carried on without an inert liquid medium, the reaction temperatures are maintained in the

range of 50° to 110° C. until approximately the theoretical amount of water is collected by distillation. The pressure should be such that the reaction mixture boils in the proper temperature range.

It is preferred to carry on the reaction in an inert liquid water-immiscible medium because the water formed during the reaction can be more rapidly removed by azeotropic distillation.

When using an inert liquid medium, the reaction should be run at a temperature of 60–100° C., and the pressure should be adjusted so that the medium boils at the reaction temperature. The reaction is generally heated for from 1 to 15 hours or until little or no water evolves from the reaction. The reaction time will, of necessity, depend upon many variables, such as temperature, pressure, reactants, catalyst, and the rate at which the solvent is distilled.

For maximum yield of product it is desirable to rapidly remove the water which is formed and to avoid high temperatures. The resulting short reaction times at moderate temperatures minimize decomposition of reactants or of the unsaturated ester intermediate.

For initiation of the reaction and its successful operation, it is necessary to have a catalyst present. This can be a hydrogen acid, a Lewis acid, an amine salt of a hydrogen acid or an ammonium sulfonate. Illustrative of these are sulfuric, hydrochloric, hydrobromic, hydrofluoric, phosphoric, polyphosphoric, formic, maleic, p-toluenesulfonic, chloroacetic, and methanesulfonic acids; $FeCl_3$, BF_3, or $AlCl_3$; and methylammonium p-toluenesulfonate. Para-toluenesulfonic acid and sulfuric acid are the preferred catalysts.

The amount of catalyst employed varies with the specific reactants used. Generally, however, 0.0005 to 1.0 mole of catalyst per mole of β-keto or γ-lactone ester is sufficient.

The reaction product is a mixture of the desired intermediate, 3-(3-substituted ureido)-2,3-unsaturated ester, the acid catalyst, and residual starting materials, with or without an inert liquid carrier. If unreacted urea is present as a solid at the end of the reaction, it can be filtered from the reaction mixture. The catalyst need not be removed since it is present in such small amounts.

The reaction mixture is used directly in step 2, without further treatment.

PROCEDURE AND PROCESS VARIABLES FOR STEP 2

If step 1 is run in the absence of a solvent, the unsaturated ester intermediate is diluted with an inert liquid such as xylene, ethanol, toluene, methanol, ispropanol, tetrahydrofuran, dioxane, benzene, or mixtures thereof. If the catalyst is first neutralized, water can also be used as a diluent.

In any event, the mixture is then heated for a short time at about 55–155° C. with 0–100% excess of a strong base such as sodium alkoxide, sodium hydroxide, or potassium hydroxide. Sodium alkoxides contained in nonaqueous liquids are preferred as bases and media for this reaction step. Heating is continued for about 15 to 60 minutes.

Ring closure occurs rapidly at this temperature and the corresponding salt of the desired 3,6-substituted uracil is obtained as a residue by removing the liquid medium. These salts can be used directly as aqueous solutions in herbicidal applications.

A technical grade of the uracil salt can be obtained in a one-vessel operation by not removing the inert liquid medium and the acid catalyst from the unsaturated ester intermediate, and by adding extra base in an amount sufficient to neutralize the acid catalyst and effect the ring closure. If the medium is water-immiscible, the salt of the uracil can be isolated as an aqueous solution by extracting with water.

PROCEDURE AND PROCESS VARIABLES FOR STEP 3

The addition of a sufficient amount of an aqueous solution of an acid to lower the pH of the reaction mixture to about 2–7 neutralizes the salts of the 3,6-substituted uracils and precipitates the acidic forms of these products as a separate phase which can be easily separated from the reaction mass by ordinary procedures. Any acid stronger than the uracil is satisfactory for this purpose. Sulfuric and hydrochloric acids are preferred.

In a one-vessel operation, the reaction mixture obtained in step 2 containing the inert liquid, the salt of the desired 3,6-substituted uracil, and the acid catalyst, is diluted with sufficient water and stirred to dissolve the salt. The inert, water-immiscible liquid separates and can be removed readily by conventional procedures. The water layer is treated with acid to neutralize the 3,6-substituted uracil salt. The acidic form of the substituted uracil then precipitates out of solution as a separate phase.

This invention will be better understood by referring to the following illustrative examples:

Example 1

To a slurry of 290 parts by weight of n-butylurea in 1600 parts of benzene is added 325 parts of ethyl acetoacetate and 6 parts of polyphosphoric acid. The mixture is stirred and refluxed for 48 hours, during which time the water formed is removed by azeotropic distillation. The resulting benzene solution is decanted from a gummy residue and the benzene is removed from the solution by distillation. To the material remaining after this solvent removal is added 135 parts of sodium methoxide in 1200 parts of ethanol. The mixture is heated to reflux for 15 minutes. The ethanol is then removed by distillation, the residue taken up in 2000 parts of water, and the aqueous mixture extracted twice with 500 parts of ethyl ether. The aqueous phase is then acidified with concentrated aqueous hydrochloric acid, causing 3-butyl-6-methyluracil to precipitate from solution. The 3-butyl-6-methyluracil is filtered, washed with water, and dried. The melting point of the product is 186°–188° C.

The uracils set out in Table I are prepared according to the method of Example 1 by replacing the butylurea and ethyl acetoacetate with molecularly equivalent amounts of the ureas, thioureas, and β-keto esters also set forth in Table I.

TABLE I

β-Keto Ester	Parts by Weight	Urea or Thiourea	Parts by Weight	Substituted Uracil Product
Ethyl acetoacetate	325	Butylthiourea	330	3-butyl-6-methyl-2-thiouracil.
Do	325	Isopropylthiourea	295	3-isopropyl-6-methyl-2-thiouracil.
Ethyl 3-ketovalerate	360	Amylurea	325	3-amyl-6-ethyluracil.
Ethyl 3-ketohexanoate	395	Isoamylthiourea	365	3-isoamyl-6-propyl-2-thiouracil.
Ethyl acetoacetate	325	Isobutylurea	290	3-isobutyl-6-methyluracil.
Do	325	Allylurea	250	3-allyl-6-methyluracil.
Ethyl 3-ketoheptanoate	430	Allylthiourea	290	3-allyl-6-butyl-2-thiouracil.
Ethyl acetoacetate	325	Propynylurea	245	3-propynyl-6-methyluracil.
Do	325	Hexylurea	360	3-hexyl-6-methyluracil.
Do	325	Phenylurea	339	3-phenyl-6-methyluracil.
Do	325	Isopropylurea	256	3-isopropyl-6-methyluracil.

Example 2

A mixture containing 102 parts by weight of isopropylurea and 800 parts by weight of toluene is stirred and refluxed, and a mixture of 10 parts by weight of p-toluenesulfonic acid and 143 parts by weight of ethyl acetoacetate is gradually added. The water given off by the reaction is continuously removed. When evolution of water ceases, the toluene is stripped off and the residue is dissolved in 500 parts by weight of absolute ethyl alcohol. To this solution is added 44 parts by weight of sodium hydroxide. The mixture is heated at reflux and stirred until complete solution is obtained. The alcohol is distilled off and the residue is taken up in water. Neutral impurities are removed by washing the solution with benzene. The aqueous solution is cooled and acidified. The 3-isopropyl-6-methyluracil which precipitates as a white solid is filtered and dried.

The uracils set out in Table II are prepared according to the method of Example 2 by replacing the isopropylurea and ethyl acetoacetate with equivalent amounts of the ureas, thioureas, and β-keto esters also set forth in Table II.

TABLE II

β-Keto Ester	Parts by Weight	Urea or Thiourea	Parts by Weight	Substituted Uracil Product
Ethyl 2-methyl-3-ketobutyrate	144	Methylurea	74	3,5,6-trimethyluracil.
Do	144	Phenylurea	136	3-phenyl-5,6-dimethyluracil.
Ethyl 2-butyl-3-ketovalerate	199	p-Chlorophenylthiourea	186	3-(p-chlorophenyl)-5-butyl-6-ethyl-2-thiouracil.
Ethyl 2-ethyl-3-ketovalerate	171	m-Tolylurea	150	3-(m-tolyl)-5,6-diethyluracil.
Ethyl 2-methyl-3-ketooctanoate	199	p-Anisylurea	166	3-(p-anisyl)-5-methyl-6-amyluracil.
Do	157	o-Nitrophenylthiourea	197	3-(o-nitrophenyl)-5-ethyl-6-methyl-2-thiouracil.
Ethyl 2-propyl-3-ketohexanoate	199	Allylurea	100	3-allyl-5,6-dipropyluracil.
Ethyl 2-methyl-3-ketobutyrate	144	β-Phenethylthiourea	180	3-(β-phenethyl)-5,6-dimethyl-2-thiouracil.

Example 3

A mixture containing 28.4 parts by weight of cyclohexylurea, 28.6 parts by weight of ethyl acetoacetate, 2.0 parts by weight of phosphoric acid, 100 parts by weight of dioxane, and 88 parts by weight of benzene is stirred and heated at reflux temperature. The water given off by the reaction is continuously distilled and trapped out of the distillate as the lower layer. The resulting solution is ring closed in situ by adding a solution containing 14 parts by weight of sodium methoxide and 40 parts by weight of methanol. The solution is refluxed for 10 minutes and then 200 parts by weight of water are added. On shaking, the sodium salt of the desired uracil product dissolves in the water. The aqueous solution is separated from the organic layer and acidified. White, solid 3-cyclohexyl-6-methyluracil is separated by filtration and dried. Its melting point is 233.5–235.5° C.

The uracil set out in Table III are prepared according to the method of Example 3 by replacing the cyclohexylurea and ethyl acetoacetate with equivalent amounts of the ureas, thioureas, and β-keto esters also set forth in Table III.

TABLE III

β-Keto Ester	Parts by Weight	Urea or Thiourea	Parts by Weight	Substituted Uracil Product
Methyl 2-methyl-3-keto-butyrate	25.4	Cyclooctylurea	33.9	3-cyclooctyl-5,6-dimethyluracil.
Do	28.8	Cyclopentylthiourea	29.1	3-cyclopentyl-5-ethyl-6-methyl-2-thiouracil.
Ethyl acetoacetate	25.4	Cycloheptylthiourea	33.9	3-cycloheptyl-6-methyl-2-thiouracil.
Methyl 2-methyl-3-ketobutyrate	25.4	Cyclopentenylurea	25.9	3-cyclopentenyl-5,6-dimethyluracil.
Ethyl 2-butoxy-3-ketobutyrate	40.2	Decylurea	38.0	3-decyl-5-butoxy-6-methyluracil.
Ethyl 2-chloro-3-ketobutyrate	32.9	3-methoxypropylurea	26.4	3-(3-methoxypropyl)-5-chloro-6-methyluracil.
Ethyl 2-fluoro-3-ketobutyrate	29.6	Norbornylmethylurea	33.6	3-(norbornylmethyl)-5-fluoro-6-methyluracil.
Ethyl 2-methoxy-3-ketobutyrate	32.0	Sec.-butylurea	23.2	3-sec.-butyl-5-methoxy-6-methyluracil.
Ethyl 2-bromo-3-ketobutyrate	41.8	n-Pentylurea	26.0	3-penytl-5-bromo-6-methyluracil.
Ethyl 2-cyano-3-ketobutyrate	31.0	4-chlorobenzylurea	36.8	3-(4-chlorobenzyl)-5-cyano-6-methyluracil.
Ethyl 2-ethoxy-3-ketobutyrate	35.6	3-methylcyclohexylmethylurea	34.0	3-(3-methylcyclohexylmethyl)-5-ethoxy-6-methyluracil.
Ethyl 2-methylthio-3-ketobutyrate	35.2	Isopropylurea	20.4	3-isopropyl-5-methylthio-6-methyluracil.
Ethyl acetoacetate	25.4	Tert.-butylurea	23.2	3-tert.-butyl-6-methyluracil.
Do	25.4	(1,3-dimethylbutyl)urea	28.8	3-(1,3-dimethylbutyl)-6-methyluracil.
Do	25.4	Norbornylmethylurea	33.6	3-(norbornylmethyl)-6-methyluracil.
Do	25.4	4-methoxycyclohexylurea	34.4	3-(4-methoxycyclohexyl)-6-methyluracil.
Ethyl 2-bromo-3-ketobutyrate	41.8	(1-ethylpropyl)urea	26.0	3-(1-ethylpropyl)-5-bromo-6-methyluracil.
Ethyl acetoacetate	25.4	Cyclohexylmethylurea	31.2	3-cyclohexylmethyl-6-methyluracil.
Ethyl 2-methyl-3-ketobutyrate	28.2	Cyclohexylurea	28.4	3-cyclohexyl-5,6-dimethyluracil.
Ethyl acetoacetate	25.4	Norbornylurea	30.8	3-norbornyl-6-methyluracil.
Do	25.4	3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-5-ylurea.	38.4	3-(3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-5-yl)-6-methyluracil.
Ethyl 2-allyl-3-ketobutyrate	34.0	(2-methylcyclohexylmethyl)urea	34.0	3-(2-methylcyclohexylmethyl)-5-allyl-6-methyluracil.

Example 4

A mixture containing 404 parts by weight of isopropylurea, 686 parts by weight of ethyl-2-cyclopentanone-1-carboxylate, 40 parts by weight of phosphoric acid, 1000 parts by weight of dioxane, and 879 parts by weight of benzene is stirred at reflux for 4 hours. During this time, the water given off by the reaction is trapped out of the distillate by azeotropic distillation. The solvent is removed by distillation and the solid residue is dissolved in 2360 parts by weight of absolute ethanol containing 248 parts by weight of sodium methoxide. This mixture is then heated at reflux for ten minutes, cooled, and filtered to remove the alcohol solvent. The filtered solid is essentially pure 3-isopropyl-5,6-trimethyleneuracil, sodium salt.

Other uracil salts, set out in Table IV, are prepared according to the method of this example by replacing the isopropylurea and ethyl-2-cyclopentanone-1-carbox-

ylate with equivalent amounts of the ureas, thioureas, and keto esters also set forth in Table IV.

TABLE IV

Keto Ester	Parts by Weight	Urea or Thiourea	Parts by Weight	Alkoxide	Uracil Salt Product
Ethyl 2-cyclopentanone-1-carboxylate	162	Methylurea	74.0	Sodium methoxide	3-methyl-5,6-trimethyleneuracil, sodium salt.
Do	162	Sec. butylurea	116.0	do	3-sec. butyl-5,6-trimethyleneuracil, Na salt.
Ethyl 2-cyclohexanone-1-carboxylate	187	Methylurea	74.0	do	3-methyl-5,6-tetramethyleneuracil, Na salt.
Do	187	Cyclohexylurea	142.0	Potassium ethoxide	3-cyclohexyl-5,6-tetramethyleneuracil, K salt.
Ethyl 2-cyclopentanone-1-carboxylate	162	do	142.0	Sodium ethoxide	3-cyclohexyl-5,6-trimethyleneuracil, Na salt.
Do	162	Allylthiourea	100.0	do	3-allyl-5,6-trimethylene-2-thiouracil, Na salt.

Uracils can be obtained from uracil salts such as those listed in Table IV by dissolving the salt in 10 parts by weight of water and adding enough hydrochloric or sulfuric acid to reduce the pH to 4.0. A solid essentially pure uracil will be formed which is easily isolated by filtration.

Example 5

A mixture of 63.8 grams of isopropylurea, 65 grams of ethylacetoacetate, 0.94 gram of ammonium p-toluene sulfonate, and 440 grams of benzene is heated at reflux temperature for 7 hours, during which time 9 milliliters of water collects in the reflux line trap.

The mixture is cooled to room temperature, and the unreacted urea is filtered off.

29.5 grams of sodium methoxide are then added to the filtrate. The resulting mixture is heated at reflux temperature for 30 minutes and then cooled to 65° C.

500 grams of water are then added, and the mixture is cooled to 30° C., whereupon the aqueous and organic phases separate.

The aqueous phase is removed and its pH adjusted to 6.2 by the addition of 13.7 milliliters of concentrated sulfuric acid. The resulting slurry is filtered, the solids are washed with 250 grams of water, and dried to give 64.5 grams of 3-isopropyl-6-methyluracil.

Example 6

The following compounds can be substituted for the ammonium p-toluene sulfonate in Example 5, with equivalent results:

	Grams
Concentrated sulfuric acid	0.18
Isopropylammonium sulfate	1.1
Triethylammonium p-toluene sulfonate	1.40
Methylammonium p-toluene sulfonate	1.0

Example 7

A mixture of 440 parts by weight of benzene, 63.7 parts by weight of isopropylurea, 65 parts by weight of ethyl acetoacetate, and 0.94 part by weight of ferric chloride is stirred and refluxed.

The water given off is azeotropically distilled out of the reaction medium and collected in a trap by upward displacement of benzene. When water evolution ceases, the mixture is cooled. Excess isopropylurea crystallizes and is filtered off.

The benzene solution containing the intermediate is now stirred and refluxed for ½ hour with 37 parts by weight of sodium methoxide. The mixture is then cooled and mixed well with 400 parts by weight of water. The basic aqueous layer is separated and neutralized with hydrocholric acid. The resulting white precipitate is filtered off, washed with 200 parts by weight of water at 10° C., and dried to give 3-isopropyl-6-methyluracil.

Example 8

A mixture of 426 parts by weight of cyclohexylurea, 423 parts by weight of 2-acetylbutyrolactone, 879 parts by weight of benzene, 1030 parts by weight of dioxane, and 40 parts by weight of 85% phosphoric acid is stirred at reflux temperature.

The water given off is removed by azeotropic distillation. When no more water is given off, the solution is cooled, decanted, and concentrated to dryness under reduced pressure. Three recrystallizations of the resulting solid from acetonitrile give 2-(2-hydroxyethyl)-3-cyclohexylureido)crotonic acid, γ-lactone.

A mixture of 302 parts by weight of the 2-(2-hydroxyethyl) - 3 - (3-cyclohexylureido)crotonic acid, γ-lactone, 1580 parts by weight of absolute ethanol, and 130 parts by weight of sodium methoxide is refluxed for 15 minutes. It is then concentrated to dryness at reduced pressure, and the residue is dissolved in 1500 parts by weight of water.

This solution is cooled, acidified with hydrochloric acid to pH 5, and the resulting white precipitate, 3-cyclohexyl-5-(2-hydroxyethyl)-6-methyluracil, is filtered off, dried, and recrystallized from a mixture of ethanol and water.

The uracils set out in Table V are prepared according to the method of Example 8 by replacing the cyclohexylurea and 2-acetylbutyrolactone with equivalent amounts of the ureas, thioureas, and γ-lactones also set forth in Table V.

TABLE V

β-Keto Lactone	Parts by Weight	Urea or Thiourea	Parts by Weight	Substituted Uracil Product
2-acetylbutyrolactone	423	Isopropylurea	306	5-(2-hydroxyethyl)-6-methyl-3-isopropyluracil.
Do	423	Isopropylthiourea	354	5-(2-hydroxyethyl)-6-methyl-3-isopropyl-2-thiouracil.
Do	423	Sec.-butylurea	348	3-sec.-butyl-5-(2-hydroxyethyl)-6-methyluracil.
Do	423	Phenylurea	407	5-(2-hydroxyethyl)-6-methyl-3-phenyluracil.
Do	423	p-Chlorophenylurea	515	3-(4-chlorophenyl)-5-(2-hydroxyethyl)-6-methyluracil.
2-acetyl-(3,4-diethyl)-butyrolactone	468	3,4-dichlorophenylurea	615	3-(3,4-dichlorophenyl)-5-(1-ethyl-2-hydroxybutyl)-6-methyluracil.

Example 9

A mixture of 657 parts by weight of isopropylurea, 725 parts by weight of methyl acetoacetate, 1350 parts by weight of xylene and 3 parts by weight of concentrated sulfuric acid is stirred and refluxed for 14 hours at 80° C. and a pressure of 110 mm. of Hg. During this time, 95 parts by weight of water is removed from the reaction mass.

To this reaction mass, at atmospheric pressure and 80° C., are added 1550 parts by weight of a 24% solution

of sodium methoxide in methanol. Fifteen hundred to 1700 parts by weight of the methanol-xylene solution are then distilled off.

Forty-eight hundred parts by weight of water are then added to the reaction mass and the mixture is agitated thoroughly. The phases are then allowed to separate at 70° C. The aqueous phase is drawn off and brought to pH 5.9 with concentrated sulfuric acid.

The resulting slurry is cooled to room temperature and the solid 3-isopropyl-6-methyluracil is filtered, washed with water, and dried.

Example 10

A mixture of 786 parts by weight of methylacetoacetate, 986 parts by weight of isopropylurea, 658 parts by weight of xylene and 3 parts by weight of sulfuric acid is stirred and refluxed for 14 hours at 87° C. and a pressure of 100 mm. of murcury. During this time, 115 parts by weight of water are removed from the reaction mass.

The vacuum is then released and 560 parts by weight of sodium methoxide are slowly added to the reaction mass at 86° C. The mixture is held at 80–90° C. for 30 minutes and is then extracted with 9000 parts by weight of water. The aqueous phase is brought to a pH of 6.5 with concentrated sulfuric acid; the resulting slurry of 3-isopropyl-6-methyluracil is filtered, washed with water, and dried.

Example 11

A mixture of 797 parts by weight (25% molar excess) of isopropylurea, 812 parts by weight of ethylacetoacetate, 1350 parts by weight of xylene, and 5 parts by weight of p-toluenesulfonic acid is stirred and refluxed for 14 hours at 85° C. and a pressure of 110 mm. of mercury. During this time, 93 parts by weight of water are removed from the reaction mass.

The reaction mass is then cooled to room temperature and excess isopropylurea is removed by filtration. The urea filter cake is washed with 260 parts by weight of xylene; this xylene is then added to the filtrate.

To this solution are added 371 parts by weight of powdered sodium methoxide. The resulting slurry is heated to 80° C. and stirred for 30 minutes. It is then cooled to 25° C. and 6500 parts by weight of water are added. This mixture is stirred for 5–10 minutes and the phases are then allowed to separate.

The aqueous phase is removed and brought to a pH of 6.1 with concentrated sulfuric acid. The resulting slurry of 3-isopropyl-6-methyluracil is filtered, washed with water, and dried.

Example 12

A mixture of 725 parts by weight of methylacetoacetate, 657 parts by weight (3% molar excess) of isopropylurea, 1350 parts by weight of xylene, and 5 parts by weight of sulfuric acid is stirred and refluxed for 14 hours at 82° C. and a pressure of 110 mm. of mercury. During this time, 93 parts by weight of water are removed from the reaction mass.

With the temperature at 80° C., 370 parts by weight of sodium methoxide are then slowly added to the mixture and the temperature is held at 80° C. for 30 minutes. The mixture is then cooled to 60° C. and extracted with 6500 parts by weight of water. The aqueous layer is separated and brought to a pH of 6.0 with concentrated sulfuric acid. The resulting slurry of 3-isopropyl-6-methyluracil is filtered, washed with water, and dried.

The methylacetoacetate in this example can be replaced with 812 parts by weight of ethylacetoacetate, with similar results.

Example 13

A mixture of 363 parts by weight of sec.-butylurea, 325 parts by weight of ethyl acetoacetate, 2500 parts by weight of xylene, and 5 parts by weight of p-toluenesulfonic acid is stirred and refluxed for 14 hours at 82° C. and a pressure of 110 mm. of mercury. During this time, 42 parts by weight of water are removed from the mixture.

To this mixture, at room temperature, are added 148 parts by weight of sodium methoxide. This mixture is then heated to 80° C. and held there for 30 minutes. The mixture is then cooled to 60° C. and extracted with 800 parts by weight of cold tap water. The aqueous phase is brought to a pH of 6.0, and the resulting slurry of 3-sec.-butyl-6-methyluracil is filtered, washed with water, and dried.

Example 14

A mixture of 130 g. sec.-butylurea, 125 g. methylacetoacetate, 225 g. xylene, and 0.75 g. sulfuric acid is heated to reflux at a pressure of 110 mm. (absolute), with agitation. Enough heat is supplied to reflux the mixture at 40 to 45 g./min. This reflux is passed to a decanter, where water is separated before returning the xylene phase to the reactor.

After four hours, during which time the temperature of the reaction mixture rises from 80 to 87° C., the rate of water removal drops to less than 0.5 g./hr., and 16.1 g. of water (calculated after analysis of the aqueous layer from the decanter) have been collected.

Reflux is terminated and a solution of 64 g. of sodium methoxide in 150 g. of methanol is rapidly added to the reactor. The mixture is then heated to 90° C., with distillation, over a period of 30 to 60 minutes. Water, 650 g. is rapidly added and the two-phase system is stirred to extract the sodium salt of 3-sec.-butyl-6-methyluracil into the aqueous phase.

This mixture is then cooled to 50° C. and the phases separated. The lower aqueous phase contains 186 g. of the sodium salt of 3-sec.-butyl-6-methyluracil and can be used directly as a herbicide, or if desired, the free uracil can be isolated from it by cooling it to 10° C. and adding sufficient 2.5 N aqueous hydrochloric acid to reduce the pH to 6.0, while maintaining the temperature below 15° C. with external cooling. The resulting slurry is then filtered, the solids washed with two ice cold 200 ml.-portions of water and dried at 60° C. in a vacuum oven. There are obtained 133 g. of 3-sec.-butyl-6-methyluracil.

Example 15

A mixture of 660 g. of sec.-butylurea, 600 g. of methylacetoacetate, 1080 g. of xylene and 3.6 g. of sulfuric acid are heated to reflux at 70 mm. pressure (absolute) to give a reflux rate of 115–125 ml./min. The reflux is passed to a decanter where water is separated from the reflux before returning the xylene phase to the reactor.

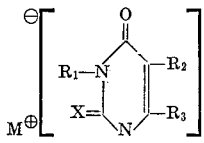
After five hours there are collected from the decanter 90 g. of a water phase analyzing 93% H_2O. At this point the rate of water removal has decreased to about 0.8 g./hr. and the reaction is terminated.

Sodium methoxide solution (1370 g., 29.3% sodium methoxide in methanol) is added rapidly and the reaction mass is heated to 90° C. over a one-hour period to distill 1180 g. of a methanol-xylene mixture. Water, 2500 g., is added to the residue which is then agitated for 15 minutes.

On separating the phases there are obtained 930 g. of a xylene phase which can be recovered for recycle, and 4100 g. of an aqueous phase analyzing 20.3% 3-sec.-butyl-6-methyluracil. This uracil is in solution as its sodium salt and, as such can be used as a herbicide. Alternatively, the purified uracil can be isolated as described in Example 14.

The claims are:

1. The process for preparing a uracil compound having the formula



where:

R_1 is selected from the group consisting of
alkyl of 1 through 10 carbon atoms,
substituted alkyl of 1 through 8 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, hydroxy, alkoxy, alkoxycarbonyl, and cyano,
aryl of 5 through 10 carbon atoms,
substituted phenyl, wherein said substituent is selected from the group consisting of chlorine, bromine, fluorine, alkoxy, alkyl of 1 through 6 carbon atoms, nitro, trifluoromethyl, 1,2-tetramethylene, and 1,2-trimethylenylene,
aralkyl of 5 through 13 carbon atoms,
substituted aralkyl of 5 through 13 carbon atoms, wherein said substituent is selected from the group consisting of chlorine, nitro, alkyl, and alkoxy,
tetrahydronaphthylalkyl,
alkenyl of 3 through 8 carbon atoms,
alkynyl of 3 through 8 carbon atoms,
cycloalkyl of 3 through 12 carbon atoms,
substituted cycloalkyl of 3 through 12 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, methoxy, and alkyl,
cycloalkenyl of 4 through 12 carbon atoms,
substituted cycloalkenyl of 4 through 12 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, methoxy, and alkyl,
cycloalkyl alkyl of 4 through 13 carbon atoms,
cycloalkenyl alkyl of 5 through 13 carbon atoms,
(substituted cycloalkyl)alkyl of 5 through 14 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, methoxy, and alkyl, and
(substituted cycloalkenyl)alkyl of 5 through 14 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, methoxy, and alkyl;

R_2 is selected from the group consisting of hydrogen, chlorine, fluorine, bromine, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, butoxy, alkenyl of 3 thruogh 6 carbon atoms, cyano, alkylthio of 1 through 4 carbon atoms, and hydroxy alkyl of 2 through 6 carbon atoms;

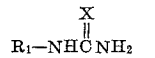
R_3 is alkyl of 1 through 5 carbon atoms;

X is selected from the group consisting of oxygen and sulfur; and

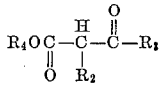
M is selected from the group consisting of hydrogen, sodium, potassium and lithium;

with the proviso that R_2 and R_3 can be linked together by a methylene bridge of the formula $-(CH_2)_n-$ where n is a number 3 through 5; said process comprising

(a) heating a urea of the formula

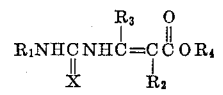


where R_1 and X have the same meaning as above with a β-keto ester of the formula



where R_2 and R_3 have the same meaning as above, and R_4 is an alkyl radical containing from 1 to 6 carbon atoms,

the ester-urea mole ratio ranging from 0.7–1.30 to 1, at a temperature of from 60° to 100° C. in the presence of from 0.0005 to 1.0 mole of an acid catalyst per mole of said β-keto ester and an inert, water-immiscible liquid medium, while effecting the continuous removal of the water of reaction from the reaction mixture by azeotropic distillation so as to form a substituted ureido ester of the formula



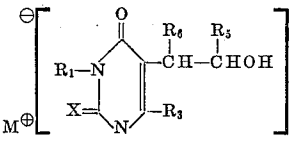
where R_1, R_2, R_3, R_4, and X have the same meaning as above;

(b) heating said substituted ureido ester at a temperature of from 55° to 155° C. for from 15 to 60 minutes with a strong base, in an inert liquid medium, to form a uracil salt;

(c) converting said uracil salt to its acidic form by contacting with an acid stronger than the uracil portion of said salt; and

(d) recovering said acidic form from the reaction mass of step (c) as the uracil product.

2. The process for preparing a uracil compound having the formula



where:

R_1 is selected from the group consisting of
alkyl of 1 through 10 carbon atoms,
substituted alkyl of 1 through 8 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, hydroxy, alkoxy, alkoxycarbonyl, and cyano,
aryl of 5 through 10 carbon atoms,
substituted phenyl, wherein said substituent is selected from the group consisting of chlorine, bromine, fluorine, alkoxy, alkyl of 1 through 6 carbon atoms, nitro, trifluoromethyl, 1,2-tetramethylene, and 1,2-trimethylenylene,
aralkyl of 5 through 13 carbon atoms,
substituted aralkyl of 5 through 13 carbon atoms, wherein said substituent is selected from the group consisting of chlorine, nitro, alkyl, and alkoxy,
tetrahydronaphthylalkyl,
alkenyl of 3 through 8 carbon atoms,
alkynyl of 3 through 8 carbon atoms,
cycloalkyl of 3 through 12 carbon atoms,
substituted cycloalkyl of 3 through 12 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, methoxy, and alkyl,
cycloalkenyl of 4 through 12 carbon atoms,
substituted cycloalkenyl of 4 through 12 carbon atoms wherein said substituent is selected from the group consisting of bromine, chlorine, methoxy, and alkyl,
cycloalkyl alkyl of 4 through 13 carbon atoms,
cycloalkenyl alkyl of 5 through 13 carbon atoms,
(substituted cycloalkyl)alkyl of 5 through 14 carbon atoms, wherein said substituent is selected from the group consisting of bromine, chlorine, methoxy, and alkyl, and
(substituted cycloalkenyl)alkyl of 5 through 14 carbon atoms, wherein said substituent is selected

from the group consisting of bromine, chlorine, methoxy, and alkyl;

R_3 is alkyl of 1 through 5 carbon atoms;

R_5 and R_6 are selected from the group consisting of hydrogen and alkyl of 1 through 4 carbon atoms;

X is selected from the group consisting of oxygen and sulfur; and

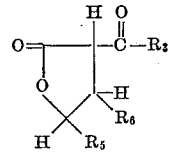
M is selected from the group consisting of hydrogen, sodium, potassium and lithium;

said process comprising

(a) heating a urea of the formula

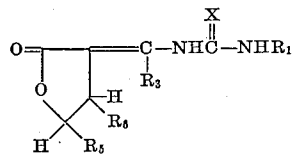


where R_1 and X have the same meaning as above with about an equivalent weight of a γ-lactone of the formula



where R_3, R_5, and R_6 have the same meaning as above,

at a temperature of from 60° to 100° C. in the presence of 0.0005 to 1 mole of an acid catalyst per mole of said γ-lactone and an inert, water-immiscible liquid medium, while effecting the continuous removal of the water of reaction from the reaction mixture by azeotropic distillation so as to form an intermediate of the formula



where R_1, R_3, R_5, R_6, and X have the same meaning as above;

(b) heating said intermediate at a temperature of from 55° to 155° C. for from 10 to 30 minutes with a base selected from the group consisting of alkali metal hydroxides and alkoxides containing from 1 to 4 carbon atoms in an inert liquid medium, to form a uracil salt;

(c) converting said uracil salt to its acidic form by contacting with an acid stronger than the uracil portion of said salt; and

(d) recovering said acidic form from the reaction mass of step (c) as the uracil product.

3. A process according to claim 1 wherein 3-sec.-butyl-6-methyluracil is formed by reacting sec.-butylurea with a compound selected from the group consisting of methyl acetoacetate and ethyl acetoacetate.

4. A process according to claim 1 wherein 3-cyclohexyl-5,6-trimethyleneuracil is formed by reacting cyclohexylurea with 2-carbethoxycyclopentanone.

5. A process according to claim 1 wherein 3-(2-norbonrylmethyl)-6-methyluracil is formed by reacting 1-(2-norbornylmethyl)urea with a compound selected from the group consisting of methyl acetoacetate and ethyl acetoacetate.

6. A process according to claim 1 wherein 3-isobutyl-6-methyluracil is formed by reacting isobutylurea with a compound selected from the group consisting of methyl acetoacetate and ethyl acetoacetate.

7. A process according to claim 1 wherein 3-(1-ethylpropyl)-6-methyluracil is formed by reacting 1-(3-amyl) urea with a compound selected from the group consisting of methyl acetoacetate and ethyl acetoacetate.

8. A process according to claim 1 wherein 3-tert.-butyl-6-methyluracil is formed by reacting tert.-butylurea with a compound selected from the group consisting of methyl acetoacetate and ethyl acetoacetate.

9. A process according to claim 1 wherein 3-(1,3-dimethylbutyl)-6-methyluracil is formed by reacting 1-(1,4- dimethylbutyl)urea with a compound selected from the group consisting of methyl acetoacetate and ethyl acetoacetate.

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