230. *Purines, Pyrimidines, and Glyoxalines. Part XII.* Some Oxaloacetic Acid Derivatives as Precursors of Orotic Acids and Related Carboxymethylenehydantoins, and a New Synthesis of 6-Methyluracils.*

By R. K. Ralph, G. Shaw, and (in part) R. N. Naylor.

cis- and *trans*-5-Carboxymethylene-1-phenylhydantoins, and *trans*-β-carboxy-β-methoxy(or chloro)acryloyl-ureas and -thioureas, have been prepared as possible precursors of orotic acids. Some reactions of these compounds are described. A new unambiguous synthesis of 1-substituted 6-methyluracils from acetoacetylurethane and primary amines is described and the oxidation of some of these compounds is discussed.

Orotic acid (IIa; R = R′ = R″ = H) and its 3-alkyl or 3-aryl derivatives † have been synthesised by base-catalysed rearrangement of 5-carboxymethylenehydantoin [1] (I; R = R′ = R″ = H, X = O) or its corresponding 3-substituted derivatives,[2] by the oxidation of 6-methyluracil (III; R = R′ = H) by alkaline potassium ferricyanide [3] or of 6-formyl-2-thiouracil by hydrogen peroxide and chromic oxide.[4] A synthesis of the biochemically important orotic acid glycosides related to and including orotidine [1-β-D-ribofuranosyl orotic acid (IIa; R = R″ = H, R′ = β-D-ribofuranosyl)] requires a method for the synthesis of 1-substituted orotic acids which could be used for the introduction of a glycosyl residue at $N_{(1)}$. 1-Methylorotic acid (IIa; R′ = Me, R = R″ = H) was prepared by oxidation of 1 : 6-dimethyluracil (III; R = Me, R′ = H) with alkaline ferricyanide,[5] an adaptation of the method used by Behrend and Struve [3] for oxidation of 6-methyluracil to orotic acid. 1-Substituted 6-methyluracils have hitherto been prepared only by vigorous alkylation of 6-methyluracil, an ambiguous method which leads to mixtures of 1- and 3-substituted pyrimidines.[6] 1 : 6-Dimethyluracil was also obtained unexpectedly from *N*-methylthiourea and diketen; [7] with other *N*-substituted ureas this reaction leads to 3-substituted uracils.

These methods appear to be unsuitable for the introduction of a glycosyl residue and in addition Fox, Yung, and Wempen [5] suggested that steric factors would hinder direct glycosylation at position 1 in orotic acid. In preliminary experiments we could find no evidence of condensation between metal derivatives of ethyl orotate and 2 : 3 : 5-tri-*O*-benzoylribosyl chloride.

We now report a preliminary examination of some possible synthetical routes to orotic acids which might be suitable for the introduction of glycosyl residues at position 1.

The ready rearrangement of 5-carboxymethylenehydantoin or its 3-substituted derivatives to orotic acids [1,2] suggested that the hitherto unknown 1-substituted carboxymethylenehydantoins might similarly give rise to 1-substituted orotic acids.

Ethyl acetylenedicarboxylate reacted vigorously with dithiourethane with loss of ethanol. Of the several structures possible for the product, the thiazoline structure (IV) is assigned for the following reasons. With aniline the compound liberated ethanethiol, and the product is regarded as the 1-phenylthiohydantoin (Ib; R = Et, R′ = Ph,

* Part XI, *J.*, 1959, 50.

† In this paper, as in others of this Series, the " pyrimidine " numbering of orotic acid is used.

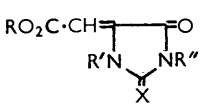
[1] Mitchell and Nyc, *J. Amer. Chem. Soc.*, 1947, **69**, 674, 1382.
[2] Atkinson, Maguire, Ralph, Shaw, and Warrener, *J.*, 1957, 2363.
[3] Behrend and Struve, *Annalen*, 1911, **378**, 153.
[4] Johnson and Schroeder, *J. Amer. Chem. Soc.*, 1931, **53**, 1989; Heidelberger and Hurlbert, *ibid.*, 1950, **72**, 4704.
[5] Fox, Yung, and Wempen, *Biochim. Biophys. Acta*, 1957, **23**, 295.
[6] Behrend and Buckendorff, *Annalen*, 1911, **385**, 314; Behrend and Thurm, *ibid.*, 1902, **323**, 160; Behrend and Hartel, *ibid.*, 1921, **422**, 83.
[7] Lacey, *J.*, 1954, 839.

R″ = H) rather than the isomeric anilinothiazoline since it was immediately soluble in dilute alkali and was stable to heat, and its ultraviolet absorption spectrum and that of the corresponding acid (Ib; R = R″ = H, R′ = Ph) derived from it by hydrolysis were very similar to that of the 3-phenylthiohydantoin (Ib; R = Et, R′ = H, R″ = Ph) which was prepared by the reaction of ethyl oxaloacetate and phenylthiourea. Alternative structures for the thiazoline would have given rise with aniline to either the 3-phenylthiohydantoin or to derivatives of thio-orotic acid.

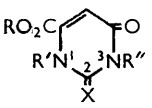
Whereas the compound (Ib; R = Et, R′ = H, R″ = Ph) behaved like its oxygen analogue and was readily converted into 3-phenyl-2-thio-orotic acid (IIb; R = R′ = H, R″ = Ph) when treated with dilute sodium hydroxide solution, as indicated by a characteristic change in its ultraviolet absorption spectrum to that of a thiouracil, the 1-phenyl derivative (Ib; R = Et, R′ = Ph, R″ = H) gave only the corresponding acid (Ib; R = R″ = H, R′ = Ph). Attempts to convert the thio-compound (Ib; R = Et, R′ = Ph, R″ = H) into the oxygen analogue by conventional methods of oxidation were unsuccessful. With ethyl iodide an ethyl derivative, presumably (V; R = Et), was obtained but hydrolysis of this with hydrogen bromide in acetic acid gave only the acid (V; R = H) and decomposition products.

The required *trans*-5-ethoxycarbonylmethylene-1-phenylhydantoin (Ia; R = Et, R′ = Ph, R″ = H) was eventually obtained by reaction of diethyl anilinofumarate (VI), prepared from aniline and ethyl oxaloacetate,[8] with the sodium derivative of urethane. The structure of the hydantoin was confirmed by a characteristic ultraviolet absorption spectrum [2] and by comparison with the *cis*-isomer described below. Hydrolysis of the ester (Ia; R = Et, R′ = Ph, R″ = H) with sodium hydroxide gave the acid (Ia; R = R″ = H, R′ = Ph) but this failed to rearrange to the related orotic acid under a variety of conditions. The amide (VII), prepared from (Ia; R = Et, R′ = Ph, R″ = H) and methanolic ammonia, equally resisted rearrangement. Further confirmation of the hydantoin structure (Ia; R = R″ = H, R′ = Ph) came from its decarboxylation when heated in quinoline containing a trace of copper powder, the methylenehydantoin (VIII; R = H) being obtained whereas a pyrimidine would have given the known 1-phenyluracil.

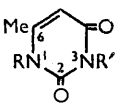
The failure of the above 1-phenylhydantoins to rearrange to orotic acids under the conditions tried prompted us to examine the preparation of possible precursors of orotic acid analogous to compounds successfully used as precursors of uracils and thiouracils,



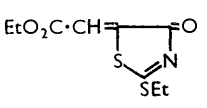
(I) a: trans, X = O
b: X = S
c: cis, X = O



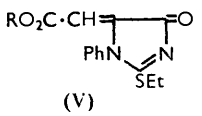
(II) a: X = O
b: X = S



(III)



(IV)



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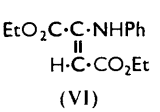

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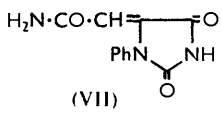

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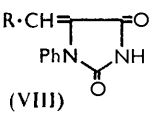


(VIII)

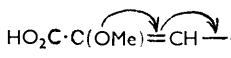
and described in other Parts of this series.[9] These compounds include β-alkoxyacryloyl *iso*cyanates and *iso*thiocyanates and derived acylurethanes and ureas, and have been used for the introduction of glycosyl radicals into uracils and thiouracils. Intermediates of this type required for the preparation of orotic acids would include β-oxaloacetyl-ureas and -thioureas (IX; R′ = H) and corresponding *O*-alkyl derivatives.

One route to the latter series required initially an alkoxy-fumaric or -maleic acid.

[8] Wislicenus and Spiro, *Ber.*, 1889, **22**, 3348.
[9] Shaw, *J.*, 1955, 1834; Shaw and Warrener, *J.*, 1958, 153, 157, 2294.

Ethoxyfumaric acid (Xa; R = R″ = H, R′ = Et) has been prepared by the reaction of ethyl *meso*-dibromosuccinate with sodium ethoxide,[10] from ethyl oxaloacetate and ethyl iodide in the presence of silver oxide,[11] and from ethyl acetylenedicarboxylate and sodium ethoxide.[12] In our hands none of these methods proved satisfactory, but an excellent yield of diethyl methoxyfumarate (Xa; R = R″ = Et, R′ = Me) was readily obtained by reaction of ethyl oxaloacetate with diazomethane. Hydrolysis of the ester gave methoxyfumaric acid (Xa; R = R″ = H, R′ = Me), the *trans*-configuration of which followed from its method of preparation and from comparison with the *cis*-isomer which was isolated in a subsequent reaction.

The acid (Xa; R = R″ = H, R′ = Me) with one equivalent of potassium hydroxide gave a crystalline acid salt regarded as (Xa; R = K, R′ = Me, R″ = H) since electron-donation from the methoxy-group across the unsaturated system would tend to leave the α-carboxyl group the more acidic (cf. A), and this was confirmed by subsequent reactions.



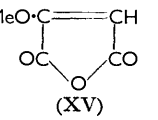
(A)

The corresponding silver salt with methyl iodide gave the acid ester (Xa; R = R′ = Me, R″ = H), isolated as a sodium salt (Xa; R = R′ = Me, R″ = Na) which with thionyl chloride gave a mixture of the acid chloride (XIa; R = Me) and methoxymaleic anhydride (XV). Hydrolysis of the anhydride gave the crystalline *cis*-acid (Xb; R = R″ = H, R′ = Me) which differed from the *trans*-derivative in melting point and paper chromatographic behaviour in much the same way as maleic differs from fumaric acid. The ratio of acid chloride to anhydride obtained in this reaction varied inversely with the temperature at which the mixture was distilled, suggesting that the heat-labile *trans*-chloride is converted into the *cis*-derivative (XIb) which then cyclises with loss of methyl chloride. Also complete hydrolysis of the acid chloride gave the *trans*-acid although paper chromatograms of the mother-liquors from the hydrolysis revealed the presence of a small amount of the *cis*-acid possibly due to the presence of a trace of *cis*-acid chloride (XIb).

$RO_2C{\cdot}C(OR'){:}CH{\cdot}CO{\cdot}NR''{\cdot}CX{\cdot}NHR'''$ (IX) (a) X = O, (b) X = S } *trans*

$RO_2C{\cdot}C(OR'){:}CH{\cdot}CO_2R''$ (X) (a) *trans*; (b) *cis*

$MeO_2C{\cdot}C(OMe){:}CH{\cdot}COCl$ (XI) (a) *trans*; (b) *cis*



(XV)

$RO_2C{\cdot}C(OMe){:}CH{\cdot}CO{\cdot}NHPh$ (XII) *trans*

$PhNH{\cdot}CO{\cdot}C(OMe){:}CH{\cdot}CO_2H$ (XIII) *cis*

$MeO_2C{\cdot}C(OMe){:}CH{\cdot}CO{\cdot}NCS$ (XIV)

The *trans*-chloride (XIa) with aniline readily gave the ester-anilide (XII; R = Me) which was hydrolysed to the acid-anilide (XII; R = H). A similar compound, presumably (XIII), was obtained from the anhydride and aniline; the direction of acylation suggested here would follow from the greater reactivity of the α-carbonyl group implied in the above discussion. Reaction of the *trans*-chloride (XIa) with potassium thiocyanate in acetonitrile gave an oil, presumably the *iso*thiocyanate (XIV), which could not be distilled without decomposition but with aniline readily gave the acylthiourea (IXb; R = R′ = Me, R″ = H, R‴ = Ph) from which the acid (IXb; R = R″ = H, R′ = Me, R‴ = Ph) was obtained by alkaline hydrolysis. Attempts to cyclise these compounds to the corresponding thio-orotic acid were unsuccessful.

Similarly, when the acid chloride (XIa) was heated in benzene solution containing a trace of sulphuric acid, with urea, methylurea, or phenylurea, the linear acylureas (IXa; R = R′ = Me, R″ = H, R‴ = H, Me, and Ph respectively) were obtained. Treatment of the urea ester (IXa; R = R′ = Me, R″ = H, R‴ = Ph) with aqueous alkali gave the

[10] Michael and Maisch, *J. prakt. Chem.*, 1892, **46**, 233; Pum, *Acad. Wissenschaft, Wien*, 1893, II*b*, **102**, 508; *Monatsh.*, 1893, **14**, 492.
[11] Nef, *Annalen*, 1893, **276**, 227; Lander, *J.*, 1903, **83**, 417.
[12] Croxall and Schneider, U.S.P. 2,535,012/1950; U.S.P. 2,571,212/1951.

acid (IXa; R = R″ = H, R′ = Me, R‴ = Ph), but further attempts to cyclise this with a variety of reagents have so far been unsuccessful. However, relatively mild treatment of the ester (IXa; R = R′ = R‴ = Me, R″ = H) with sodium hydroxide gave a mixture which included 1-methyluracil. By contrast the urea (IXa; R = R′ = Me, R″ = R‴ = H) with dilute alkali very readily afforded orotic acid. The formation of orotic acid confirmed the structures assigned to these intermediates since an α-methoxyacylurea would have given the hydantoin (I; R = R′ = R″ = H, X = O). In addition, the products from the *trans*-chloride (XIa) and phenylurea afforded a small amount of a compound, probably (IXa; R = R′ = Me, R″ = Ph, R‴ = H), which with alkali readily gave 3-phenylorotic acid (IIa; R = R′ = H, R″ = Ph).

The results suggest that in compounds of type (IX) only those structures which contain a terminal NH_2 group are able to cyclise readily. The formation of 1-methyluracil from the urea (IXa; R = R′ = R‴ = Me, R″ = H) is of special interest and indicates that decarboxylation is occurring at some intermediate aliphatic stage since orotic acids are known to resist decarboxylation *in vitro*, although they readily undergo enzymic decarboxylation.

In a similar series of reactions, chlorofumaric acid (XVI; R = R′ = H), prepared from tartaric acid and phosphorus pentachloride,[13] was converted *via* the acid potassium salt and the silver salt into the half-ester salt (XVI; R = Me, R′ = K) which with thionyl chloride gave the acid chloride (XVII). The orientation of substituents is assumed to be the same as in the compounds derived from methoxyfumaric acid. The chloride (XVII) with aniline gave the anilide (XVIII) and with phenylurea the linear acylurea (XIX). The latter product with aqueous sodium hydroxide gave the *cis*-1-phenylhydantoin (Ic; R = R″ = H, R′ = Ph); the structure assigned to this compound is confirmed by its ultraviolet absorption spectrum which was similar to that of the *trans*-form, and by decarboxylation which gave the methylenehydantoin (VIII; R = H) identical with the substance obtained by decarboxylation of the *trans*-acid. The *cis*-hydantoin is apparently formed by *cis*-addition of the terminal NH group in the acetylene (XX).

$RO_2C{\cdot}CCl{:}CH{\cdot}CO_2R'$ (XVI) *trans*

$MeO_2C{\cdot}CCl{:}CH{\cdot}COCl$ (XVII) *trans*

$MeO_2C{\cdot}CCl{:}CH{\cdot}CO{\cdot}NHPh$ (XVIII) *trans*

$MeO_2C{\cdot}CCl{:}CH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NHPh$ (XIX) *trans*

$MeO_2C{\cdot}C{\vdots}C{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NHPh$ (XX)

Since 1-methylorotic acid was prepared by oxidation of 1 : 6-dimethyluracil with alkaline ferricyanide, we examined more general unambiguous routes to 1-substituted 6-methyluracils than those available and mentioned earlier.

Initially, β-chlorocrotonyl chloride, prepared from β-chlorocrotonic acid and thionyl chloride,[14] was treated with silver cyanate; the product, presumably β-chlorocrotonyl *iso*cyanate with aniline and methylamine gave the acylureas (XXI; R = Ph and Me respectively). The last compound (XXI; R = Me) with sodium hydroxide gave a low yield of 1 : 6-dimethyluracil, and similarly the phenyl analogue (XXI; R = Ph) gave a compound with properties expected of 6-methyl-1-phenyluracil (III; R = Ph, R′ = H), but in view of the results obtained with the chlorofumaric acid derivatives the alternative ethylidenehydantoin structure (VIII; R = Me) for this compound could not be neglected since ultraviolet absorption data for this type of compound are scanty. These doubts were resolved by the preparation of acetoacetylurethane (XXII) from diketen and urethane in acetic acid. The acylurethane reacted rapidly with ethylamine, propylamine, *cyclo*hexylamine, and aniline, giving the linear derivatives (XXIII; R = Et, Pr, C_6H_{11}, and Ph), and with methylamine giving 1 : 6-dimethyluracil directly. The linear compounds

[13] Perkin, *J.*, 1888, **53**, 695.
[14] Autenrieth, *Ber.*, 1896, **29**, 1667.

readily cyclised to 6-methyluracils (III; R = Et, Pr, C_6H_{11}, and Ph, R′ = H) when heated alone or, better, in collidine. The phenyl derivative obtained here was identical with that obtained from β-chlorocrotonic acid. In contrast to 1 : 6-dimethyluracil which is readily oxidised by ammoniacal ferricyanide to 1-methylorotamide, the compounds (III; R = Et, Pr, C_6H_{11}, and Ph) were recovered in good yield after long treatment with this oxidising agent. Other oxidising agents used so far have proved equally unsuccessful, but the method remains of potential value, and alternative methods of oxidation are being examined in an attempt to overcome the steric effect of the 1-substituent in these compounds.

$Me{\cdot}CCl{:}CH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NHR$ (XXI) *trans*

$Me{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CO_2Et$ (XXII)

$Me{\cdot}C(NHR){:}CH{\cdot}CO{\cdot}NH{\cdot}CO_2Et$ (XXIII)

Experimental

5-Ethoxycarbonylmethylene-2-ethylthio-4-oxothiazole.—Diethyl acetylenedicarboxylate [15] (8·5 g.) was added to ethyl dithiocarbamate [16] (6·05 g.), a hot, homogeneous, dark solution being soon obtained. This was cooled when the temperature exceeded 60°, to give a solid. *5-Ethoxycarbonylmethylene-2-ethylthio-4-oxothiazole* (10·3 g.) separated from ethanol as yellow needles, m. p. 85° (Found: C, 44·1; H, 4·5; N, 5·7. $C_9H_{11}O_3NS_2$ requires C, 43·8; H, 4·3; N, 5·7%), $\lambda_{max.}$ 272 mμ (ε 5025) in ethanol.

5-Carboxymethylene-1-phenyl-2-thiohydantoin.—The preceding thiazole (1·23 g.) in benzene (10 ml.) was warmed with aniline (0·5 ml.). Ethanethiol was soon liberated and a solid separated. The mixture was kept at room temperature for 24 hr. and the solid collected. *5-Ethoxycarbonylmethylene-1-phenyl-2-thiohydantoin* (1·13 g.) crystallised from ethanol as yellow plates, m. p. 210° (Found: C, 56·3; H, 4·35; N, 9·95. $C_{13}H_{12}O_3N_2S$ requires C, 56·5; H, 4·35; N, 10·15%), $\lambda_{max.}$ 327 mμ (ε 17,000) in ethanol. A mixed m. p. with the 3-phenyl derivative was depressed. This thiohydantoin (0·1 g.) was heated at 100° with 1·5N-sodium hydroxide (1 ml.) for 30 min. Acidification of the cooled solution gave a solid precipitate. *5-Carboxymethylene-1-phenyl-2-thiohydantoin* (0·05 g.) separated from methanol as pale yellow needles, m. p. 300° (decomp.) (Found: C, 53·1; H, 3·05; N, 11·05. $C_{11}H_8O_3N_2S$ requires C, 53·25; H, 3·25; N, 11·3%), $\lambda_{max.}$ 323 mμ (ε 16,230) and 225 mμ (ε 16,200) in ethanol. The compound was recovered unchanged after being heated with 2N-sodium hydroxide for several hr., and was not desulphurised by alkaline hydrogen peroxide or chloroacetic acid.

5-Ethoxycarbonylmethylene-3-phenyl-2-thiohydantoin.—Dry hydrogen chloride was passed through a hot (steam-bath) solution of diethyl oxaloacetate [from the sodium salt (22 g.)] and phenylthiourea (15·2 g.) in acetic acid (24 ml.) for 30 min. The solution was set aside at 0° for 24 hr. and a crystalline precipitate collected. *5-Ethoxycarbonylmethylene-3-phenyl-2-thiohydantoin* (4 g.) recrystallised from ethanol as slender pale yellow needles, m. p. 175° (Found: C, 56·5; H, 4·35; N, 10·35. $C_{10}H_{12}O_3N_2S$ requires C, 56·5; H, 4·4; N, 10·35%), $\lambda_{max.}$ 340 mμ (ε 26,680) in ethanol.

3-Phenyl-2-thio-orotic Acid.—The last-mentioned thiohydantoin (0·1 g.) was stirred with 2N-sodium hydroxide at 20° until a clear solution was obtained. This was acidified to precipitate *3-phenyl-2-thio-orotic acid* (0·08 g.) which separated from ethanol as an ethanol *solvate*, m. p. 200° (decomp.) (Found: C, 53·45; H, 4·95; N, 8·75. $C_{11}H_8O_3N_2S,1\frac{1}{4}C_2H_6O$ requires C, 53·05; H, 5·1; N, 9·15%), or from water as a *hydrate*, m. p. 226° (decomp.) (Found: C, 48·8; H, 3·65; N, 10·25. $C_{11}H_8O_3N_2S,1\frac{1}{4}H_2O$ requires C, 48·8; H, 3·8; N, 10·35%), $\lambda_{max.}$ 275 mμ (ε 16,000) in ethanol.

5-Ethoxycarbonylmethylene-2-ethylthio-4 : 5-dihydro-4-oxo-1-phenylglyoxaline.—A solution of 5-ethoxycarbonylmethylene-1-phenyl-2-thiohydantoin (0·5 g.) in ethanol (10 ml.) containing sodium ethoxide (0·136 g.) and ethyl iodide (1 ml.) was heated under reflux for 6 hr.; the solution had by then become neutral. The solvent was evaporated and the residue with ethanol gave crystals. The *glyoxaline* (0·29 g.) separated from ethanol as yellow needles, m. p. 120° (Found: C, 58·6; H, 5·3; N, 8·9. $C_{15}H_{16}O_3N_2S$ requires C, 59·0; H, 5·25; N, 9·2%).

[15] Michael, *J. prakt. Chem.*, 1892, **46**, 224.
[16] Delépine, *Bull. Soc. chim. France*, 1903, **29**, 52.

This ester (0·33 g.) was boiled with 30% hydrogen bromide in acetic acid (2 ml.) for 1 hr. The solution was evaporated *in vacuo* and the residue dissolved in N-sodium hydroxide, and the filtered solution acidified to precipitate the *glyoxaline-acid* (0·22 g.) which separated from ethanol as needles, m. p. 200° (decomp.) (Found: C, 56·8; H, 4·5; N, 10·0. $C_{13}H_{12}O_3N_2S$ requires C, 56·8; H, 4·4; N, 10·15%).

trans-5-*Ethoxycarbonylmethylene*-1-*phenylhydantoin*.—Diethyl anilinofumarate [8] (7·9 g.) was added to a suspension of sodium urethane (3·35 g.) in ether (40 ml.). The mixture was warmed, rapidly darkening while the solid dissolved. After 10 min. the solution was added to water (10 ml.), and the ether evaporated to leave a solid. The *sodium salt* of the hydantoin separated from ethanol as a *dihydrate* which formed needles, m. p. 126° (Found: C, 48·55; H, 4·9; N, 8·7. $C_{13}H_{11}O_4N_2Na,2H_2O$ requires C, 49·05; H, 4·7; N, 8·8%). The salt (0·626 g.) was stirred with 2N-hydrochloric acid (5 ml.), and the resulting solid collected; trans-5-*ethoxycarbonylmethylene*-1-*phenylhydantoin* (0·5 g.) recrystallised from water as needles, m. p. 167° (Found: C, 60·05; H, 5·6; N, 10·85. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·75%), $\lambda_{max.}$ 297 (ε 6100) and 232 mμ (ε 11,350) in water.

The ester (1 g.) was heated at 100° with 2N-sodium hydroxide (5 ml.) for 30 min., and the cooled solution acidified, precipitating the *hydantoin-acid* (0·6 g.) which separated from water as hydrated prisms, m. p. 222° (decomp.) (Found: C, 52·4; H, 3·85; N, 11·3. $C_{11}H_8O_4N_2,H_2O$ requires C, 52·8; H, 3·2; N, 11·2. $C_{11}H_8O_4N_2,1\frac{1}{2}H_2O$ requires C, 52·3; H, 4·05; N, 11·1%), $\lambda_{max.}$ 308 (ε 6960) and 230 mμ (ε 11,790) in ethanol. Attempts to rearrange this compound to a pyrimidine failed. Prolonged treatment with aqueous alkali at 100° or with sodium methoxide caused decomposition.

5-*Methylene*-1-*phenylhydantoin*.—A solution of the foregoing acid (0·423 g.) in quinoline (3 ml.) containing copper powder (0·1 g.) was boiled under reflux for 1 hr. The cooled solution was extracted with N-sodium hydroxide (5 ml.), and the aqueous phase washed with ether, then acidified to precipitate 5-*methylene*-1-*phenylhydantoin* (0·023 g.) which separated from water as needles, m. p. 160° (Found: C, 63·6; H, 4·3; N, 14·65. $C_{10}H_8O_2N_2$ requires C, 63·9; H, 4·25; N, 14·9%).

trans-5-*Carbamoylmethylene*-1-*phenylhydantoin*.—The last-mentioned ester (0·164 g.) was heated in a sealed tube at 100° with saturated methanolic ammonia (5 ml.) for 1 hr. The solvent was evaporated and the residue washed with dilute hydrochloric acid. The *amide* (0·125 g.) separated from ethanol as needles, m. p. 276 (decomp.) (Found: C, 57·15; H, 4·05; N, 18·0. $C_{11}H_9O_3N_3$ requires C, 57·15; H, 3·9; N, 18·2%), $\lambda_{max.}$ 307 (ε 4650) and 235 mμ (ε 7430) in water.

Diethyl Methoxyfumarate.—Diazomethane was prepared from *N*-methyl-*N*-nitrosourea (90 g.) and 50% aqueous potassium hydroxide under ether (1300 ml.). The dried (KOH) ether solution was added to a solution of diethyl oxaloacetate (94 g.) in ether (100 ml.) at 0°. A vigorous reaction occurred and nitrogen was briskly liberated. After 30 min., excess of diazomethane was removed with acetic acid, and the solution washed with sodium hydrogen carbonate solution and water, dried, and evaporated to an oil which was distilled *in vacuo* to give *diethyl methoxyfumarate* (82 g.), b. p. 100°/0·5 mm., n_D^{25} 1·4725 (Found: C, 53·15; H, 6·75. $C_7H_{14}O_5$ requires C, 53·45; H, 7·0%). An alcoholic solution of the ester failed to give a colour with ferric chloride.

Methoxyfumaric Acid.—The ester (10 g.) was shaken with 4·08N-sodium hydroxide (25 ml.) at room temperature until a clear solution was obtained (3 hr.). This was cooled to 0° and acidified with 10N-hydrochloric acid (20 ml.), and the solution extracted with ether (6 × 20 ml.). Evaporation of the combined and dried extracts left a crystalline residue. *Methoxyfumaric acid* (5·3 g.) recrystallised from ethyl acetate–hexane as needles, m. p. 146° (Found: C, 41·0; H, 3·95%; equiv., 145·4. $C_5H_6O_5$ requires C, 41·1; H, 4·1%; equiv., 146%. On an ascending paper chromatogram, in butanol–formic acid–water (10 : 2 : 15), the acid travelled as a discrete acidic spot, R_F 0·86.

Potassium Hydrogen Methoxyfumarate.—(*a*) One half of a solution of methoxyfumaric acid (14 g.) in water (400 ml.) was neutralised to phenolphthalein with potassium hydroxide and then added to the remaining half of the solution. The solvent was removed *in vacuo* (bath 50°) to give the *potassium salt*, which crystallised from aqueous methanol as prisms (Found: C, 32·4; H, 2·8. $C_5H_5O_5K$ requires C, 32·6; H, 2·7%). (*b*) Diethyl methoxyfumarate (20·2 g.) was shaken with 3·62N-potassium hydroxide (55·25 ml.) until a clear solution of near neutrality was obtained. This was cooled to 5° and treated with acetic acid (6 ml.), to give a crystalline

precipitate; evaporation of the filtrate to 30 ml. gave a further small quantity of the salt. The potassium salt (13 g.) separated from aqueous methanol as prisms, m. p. >300° (Found: C, 32·7; H, 2·75%).

Sodium trans-β-*Methoxy*-β-*methoxycarbonylacrylate*.—The foregoing potassium salt (12·75 g.) in warm water (100 ml.) with silver nitrate (12·8 g.) in water (12 ml.) gave a solid precipitate (11·7 g.) which was collected and washed with water, ethanol, and ether, and dried *in vacuo* in the dark. A suspension of the silver salt (11·42 g.) in ether (50 ml.) containing methyl iodide (10 ml.) was boiled under reflux for 6 hr. The mixture was filtered, and the filtrate evaporated *in vacuo* to a strongly acidic oil (5·25 g.). This was suspended in water (10 ml.) and titrated to pH 8 (external indicator) with sodium hydroxide solution. The clear solution was evaporated *in vacuo* (bath <50°) and the solid residue dried over phosphoric oxide *in vacuo* and then at 100°/0·1 mm. The *sodium salt* (5·1 g.) separated from ethanol–ether as prisms, m. p. >300° (Found: C, 39·0; H, 4·05. $C_6H_7O_5Na$ requires C, 39·55; H, 3·85%).

Reaction of Sodium trans-β-*Methoxy*-β-*methoxycarbonylacrylate with Thionyl Chloride*.—(*a*) Freshly distilled thionyl chloride (20 ml.) was added to a suspension of the sodium salt (17·1 g.) in ether (50 ml.): a vigorous reaction occurred. The mixture was refluxed for 3 hr., then distilled *in vacuo* from an excess of glass wool to give trans-β-*methoxy*-β-*methoxycarbonylacryloyl chloride* (8 g.), b. p. 65°/0·1 mm. (Found: C, 41·0; H, 3·8. $C_6H_7O_4Cl$ requires C, 40·35; H, 3·9%), and *methoxymaleic anhydride* (2·1 g.), b. p. 100°/0·1 mm. (Found: C, 47·05; H, 3·2. $C_5H_4O_4$ requires C, 46·9; H, 3·15%). (*b*) In a similar reaction the sodium salt (12·3 g.) and thionyl chloride (10 ml.) gave the acid chloride (3·88 g.), b. p. 98—100°/8 mm., and the anhydride (2·16 g.), b. p. 140°/8 mm.

Methoxymaleic Acid.—The foregoing anhydride (0·5 ml.) was stirred and gently warmed with water (0·5 ml.) until a homogeneous solution was obtained. This was cooled to give a crystalline precipitate. *Methoxymaleic acid* (0·5 g.) separated from a little ethyl acetate as prisms, m. p. 126° (Found: C, 41·3; H, 4·0%; equiv., 148). The acid ran as a single acidic spot, R_F 0·57, on paper in butanol–formic acid–water (10 : 2 : 15).

Hydrolysis of trans-β-*Methoxy*-β-*methoxycarbonylacryloyl Chloride*.—A little acid chloride was treated with water, the resulting solution evaporated *in vacuo*, and the residue crystallised from ethyl acetate–hexane to give methoxyfumaric acid, m. p. and mixed m. p. 146°. The mother-liquors were chromatographed on paper with butanol–formic acid–water (10 : 2 : 15). A strongly acidic spot (R_F 0·86) corresponding to methoxyfumaric acid, and a weakly acidic spot corresponding to methoxymaleic acid (R_F 0·57), were obtained.

trans-β-*Carboxy*-β-*methoxy*-N-*phenylacrylamide*.—The above acid chloride (0·1 ml.) and aniline (0·1 ml.) were mixed, a vigorous reaction occurring. The solid residue was triturated with dilute hydrochloric acid and the solid filtered off. trans-β-*Methoxycarbonyl*-β-*methoxy*-N-*phenylacrylamide* (0·074 g.) crystallised from aqueous ethanol as plates, m. p. 106° (Found: C, 61·35; H, 5·4; N, 6·1. $C_{12}H_{13}O_4N$ requires C, 61·25; H, 5·55; N, 5·95%). The ester (0·126 g.) was warmed with N-sodium hydroxide (2 ml.) for 5 min. at 60°. The cooled solution when acidified precipitated trans-β-*carboxy*-β-*methoxy*-N-*phenylacrylamide* (0·07 g.) which separated from water as plates, m. p. 125° (Found: C, 60·0; H, 5·05; N, 6·45. $C_{11}H_{11}O_4N$ requires C, 59·75; H, 5·0; N, 6·35%).

cis-β-*Carboxy*-α-*methoxy*-N-*phenylacrylamide*.—Methoxymaleic anhydride (0·5 g.) and aniline (0·5 ml.) were mixed and the resulting solid was washed with dilute hydrochloric acid. The cis-*acid* (0·33 g.) separated from ethanol as needles, m. p. 160° (sealed tube) (Found: C, 59·55; H, 4·7; N, 6·65%).

trans-N-(β-*Methoxy*-β-*methoxycarbonylacryloyl*)-N′-*phenylthiourea*.—The above acid chloride (1·26 g.) in dry acetonitrile (10 ml.) was shaken with dry potassium thiocyanate (0·7 g.) for 1 hr. The resulting orange mixture was evaporated *in vacuo* to a gum which was stirred with dry ether (20 ml.). The mixture was filtered, and the yellow filtrate treated with aniline (0·6 g.), a vigorous exothermal reaction occurring. The cooled solution was washed with dilute hydrochloric acid, dried, and evaporated to a gum which dissolved in ethanol (2 ml.). The solution gave a crystalline precipitate after a short time. trans-N-(β-*Methoxy*-β-*methoxycarbonylacryloyl*)-N′-*phenylthiourea* (0·945 g.) separated from ethanol as prisms, m. p. 140° (Found: C, 53·3; H, 4·85; N, 9·8. $C_{13}H_{14}O_4N_2S$ requires C, 53·05; H, 4·8; N, 9·5%).

trans-N-(β-*Carboxy*-β-*methoxyacryloyl*)-N′-*phenylthiourea*.—The foregoing ester (0·62 g.) was heated with 2N-sodium hydroxide (3 ml.) for 30 min. at 100°. The cooled solution was diluted with water (2 ml.), treated with charcoal, and acidified. The precipitated trans-*acid*

(0·5 g.) crystallised from water as laths, m. p. 220° (decomp.) (Found: C, 51·35; H, 4·4; N, 9·75. $C_{12}H_{12}O_4N_2S$ requires C, 51·45; H, 4·3; N, 10·0%).

cis-N-(β-*Carboxy*-β-*methoxyacryloyl*)-N′-*phenylthiourea*.—When the last-mentioned reaction was carried out with unrecrystallised ester, the acid mother-liquors gave cis-N-(β-*carboxy*-β-*methoxyacryloyl*)-N′-*phenylthiourea* (0·02 g.) which recrystallised from water as prisms, m. p. 166° (Found: C, 51·85; H, 4·2; N, 9·8%).

The foregoing *trans*-ester was unaffected by ethanolic sodium ethoxide and was converted into the *trans*-acid by dry hydrogen chloride in acetic acid. Aqueous or aqueous-alcoholic solutions of the ester were degraded by prolonged treatment with acid, to red tars.

trans-N-(β-*Methoxy*-β-*methoxycarbonylacryloyl*)*urea*.—The above acid chloride (0·56 g.) with urea (0·26 g.) in benzene (20 ml.) containing sulphuric acid (0·01 ml.) was boiled under reflux for 4 hr. The solution was decanted from a dark insoluble gum, then cooled to give a crystalline precipitate. trans-N-(β-*methoxy*-β-*methoxycarbonylacryloyl*)*urea* (0·148 g.) separated from ethanol as needles, m. p. 100° (Found: C, 41·55; H, 5·05; N, 13·7. $C_7H_{10}O_5N_2$ requires 41·6; H, 5·0; N, 13·85%)

Orotic Acid.—The last-mentioned urea (0·25 g.) was warmed for a few min. with 2N-sodum hydroxide (3 ml.), cooled, and acidified to precipitate orotic acid (0·15 g.), m. p. and mixed m. p. 340°. The filtrate was chromatographed on paper in butanol–formic acid–water (77 : 13 : 10): only orotic acid (R_F 0·21) was detected. There was no spot corresponding to carboxymethylenehydantoin (R_F 0·56) which was chromatographed at the same time.

trans-N-(β-*Methoxy*-β-*methoxycarbonylacryloyl*)-N′-*methylurea*.—The above acid chloride (1·026 g.), methylurea (0·413 g.), sulphuric acid (0·02 ml.), and benzene (10 ml.) were boiled together under reflux for 3 hr. The solution was cooled and a crystalline precipitate collected. The trans-*methylurea* (0·35 g.) separated from ethanol as needles, m. p. 138° (Found: C, 44·4; H, 5·65; N, 13·2. $C_8H_{12}O_5N_2$ requires C, 44·45; H, 5·6; N, 12·95%). The compound gave a single absorbing spot (R_F 0·92) when chromatographed on paper in butanol–formic acid–water (77 : 13 : 10). It sublimed unchanged *in vacuo* at temperatures above the m. p., but decomposed when heated at 195° for 30 min. The compound was also recovered after treatment with hydrogen chloride in acetic acid. The urea (0·5 g.) was warmed with 2N-sodium hydroxide (5 ml.) at 50° for 5 min. The cooled solution was acidified to give a solid precipitate. This crystallised from water to give as a first crop unchanged methylurea, m. p. and mixed m. p. 136—137°; a second fraction, m. p. 175—180°, could not be obtained pure. The mother-liquors were chromatographed in butanol–formic acid–water (77 : 13 : 10): absorbing spots of R_F's 0·9, 0·6, and 0·45 were observed. The first of these corresponded to the original methylurea (R_F 0·92) and the last to 1-methyluracil (R_F 0·45). In a solvent system of propanol–hydrochloric acid–water (68 : 20 : 12) an absorbing spot corresponding to 1-methyluracil (R_F 0·88) was again observed. The original acid filtrate was extracted with ethyl acetate. Evaporation of the dried extract and recrystallisation of the residue from ethyl acetate–light petroleum (b. p. 40—60°) gave a small amount of 1-methyluracil (0·03 g.), m. p. and mixed m. p. 233—234°.

trans-N-(β-*Methoxy*-β-*methoxycarbonylacryloyl*)-N′-*phenylurea*.—The above acid chloride (2·61 g.), phenylurea (1·99 g.), sulphuric acid (0·02 ml.), and benzene (40 ml.) were boiled together under reflux for 3 hr. The solvent was removed *in vacuo*: the residual gum crystallised when triturated with ethanol. The *phenylurea* (1·28 g.) recrystallised from ethanol as needles, m. p. 130° (Found: C, 56·0; H, 4·9; N, 10·3. $C_{13}H_{14}O_5N_2$ requires C, 56·1; H, 5·05; N, 10·05%). In this reaction a small amount of crystalline material was insoluble in hot ethanol, had m. p. 234°, and was insoluble in sodium hydrogen carbonate solution. It dissolved when warmed for a few min. with 2N-sodium hydroxide. Acidification of the cooled solution precipitated 3-phenylorotic acid hydrate, m. p. and mixed m. p. 278—280° (decomp.) (Found: C, 52·95; H, 3·75; N, 11·2. Calc. for $C_{11}H_8O_4N_2,H_2O$: C, 52·8; H, 4·05; N, 11·2%).

trans-N-(β-*Carboxy*-β-*methoxyacryloyl*)-N′-*phenylurea*.—The last-mentioned ester (0·433 g.) was heated at 100° for 1 hr. with 2N-sodium hydroxide (2 ml.). The cooled solution was acidified to precipitate the phenylurea (0·4 g.) which separated from water as needles of a *hydrate*, m. p. 180° (Found: C, 51·15; H, 4·75; N, 9·8. $C_{12}H_{12}O_5N_2,\frac{3}{4}H_2O$ requires C, 51·9; H, 4·85; N, 10·1%); a sample dried at 120° for 1 hr. gave analytical figures for the anhydrous *acid* (Found: C, 54·2; H, 4·7; N, 10·55. $C_{12}H_{12}O_5N_2$ requires C, 54·5; H, 4·6; N, 10·6%). The foregoing ester was largely decomposed when treated with hydrogen bromide in acetic acid, aluminium chloride in benzene, or sodium in ammonia, and was converted into the above acid by sodium ethoxide in ethanol at 100° for 2 hr.

trans-β-*Chloro*-β-*methoxycarbonylacryloyl Chloride*.—Half of a solution of chlorofumaric acid [13] (43 g.) in warm water (90 ml.) was neutralised with 10N-potassium hydroxide (to phenolphthalein), then mixed with the remaining solution to give a precipitate. This was collected and a further quantity of the acid *potassium salt* was obtained by evaporation of the filtrate *in vacuo*. The yield of salt, washed with ethanol and ether and dried, was 54 g. A portion of the salt separated from aqueous ethanol as prisms (Found: C, 25·6; H, 1·2. $C_4H_2O_4ClK$ requires C, 25·45; H, 1·05%). The salt (54 g.) was dissolved in water and treated with silver nitrate (50 g.) in a minimum of water, to give a solid precipitate (55 g.). The dry silver salt (55 g.), suspended in ether (250 ml.) containing methyl iodide (70 g.), was boiled under reflux for 6 hr. The mixture was filtered, and the filtrate evaporated *in vacuo* to an acidic oil. This was dissolved in ethanol and titrated with 7·15N-potassium hydroxide solution until neutral, and the solution evaporated *in vacuo* to a solid residue (18·2 g.). The dried salt (18 g.) in ether (50 ml.) containing thionyl chloride (20 g.) was refluxed for 3 hr. The solvent was removed and the residue distilled directly *in vacuo* from an excess of glass wool to give the *acid chloride* (7·5 g.), b. p. 98—100°/14 mm. (Found: Cl, 38·3. $C_5H_4O_3Cl_2$ requires Cl, 38·8%). This chloride with aniline gave trans-β-*chloro*-β-*methoxycarbonyl*-N-*phenylacrylamide*, which separated from hexane as needles m. p. 78° (Found: C, 55·2; H, 4·15; N, 5·85. $C_{11}H_{10}O_3NCl$ requires C, 55·3; H, 4·05; N, 5·95%).

trans-N-(β-*Chloro*-β-*methoxycarbonylacryloyl*)-N′-*phenylurea*.—A mixture of the acid chloride (1·475 g.) and phenylurea (1·36 g.) in benzene (20 ml.) containing sulphuric acid (0·02 ml.) was boiled under reflux for 3 hr. An upper layer was decanted from the cooled mixture and evaporated to a solid. The *phenylurea* (0·34 g.) separated from hexane as needles, m. p. 126° (Found: C, 51·0; H, 3·9; N, 9·9. $C_{12}H_{11}O_4N_2Cl$ requires C, 50·95; H, 3·9; N, 9·9%).

cis-5-*Carboxymethylene*-1-*phenylhydantoin*.—The foregoing phenylurea (0·127 g.) was heated on a water-bath for 10 min. with 2N-sodium hydroxide (1 ml.). The cooled solution was acidified to give a solid precipitate (0·075 g.) which was chlorine-free. The cis-*hydantoin* separated from water as needles, m. p. 220° (decomp.) (Found: C, 56·75; H, 3·7; N, 12·1. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·45; N, 12·05%), $\lambda_{max.}$ 298 (ε 6280) and 230 mμ (ε 14,090) in ethanol. A mixed m. p. with the *trans*-isomer was depressed considerably. The *cis*-isomer was also obtained by reaction of the above phenylurea with ethanolic potassium acetate. The *cis*-hydantoin (0·14 g.) was decarboxylated in quinoline and worked up as for the *trans*-isomer, to give 5-methylene-1-phenylhydantoin (0·048 g.), m. p. and mixed m. p. 162°.

N-β-*Chlorocrotonoyl*-N′-*phenylurea*.—A solution of β-chlorocrotonoyl chloride [14] (2·41 g.) in benzene (20 ml.) was boiled under reflux with silver cyanate (7·1 g.) for 1 hr. The mixture was treated with aniline (2·18 g.), then filtered, and the filtrate evaporated to a solid. The *phenylurea* (1·1 g.) separated from ethanol as needles, m. p. 188° (Found: C, 55·35; H, 4·85; N, 11·3. $C_{11}H_{11}O_2N_2Cl$ requires C, 55·35; H, 4·6; N, 11·75%).

6-*Methyl*-1-*phenyluracil*.—The preceding phenylurea (0·57 g.) was warmed with 2N-sodium hydroxide (4 ml.) for 10—15 min. at 100°. The clear solution was cooled and a precipitate of phenylurea (0·15 g.), m. p. and mixed m. p. 147°, filtered off. The filtrate with acid gave 6-*methyl*-1-*phenyluracil* (0·05 g.) which crystallised from water as plates, m. p. 276° (Found: C, 65·1; H, 5·15; N, 13·6. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 5·0; N, 13·85%), $\lambda_{max.}$ 265 mμ (ε 12,800) in ethanol.

N-β-*Chlorocrotonoyl*-N′-*methylurea*.—A mixture of β-chlorocrotonyl chloride (2·4 g.), silver cyanate (7·1 g.), and benzene (20 ml.) was boiled under reflux for 1 hr., then decanted into 33% ethanolic methylamine (4 ml.) and filtered, and the filtrate was evaporated *in vacuo*. The residue solidified with ethanol. The *methylurea* (0·39 g.) separated from ethanol as prisms, m. p. 154° (Found: C, 40·95; H, 5·2; N, 15·4. $C_6H_9O_2N_2Cl$ requires C, 40·8; H, 5·1; N, 15·85%). It (0·2 g.) was warmed for 10 min. with 2N-sodium hydroxide (2 ml.). The solution was acidified and extracted with ethyl acetate, and the dried extract evaporated to give 1 : 6-dimethyluracil (0·03 g.), m. p. and mixed m. p. 210—220°.

N-*Acetoacetylurethane*.—Diketen (25 g.) was added to a cold solution of urethane (20 g.) in acetic acid (75 ml.). The solution was boiled under reflux for 25 min., then evaporated *in vacuo* to a crystalline residue. N-*Acetoacetylurethane* (11·7 g.) separated from benzene as needles, m. p. 77—78° (Found: C, 48·8; H, 6·4; N, 8·0. $C_7H_{11}O_4N$ requires C, 48·55; H, 6·4; N, 8·1%). A further quantity of the urethane (6·8 g.) was obtained by evaporation of the benzene solution. The compound gave a red colour with ferric chloride in ethanol.

Reaction of N-*Acetoacetylurethane with Primary Amines*.—(*a*) The urethane (0·2 g.) was

heated on a steam-bath with aqueous 20% methylamine (5 ml.) for 20 min. The cooled solution was acidified and extracted with ethyl acetate. Evaporation of the dried extract gave 1 : 6-dimethyluracil (0·1 g.), m. p. and mixed m. p. 220—222°. (*b*) The urethane (1·5 g.) in ethanol (5 ml.) was treated with ethylamine (1 ml.). The warm solution was evaporated *in vacuo* to a solid residue. N-β-*Ethylaminocrotonoylurethane* (1·4 g.) separated from light petroleum (b. p. 60—80°) as needles, m. p. 99° (Found: C, 50·8; H, 7·9; N, 12·95. $C_9H_{16}O_3N_2,\frac{1}{2}H_2O$ requires C, 50·6; H, 8·2; N, 13·0%). (*c*) The urethane (0·2 g.) and propylamine (0·2 ml.) similarly gave N-β-*propylaminocrotonoylurethane* (0·18 g.) as needles [from light petroleum (b. p. 60—80°)], m. p. 110° (Found: C, 56·2; H, 8·3; N, 13·0. $C_{10}H_{18}O_3N_2$ requires C, 56·05; H, 8·45; N, 13·1%). (*d*) The starting urethane (2 g.) and *cyclo*hexylamine (1·5 ml.) in ethanol (5 ml.) gave N-β-cyclo*hexylaminocrotonoylurethane* (2 g.) which crystallised from light petroleum (b. p. 80—100°) as needles, m. p. 119° (Found: C, 61·45; H, 8·55; N, 10·95. $C_{13}H_{22}O_3N_2$ requires C, 61·4; H, 8·7; N, 11·0%). (*e*) The urethane (0·2 g.) and aniline (0·2 ml.) gave N-β-*anilinocrotonoylurethane* (0·21 g.) which crystallised from ethanol as needles, m. p. 107° (Found: C, 62·9; H, 6·25; N, 11·2. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·5; N, 11·3%).

Preparation of 6-*Methyluracils.*—(*a*) *N*-β-Ethylaminocrotonoylurethane (1·2 g.) in collidine (2 ml.) was boiled under reflux for 1 hr. The cooled solution gave a crystalline precipitate; 1-ethyl-6-methyluracil (0·25 g.) separated from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 195° (Found: N, 18·2. Calc. for $C_7H_{10}O_2N_2$: N, 18·2%); Behrend and Buckendorff [6] give m. p. 195°. (*b*) *N*-β-Propylaminocrotonoylurethane (0·2 g.) similarly gave 6-*methyl*-1-*propyluracil* (0·18 g.) which separated from ethanol as needles, m. p. 173° (Found: N, 17·3. $C_8H_{12}O_2N_2$ requires N, 16·65%). (*c*) *N*-β-*cyclo*Hexylaminocrotonoylurethane (3·3 g.) was heated at 170° (bath) for 1 hr. The melt was cooled to give a semi-solid residue. This was extracted with dilute sodium hydroxide and filtered from an insoluble oil. The filtrate was just neutralised, to precipitate 1-cyclo*hexyl*-6-*methyluracil* (1·3 g.) which recrystallised from ethanol as needles, m. p. 233—235° (Found: C, 63·35; H, 7·7; N, 13·6. $C_{11}H_{16}O_2N_2$ requires C, 63·45; H, 7·75; N, 13·45%). (*d*) *N*-β-Anilinocrotonoylurethane (0·5 g.) was heated on a steam-bath with 2N-sodium hydroxide (2 ml.) and ethanol (2 ml.) for 1 hr. The solution was evaporated to about 1 ml. and carefully acidified to precipitate 6-methyl-1-phenyluracil (0·11 g.), m. p. and mixed m. p. with the material obtained from chlorocrotonic acid (see above) 275—276°. An improved yield of the uracil (75%) was obtained when the cyclisation was carried out in collidine as under (*a*).

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UNIVERSITY OF N.S.W., SYDNEY, AUSTRALIA. [*Received, November 10th,* 1958.]