Heterocyclic Studies. Part XIX.[1] Some 6-(Substituted phenyl)-uracil and -thiouracil Derivatives

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Ten β-(*m*- and *p*-substituted phenyl)-β-oxopropionates (I and II; X = F, Cl, Br, Me, or OMe) were synthesised and condensed with thiourea to yield the corresponding 6-(*m*- and *p*-substituted phenyl)thiouracils [(V) and (VI)], which were converted into the analogous uracils [(VII) and (VIII)] by treatment with chloroacetic acid. Nitration of 6-(*p*-substituted phenyl)uracil derivatives gave 5-nitro- or *m*,5-dinitro-compounds according to reaction conditions. ^{1}H N.m.r. spectra of most of the compounds are recorded.

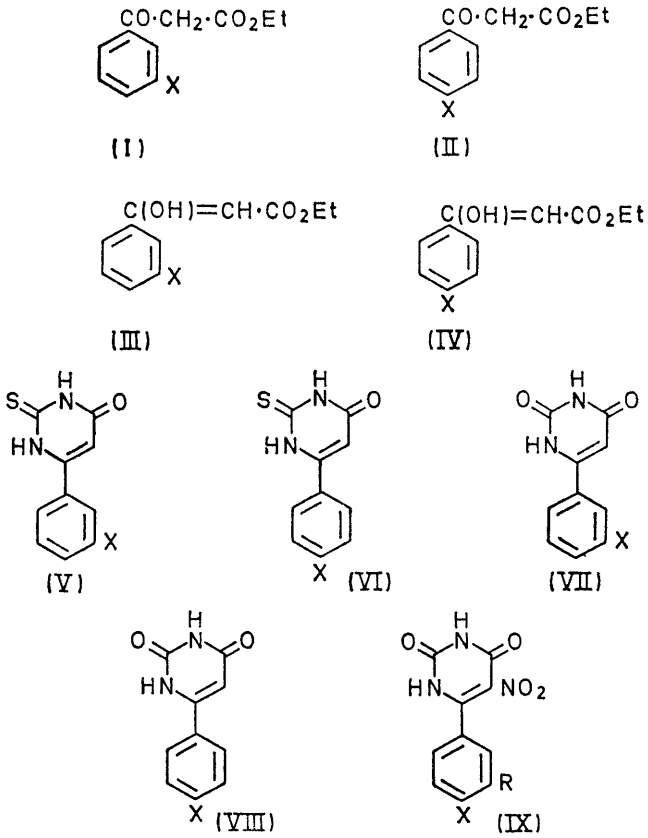
THIS paper describes the synthesis of some uracil and thiouracil derivatives with a substituted phenyl group in the 6-position. These compounds are of interest as potential pharmaceutical agents and as intermediates in a programme [2] for the synthesis of phenyl-substituted pteridines. 2-Thiouracil has been widely used for the treatment of hyperthyroidism [3] and many of its derivatives have similar activity.[4–6] 6-Phenyluracil and its *p*-nitrophenyl analogue are thymidine phosphorylase enzyme inhibitors.[7]

Ethyl β-(substituted phenyl)-β-oxopropionates (I and II; X = F, Cl, Br, Me, or OMe), required for the present syntheses, were made by condensing the relevant substituted benzoyl chlorides with ethyl acetoacetate and cleaving the products [$ArCO{\cdot}CHAc{\cdot}CO_2Et$] with ammonia. This procedure had previously been used for preparing some of the required esters [6,8–13] but most of the compounds had been reported without analytical data or with only a halogen analysis. Some of the compounds could be purified by distillation but others, particularly those with a *p*-substituted phenyl group, decomposed. Purification *via* the potassium salts was a useful alternative.

^{1}H N.m.r. spectra of some examples of the esters (neat liquids) (Table 1) showed that both keto [(I) and (II)] and enol [(III) and (IV)] forms were present, with the former in preponderance.

Condensation of the β-oxo-esters (I) and (II) with thiourea, essentially as described for the synthesis of 6-phenylthiouracil,[14] gave two series of 6-(substituted phenyl)thiouracils (V and VI; X = F, Cl, Br, Me, or OMe). The *m*- and *p*-methoxyphenyl derivatives (V and VI; X = OMe) have been reported previously [6] but the m.p. recorded for the *meta*-isomer is that of the *para*-compound and *vice versa* (see Experimental section).

The thiouracils were converted into the corresponding uracils by hydrolysis of their *S*-carboxymethyl derivatives. Simple treatment of the thiouracils with chloro-



acetic acid and water, as in the corresponding conversion of 6-phenylthiouracil,[14] was ineffective for the less-soluble compounds, particularly the bromo-derivatives

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TABLE 1

^{1}H N.m.r. spectra (τ values) of β-(substituted phenyl)-β-oxopropionates [a]

	Keto form						Enol form					
Structure	CH_3·-CH_2 [b]	CH_2·-CH_3 [c]	CH_2 [d]	Me [d]	Aromatics	Structure	CH_3·-CH_2 [b]	CH_2·-CH_3 [c]	CH [d]	Me [d]	Aromatics	Approx. % enol
(I; X = H)	8·83	5·82	5·90		1·80—2·80(m)	(III; X = H)	8·70	5·75	4·22		1·80—2·80(m)	21
(I; X = F)	8·77	5·77	5·90		2·07—2·83(m)	(III; X = F)	8·70	5·72	4·27		2·07—2·83(m)	29
(I; X = Cl)	8·78	5·78	5·93		1·98—2·68(m)	(III; X = Cl)	8·70	5·72	4·30		1·98—2·68(m)	29
(I; X = Me)	8·82	5·82	6·00	7·70	2·12—2·77(m)	(III; X = Me)	8·73	5·68	4·25	7·70	2·12—2·77(m)	23
(I; X = OMe)	8·80	5·80	5·93	6·22	2·34—3·00(m)	(III; X = OMe)	8·70	5·72	4·23	6·22	2·34—3·00(m)	23
(II; X = Br)	8·78	5·77	5·93		2·13,[e] 2·42 [e]	(IV; X = Br)	8·70	5·72	4·30		2·15,[e] 2·44 [e]	27

[a] Measured with a Varian A60A spectrometer at normal probe temperature. Compounds examined as neat liquids with tetramethylsilane as internal standard. [b] t, J 7·2 Hz. [c] q, J 7·2 Hz. [d] s. [e] Half of A_2B_2q, J 9 Hz.

TABLE 2

^{1}H N.m.r. spectra (τ values) of uracil and thiouracil derivatives *

Compound	5-H	Me	Aromatics	Compound	5-H	Me	Aromatics
(V; X = H)	3·85		2·37—2·50(m)	(VII; X = H)	4·10		2·01—2·52(m)
(V; X = F)	3·80		2·15—2·60(m)	(VII; X = F)	4·05		2·16—2·58(m)
(V; X = Cl)	3·80		2·00—2·50(m)	(VII; X = Cl)	4·07		2·08—2·50(m)
(V; X = Br)	3·82		1·93—2·53(m)	(VII; X = Br)	4·07		1·92—2·63(m)
(V; X = Me)	3·90	7·60	2·32—2·67(m)	(VII; X = Me)	4·17	7·62	2·32—2·65(m)
(V; X = OMe)	3·85	6·15	2·47—2·94(m)	(VII; X = MeO)	4·08	6·12	2·48—2·92(m)
(VI; X = F)	3·85		1·95—2·75(m)	(VIII; X = F)	4·13		1·97—2·78(m)
(VI; X = Cl)	3·83		2·17,‡ 2·38 ‡	(VIII; X = Cl)	4·12		2·18,† 2·40 †
(VI; X = Br)	3·83		2·25(s)	(VIII; X = Br)	4·12		2·25(s)
(VI; X = Me)	3·88	7·60	2·32,† 2·63 †	(VIII; X = Me)	4·15	7·63	2·28,† 2·63 †
(VI; X = OMe)	3·92	6·14	2·23,‡ 2·90 ‡	(VIII; X = OMe)	4·18	6·13	2·22,‡ 2·92 ‡
(IX; X = F, R = H)			2·17—2·70(m)	(IX; X = F, R = NO_2)			1·33—2·35(m)
(IX; X = Cl; R = H)			2·35(s)	(IX; X = Cl, R = NO_2)			1·50—2·10(m)
(IX; X = Me, R = H)		7·60	2·57(s)	(IX; X = OMe, R = NO_2)		5·92	1·70—2·50(m)

* Measured with Varian A60A spectrometer at normal probe temperature. Compounds were in [$^2H_6$]dimethyl sulphoxide solution with tetramethylsilane as internal standard. Signals are singlets except where specified. † Half of A_2B_2q, J 8 Hz. ‡ Half of A_2B_2q, J 9 Hz.

(V and VI; X = Br). However all were readily hydrolysed by chloroacetic and hydrochloric acids in aqueous 2-ethoxyethanol.

Nitration of the uracil derivatives gave mono- or di-nitro-compounds, depending on reaction conditions. Treatment of halogenophenyluracils (VIII; X = F or Cl) with fuming nitric acid, acetic acid, and acetic anhydride, a mixture previously used for specific 5-nitration of 6-phenyluracil [15] gave the corresponding 5-nitro-derivatives (IX; X = F or Cl, R = H). Some ring cleavage also occurred during these reactions and halogenobenzoic acids were isolated as by-products.

Halogenophenyluracils (VIII; X = F or Cl) were dinitrated when treated with fuming nitric acid alone or with fuming nitric and concentrated sulphuric acids. ^{1}H N.m.r. spectra of the products (Table 2) showed that the *p*-halogeno-compounds gave *m*,5-dinitro-derivatives (IX; X = F or Cl, R = NO_2). The *p*-tolyluracil (VIII;

TABLE 3

β-(Substituted phenyl)-β-oxopropionates

				Found			Required		
Compound	B.p.	Yield (%)	Formula	C (%)	H (%)	M^+ *	C(%)	H (%)	M
(I; X = F)	114—115°/1·2 mm.	90	$C_{11}H_{11}FO_3$	63·1	5·6	210	62·9	5·3	210
(I; X = Cl) [6,13]	117—120°/0·4 mm.†	52		(Lit.,[6] b.p. 118—121°/0·2 mm.)					
(I; X = Br)	140—144°/0·6 mm.‡	62	$C_{11}H_{11}BrO_3$	49·1	4·1	270	48·7	4·1	270
(I; X = Me)	116—118°/0·5 mm.	54	$C_{12}H_{14}O_3$	69·9	6·8	206	69·9	6·8	206
(I; X = OMe)	162—166°/2·5 mm.	47	$C_{12}H_{14}O_4$	64·8	6·4	222	64·9	6·3	222
(II; X = F) [11]	117—120°/1 mm.‡	99							
(II; X = Cl) [8,10]	(M.p. 38°)	66		(Lit.,[8] m.p. 38°)					
(II; X = Br) [9]	152—158°/1·2 mm.†	46	$C_{11}H_{11}BrO_3$	49·2	4·1	270	48·7	4·1	270
(II; X = Me)	138—140°/1·5 mm.‡	59							
(II; X = OMe) [10,12]	164—168°/1 mm.‡	41	$C_{12}H_{13}KO_4$ §	55·7	5·0		55·4	5·0	222

* Mass spectrum. † With some decomposition. ‡ With extensive decomposition. § Potassium salt.

[15] J. Clark and P. N. T. Murdoch, *J. Chem. Soc.* (*C*), 1969, 1883.

X = Me) behaved like the halogeno-substituted compounds, but the methoxy-compound (VIII; X = OMe), with a still more reactive benzene ring, gave the *m*,5-dinitro-derivative (IX; X = OMe, R = NO_2), even under the milder nitrating conditions mentioned.

EXPERIMENTAL

β-(*Substituted phenyl*)-β-*oxopropionates* (I) *and* (II).—A solution of sodium (2 moles) in ethanol (720 ml.) was divided into portions containing 1, 0·5, 0·25, 0·125, and 0·125 mole of sodium ethoxide. A solution of the relevant substituted benzoyl chloride (1 mole) in ether (400 ml.) was similarly divided into portions containing 0·5, 0·25, 0·125, 0·0625, and 0·0625 mole of acid chloride.

Ethyl acetoacetate (1 mole) was added to the 1 mole portion of sodium ethoxide and the mixture was stirred and cooled to 5°. The 0·5 mole portion of substituted benzoyl chloride was gradually added with stirring while the temperature was kept below 12°. After 0·5 hr. gradual additions of the remaining portions of sodium ethoxide and acid chloride were made alternately while the mixture was stirred and kept below 12°. Next day the precipitated sodium salt was filtered off, washed with ether, and dissolved in water (400 ml.). Ammonium chloride (30 g.) and aqueous ammonia (*d* 0·88; 30 ml.) were added and the solution was shaken frequently and kept at 40—55° for 6 hr. The product was extracted with ether and the ether layer was washed with water and dried. Removal of the ether left the β-*oxo-ester* in a sufficiently pure state for use in the next stage. Analytical specimens were prepared by distillation under reduced pressure where possible [(I; X = F, Cl, Br, Me, or MeO) and (II; X = Br)]. The *p*-substituted phenyl compounds which underwent extensive decomposition on distillation could be purified through their potassium salts.

6-(*Substituted phenyl*)*thiouracils* (V) *and* (VI).—Thiourea

[16] E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 4466.

TABLE 4

6-(Substituted phenyl)thiouracils

Compound	M.p.*	Yield (%)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(V; X = F)	279—280°	73	$C_{10}H_7FN_2OS$	53·9	3·2	12·6	54·0	3·2	12·7
(V; X = Cl) [6]	266—267	95		(Lit.,[6] m.p. 266—266·5°)					
(V; X = Br)	267—269	91	$C_{10}H_7BrN_2OS$	42·5	2·6	10·1	42·4	2·5	9·9
(V; X = Me)	216—218	61	$C_{11}H_{10}N_2OS$	59·9	4·5	12·7	60·5	4·6	12·8
(V; X = OMe) [6]	226—227 †	77	$C_{11}H_{10}N_2O_2S$	56·0	4·3	11·7	56·4	4·3	11·9
(VI; X = F)	274—276	72	$C_{10}H_7FN_2OS$	54·5	3·2	12·9	54·0	3·2	12·7
(VI; X = Cl) [5,6]	279—281	63		(Lit.,[16] m.p. 281—282°; lit.,[5] m.p. 289—291°)					
(VI; X = Br)	290—292	75	$C_{10}H_7BrN_2OS$	42·6	2·5	9·7	42·4	2·5	9·9
(VI; X = Me)	276—278	50	$C_{11}H_{10}N_2OS$	60·0	4·7	12·9	60·5	4·6	12·8
(VI; X = OMe) [6]	291—293 ‡	48	$C_{11}H_{10}N_2O_2S$	56·3	4·4	11·5	56·4	4·3	11·9

* From glacial acetic acid, except (V; X = Me) from methanol. † Lit.,[6] m.p. 292—293°. ‡ Lit.,[6] m.p. 226—227°. The published m.p.s of the *m*- and *p*-methoxy-derivatives appear to refer to the wrong isomers.

TABLE 5

6-(Substituted phenyl)uracils

Compound	M.p.	Procedure	Yield * (%)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(VII; X = F)	289—290°	*a*	43	$C_{10}H_7FN_2O_2$	57·9	3·4	13·6	58·2	3·4	13·6
(VII; X = Cl)	285—287	*b*	27	$C_{10}H_7ClN_2O_2$	53·7	3·3	12·4	53·9	3·2	12·6
(VII; X = Br)	290—291	*b*	49	$C_{10}H_7BrN_2O_2$	45·3	2·7	11·1	45·0	2·6	10·5
(VII; X = Me)	274—276	*a*	91	$C_{11}H_{10}N_2O_2$	65·3	4·9	13·9	65·3	5·0	13·9
(VII; X = OMe)	275—277	*b*	68	$C_{11}H_{10}N_2O_3$	60·2	4·6	12·7	60·5	4·6	12·8
(VIII; X = F)	311—313 †	*b*	55	$C_{10}H_7FN_2O_2$	57·9	3·3	13·4	58·2	3·4	13·6
(VIII; X = Cl)	326 (decomp.)	*b*	36	$C_{10}H_7ClN_2O_2$	53·8	3·2	12·8	53·9	3·2	12·6
(VIII; X = Br)	347—350	*b*	71	$C_{10}H_7BrN_2O_2$	45·6	2·8	10·4	45·0	2·6	10·5
(VIII; X = Me)	315—318	*a*	100	$C_{11}H_{10}N_2O_2$	65·0	4·9	13·5	65·3	5·0	13·9
(VIII; X = OMe)	288—291	*a*	97	$C_{11}H_{10}N_2O_3$	59·9	4·6	12·7	60·5	4·6	12·8

* Yields obtained by procedures (*b*) could be improved by recovering more material from the filtrates. † From aqueous dimethylformamide.

TABLE 6

Nitration of 6-(substituted phenyl)uracils

Starting material	Nitration procedure	Product	M.p.*	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N	By-product
(VIII; X = F)	*a*	(IX; X = F, R = H)	273—275°	29	48·0	2·6	16·5	47·8	2·4	16·7	*p*-FC_6H_4·CO_2H (18%)
(VIII; X = F)	*c*	(IX; X = F, R = NO_2)	260	61	39·9	1·9	19·0	40·55	1·70	18·9	
(VIII; X = Cl)	*a*	(IX; X = Cl, R = H)	305—306	29	44·7	2·3	15·9	44·9	2·25	15·7	*p*-ClC_6H_4·CO_2H (54%)
(VIII; X = Cl)	*b*	(IX; C = Cl, R = NO_2)	258—261	61	38·9	1·8	18·2	38·4	1·6	17·9	
(VIII; X = Me)	*a*	(IX; X = Me, R = H)	284—285	73	53·3	3·8	17·2	53·4	3·7	17·0	
(VIII; X = OMe)	*a*	(IX; X = OMe, R = NO_2)	>275	59	43·5	2·9	17·7	42·9	2·6	18·2	

* From ethanol except for the two chloro-compounds, which were crystallised from aqueous dimethylformamide.

(1·5 mole) and the relevant β-oxo-ester (1 mole) were added to sodium ethoxide solution (2 moles of sodium in 20 parts of ethanol) and the mixture was heated under reflux for 4—8 hr. Excess of ethanol was evaporated off and the residue was dissolved in water. Acidification with hydrochloric acid precipitated the *thiouracil*, which was crystallised from a suitable solvent.

6-(*Substituted phenyl*)*uracils* (VII) *and* (VIII).—(*a*) The relevant thiouracil (1 part), chloroacetic acid (2 parts), and water (25—50 parts) were heated under reflux until a clear solution was obtained (1—2 hr.). Concentrated hydrochloric acid (2 parts) was added and the mixture was refluxed until reaction was complete (12—24 hr.). The *uracil* separated from the cooled solution and was crystallised from ethanol or 2-ethoxyethanol.

(*b*) This procedure was as in (*a*) except that the water was replaced by aqueous 2-ethoxyethanol (1 : 1). The second reflux period was usually 4—8 hr.

Nitration of 6-(*Substituted phenyl*)*uracils*.—(*a*) A mixture of nitric acid (*d* 1·5; 4 ml.), glacial acetic acid (3 ml.), and acetic anhydride (3 ml.) was gradually added to a suspension of the uracil derivative (1 g.) in acetic anhydride (10 ml.) which was stirred at 10°. The mixture was allowed to reach 20° and stirred for a further 1 hr. before being poured on ice. Any benzoic acid derivative formed was filtered off and the filtrate was kept until the nitrouracil derivative separated.

(*b*) The uracil derivative (1 g.) was added during 15 min. to stirred nitric acid (*d* 1·5; 20 ml.) kept at 5—10°. The mixture was allowed to warm to 20°, stirring was continued for 15 min., and the mixture was poured on ice. The nitro-derivative was filtered off and crystallised.

(*c*) The uracil derivative (0·4 g.) was added during 15 min. to a stirred mixture of nitric acid (*d* 1·5; 1·5 ml.) and concentrated sulphuric acid (*d* 1·84; 1·5 ml.) at 20°. After 0·5 hr. at 20° the mixture was poured on ice and the *product* was filtered off.

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