SYNTHESIS OF URACILS SUBSTITUTED IN THE POSITION 5 OR 5,6 WITH ALKYL OR CYCLOALKYL GROUPS AND THEIR UV SPECTRA*

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Lithium diisopropylamide used as a base in the Claisen condensation of alkylacetates and cycloalkylacetates with ethyl formate or acetate gave substantially higher yields of β-oxo esters than sodium hydride or sodium bis(trimethylsilyl)amide. Reaction of the obtained β-oxo esters with thiourea in an alkaline medium afforded 5- or 5,6-disubstituted 2-thiouracils *Ib*—*XIIb* which on subsequent reaction with chloroacetic acid were transformed into the uracil derivatives *Ia*—*XIIa*. The UV spectra of uracils substituted in the positions 5 or 6 with cyclopropane ring exhibit in the 265 nm region bathochromic shifts of 1 to 6·5 nm as compared with the correspondingly substituted alkyl derivatives. A qualitative correlation of these shifts with the electron deficit on the carbon atom bonded to the cyclopropane ring was attempted.

For our spectral and photochemical studies we needed a series of uracils, substituted in the positions 5 and 5,6 with alkyl or cycloalkyl groups. Since the substituted acetic acids *XVIII*—*XXI* are easily accessible, the method of Burckhalter and Scarborough[1] seemed to be suitable for the preparation of the compounds *Ia*—*VIIIa*. This method, however, gives low yields caused by difficult formylation of alkylacetates. Draminski and Fiszer[2,3] obtained significantly higher yields of 5-alkyluracils by using triphenylmethyl sodium instead of the usually employed sodium[1,4–6] or sodium hydride[7,8] as condensation agent in the formylation of esters of alkylacetic acids with ethyl formate. Although triphenylmethyl sodium proved to be efficient in the mentioned formylation[2,3] and also in other Claisen condensations[9,10], its preparation is not facile and it is very sensitive to the air oxygen. Moreover, triphenylmethane derivatives, present in the reaction mixture, make the product isolation difficult and do not allow a direct photometric monitoring of the formylation. For all these reasons we tried sodium bis(trimethylsilyl)amide[11] as a base.

Methyl 3-methylbutanoate reacted with ethyl formate in the presence of the above-mentioned base to give methyl 2-formyl-3-methylbutanoate which on reaction with

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thiourea in an alkaline medium afforded 5-isopropyl-2-thiouracil (*XIb*) in 13% yield (based on the starting methyl 3-methylbutanoate), whereas with sodium hydride the compound *XIb* was obtained in yields not higher than 5%. The formylation of methyl 3-methylbutanoate must be performed in an excess of ethyl formate, otherwise self-condensation takes place and the reaction with thiourea leads to the compound *VIb*. This self-condensation is accompanied by formation of 3-methylbutanamide

TABLE I

Yields and Melting Points of 5-Substituted and 5,6-Disubstituted 2-Thiouracils, Prepared Using Lithium Diisopropylamide

Compound	R^1 R^2	Yield[a], % method	M.p., °C solvent
Ib	cyclo-C_3H_5 CH_3	21·5 B	208–209 (methanol)
IIb	CH_3 cyclo-C_3H_5	23·5 B	220–230 (methanol)
IIIb	cyclo-C_3H_5 cyclo-C_3H_5—CH_2	12·5 B	197–198 (methanol)
IVb	$CH(CH_3)_2$ CH_3	10·2 B	257–258[b] (ethanol)
Vb	CH_3 $CH(CH_3)_2$	12·6 B	179–180 (ethanol)
VIIb	cyclo-C_4H_7 H	53·7 B	206–208 (ethanol)
VIIIb	cyclo-C_5H_9 H	48·9 B	233–234 (ethanol)
IXb	cyclo-C_3H_5 H	44·0 A	210–212[c] (methanol–water)
Xb	$(CH_2)_2CH_3$ H	38·0 B	160–161[d] (water)
XIb	$CH(CH_3)_2$ H	31·0 A	237–239[e] (acetic acid–water)
XIIb	$C(CH_3)_3$ H	25·3 B	280–300[f] (decomposition) (acetic acid–water)

[a] Yields based on the starting methyl esters of substituted acetic acids; [b] ref.[28] 257·5°C; [c] ref.[8] 211–212°C; [d] 159–161°C, (ref.[3]), 161–163°C (ref.[4]); [e] 238–239°C (ref.[3]), 242–244°C (ref.[4]); [f] ref.[3] 321–325°C (sublimation).

and 5-methyl-2-(1-methylethyl)-3-oxohexanamide as side-products. Attempted formylation of methyl 3,3-dimethylbutanoate in the presence of sodium bis(trimethylsilyl)-amide did not afford detectable amounts of the desired formyl derivative.

Recently, lithium salts of dialkylacetic acids[12] and esters of alkylacetic acids[13] were reported to be acylated using lithium diisopropylamide. The yields of these acylations are satisfactory and they are not significantly affected by steric factors. We formylated therefore methyl 3,3-dimethylbutanoate in the presence of lithium diisopropylamide and subjected the product to reaction with thiourea. The overall yield of the resulting 5-tert-butyl-2-thiouracil (*XIIb*) was 25%, comparable with that reported[2,3] for using triphenylmethyl sodium in the formylation reaction. The advantage of using lithium diisopropylamide is its facile preparation and easy isolation of the products. Moreover, the formylation course can be followed spectrophotometrically since β-oxo esters in alkaline medium exhibit a strong absorption band at about 275 nm.

Similarly to the compound *XIIb* we prepared the derivatives *Ib – Vb* and *VIIb – XIb* some of which have already been described (see footnotes in Table I). Our method

TABLE II

UV Spectra of 5-Substituted and 5,6-Disubstituted Uracils *Ia – XIIa* and Standards *XIIIa – XVIIa* in Methanol

Compound[a]	R^1	R^2	λ_{max}, nm	log ε
Ia	cyclo-C_3H_5	CH_3	268·0	3·96
IIa	CH_3	cyclo-C_3H_5	272·0	4·06
IIIa	cyclo-C_3H_5	cyclo-C_3H_5-CH_2	272·0	4·06
IVa	$CH(CH_3)_2$	CH_3	267·0	3·99
Va	CH_3	$CH(CH_3)_2$	267·0	3·97
VIa	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	268·0	3·99
VIIa	cyclo-C_4H_7	H	266·0	3·93
VIIIa	cyclo-C_5H_9	H	265·0	3·87
IXa	cyclo-C_3H_5	H	269·0	3·88
Xa	$CH(CH_3)_2$	H	263·0	3·92
XIa	$(CH_2)_2CH_3$	H	264·5	3·97
XIIa	$C(CH_3)_3$	H	260·0	3·90
XIIIa	C_2H_5	H	264·5	3·92
XIVa	H	cyclo-C_3H_5	267·0	3·96
XVa	CH_3	CH_3	267·0	4·00
XVIa	CH_3	H	264·5	3·97
XVIIa	H	CH_3	260·0	3·92

[a] For preparation of the compounds *IXa – XVa* see references[8,3,1,3,1,8] and [33], respectively.

affords satisfactory yields particularly for 5-cycloalkyl-2-thiouracils (Table I). The low yields of 5,6-disubstituted 2-thiouracils *Ib–IVb* are probably due to a lower reactivity of the acetyl than of the formyl group towards the carbanion. The β-oxo esters were not isolated, except for methyl 2-formyl-3-methylbutanoate (*XXII*) and methyl α-formylcyclopropylacetate (*XXIII*). As shown by ^{1}H-NMR spectra, both these compounds exist as tautomeric mixtures: the enol form prevails in *XXIII* whereas the compound *XXII* exists predominantly in the keto form. The higher population of the enol form in the former ester is probably due to the conjugative effect[14,18] of the cyclopropane ring. Attempted preparation of 5,6-dicyclopropyl--2-thiouracil by reaction of methyl cyclopropylacetate with methyl cyclopropanecarboxylate in the presence of lithium diisopropylamide afforded an enolate which on subsequent reaction with thiourea was transformed into the compound *IIIb*, whose structure proves self-condensation of methyl cyclopropylacetate during the reaction.

The 2-thiouracils *Ib–XIIb* were transformed in high yields into the uracil derivatives *Ia–XIIa* by reaction with chloroacetic acid[15].

TABLE III

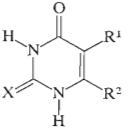
UV Spectra of 5-Substituted and 5,6-Disubstituted 2-Thiouracils *Ib–XIIb* and the Standards *XIII–XVIIb* in Methanol

Compound[a]	R^1	R^2	λ_{max}, nm	(log ε)
Ib	cyclo-C_3H_5	CH_3	220·0 (4·12)	281·0 (4·26)
IIb	CH_3	cyclo-C_3H_5	220·0 (4·09)	278·0 (4·24)
IIIb	cyclo-C_3H_5	cyclo-C_3H_5—CH_2	220·0 (4·13)	280·0 (4·27)
IVb	$CH(CH_3)_2$	CH_3	220·0 (4·24)	279·0 (4·33)
Vb	CH_3	$CH(CH_3)_2$	220·0 (4·17)	282·0 (4·30)
VIb	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	220·0 (4·16)	281·0 (4·30)
VIIb	cyclo-C_4H_7	H	218·0 (4·18)	279·0 (4·27)
VIIIb	cyclo-C_5H_9	H	217·5 (4·19)	278·0 (4·24)
IXb	cyclo-C_3H_5	H	218·0 (4·17)	278·0 (4·29)
Xb	$(CH_2)_2CH_3$	H	216·0 (4·20)	277·0 (4·27)
XIb	$CH(CH_3)_2$	H	217·0 (4·18)	277·0 (4·29)
XIIb	$C(CH_3)_3$	H	215·0 (4·13)	277·0 (4·23)
XIIIb	C_2H_5	H	215·5 (4·23)	276·5 (4·30)
XIVb	H	cyclo-C_3H_5		274·5 (4·29)
XVb	CH_3	CH_3	218·0 (4·19)	279·0 (4·25)
XVIb	CH_3	H	215·5 (4·19)	276·0 (4·25)
XVIIb	H	CH_3	213·5 (4·19)	277·0 (4·18)

[a] For preparation of the compounds *XIIIb–XVb* see references[7,24] and [34], respectively.

Ultraviolet Spectra

Since the 5,6-disubstituted uracils *Ia – VIa* and 2-thiouracils *Ib – VIb* were sparingly soluble in water, the spectra of the synthesized compounds and the standards *Ia – XVIIa* were measured in methanol (Table II and III). The long-wavelength band of 5-alkyl- and 5,6-dialkyluracils (Table II) is practically independent of the alkyl group structure, except the case of the isopropyl and tert-butyl groups (compounds *XIa* and *XIIa*) which cause a small hypochromic shift. (This shift was not observed in the spectra of the compounds *XIa* and *XIIa* taken in 0·1M-HCl solution[8]). Of 5-cycloalkyluracils, 5-cyclopropyluracil (*IXa*) exhibits the greatest bathochromic shift. The small shift to longer wavelengths, found for 5-cyclobutyluracil (*VIIa*), corresponds to low conjugation ability of the cyclobutane ring[16,17]. Cyclopropyluracils with methyl group in the vicinity of the cyclopropyl group (compounds *Ia* and *IIa*) exhibit bathochromic shifts smaller than those found for 5- and 6-cyclopropyluracil (the shifts relate to 5,6-dimethyluracil and 5- and 6-methyluracil). This lower bathochromic shift, observed for the compounds *Ia* and *IIa*, can be ascribed to the steric effect of the vicinal methyl group which forces the cyclopropane ring to deviate form the "bisected" conformation[14], decreasing thus its conjugation ability[18].



Ia – XIIa; X = O *Ib – XIIb*; X = S

I; R^1 = cyclo-C_3H_5, R^2 = CH_3
II; R^1 = CH_3, R^2 = cyclo-C_3H_5
III; R^1 = cyclo-C_3H_5, R^2 = cyclo-$C_3H_5CH_2$
IV; R^1 = $CH(CH_3)_2$, R^2 = CH_3
V; R^1 = CH_3, R^2 = $CH(CH_3)_2$
VI; R^1 = $CH(CH_3)_2$, R^2 = $CH_2CH(CH_3)_2$
VII; R^1 = cyclo-C_4H_7, R^2 = H
VIII; R^1 = cyclo-C_5H_9, R^2 = H
IX; R^1 = cyclo-C_3H_5, R^2 = H
X; R^1 = $(CH_2)_2CH_3$, R^2 = H
XI; R^1 = $CH(CH_3)_2$, R^2 = H
XII; R^1 = $C(CH_3)_3$, R^2 = H

RCH_2COOH

XVIII; R = cyclo-C_3H_5 *XX*; R = cyclo-C_5H_9
XIX; R = cyclo-C_4H_7 *XXI*; R = $CH(CH_3)_2$

The conjugation ability is suppressed probably also by the +I effect of the methyl group. According to Kellogg and Buter[19], the conjugation ability of the cyclopropane ring is enhanced by an electron deficit on the carbon atom adjacent to the cyclopropane ring. The decrease in the electron deficit on the double bond carbon atoms in uracil, caused by the attached methyl group, reduces thus the conjugation ability of the cyclopropane ring in the compounds *Ia* and *IIa*. The higher bathochromic shift in 6-cyclopropyluracil than in 5-cyclopropyluracil can be due to a greater electron deficit on the carbon atom $C_{(6)}$ than on the carbon $C_{(5)}$ of the uracil nucleus[20]. However, this hypothesis is not able to explain why the compound *IIIa* has a higher bathochromic shift than the compound *Ia*.

UV spectra of the 2-thiouracils *Ib*–*XIIb* and the corresponding standards (Table III), measured in methanol, display an absorption maximum at long wavelengths; its position depends less on the structure of the substituents than found for the corresponding uracil derivatives (Table II). The unsymmetrical character of the absorption curve of 2-thiouracils at ~270 nm indicates the presence of at least two electronic transitions in this region.

EXPERIMENTAL

Analytical samples were dried at 25°C/6·6 Pa. Melting points were determined on a Kofler block. UV spectra were measured on a Specord UV VIS (Zeiss, Jena) instrument, IR spectra on a UR-10 (Zeiss, Jena) spectrophotometer. Mass spectra (70 eV) were taken on a mass spectrometer MS 902. ^{1}H-NMR spectra were measured on Varian HA (at 100 MHz) and Tesla BS 467 (at 60 MHz) instruments using tetramethylsilane as internal standard; chemical shifts are given in ppm. Elemental analyses were carried out in the Analytical Laboratory of this Institute (Dr J. Horáček, Head). Gas–liquid chromatography was performed on a Chrom III instrument (Laboratorní přístroje, Prague).

Starting Compounds

Methyl 3-methylbutanoate[21] (b.p. 115·5°C/100 kPa; n_D^{20} 1·3932) was prepared by esterification of 3-methylbutanoic acid (Lachema, Brno, Czechoslovakia). Methyl cyclopropylacetate (b.p. 125°C/100 kPa; n_D^{20} 1·4200) was synthesized according to a known[8] procedure. The preparation of methyl cyclobutylacetate by Wolff rearrangement of cyclobutyl diazomethyl ketone[22], catalysed by silver benzoate[23], is described below. Methyl cyclopentylacetate (b.p. 178–179°C/100 kPa; n_D^{20} 1·4378; for $C_8H_{14}O_2$ (142·2) calculated: 67·57% C, 9·92%; found: 67·56% C, 9·86% H. ^{1}H-NMR spectrum ($CDCl_3$): 1·07 (m, 8 H, 4 CH_2), 2·30 (d, 2 H, $CH_2CO_2CH_3$), 3·63 (s, 3 H, CO_2CH_3)) was prepared by esterification of cyclopentylacetic acid[24]. 3,3-Dimethylbutanoic acid was synthesized from 2-chloro-2-methylpropane and 1,1-dichloroethene according to Bott[25]; its methyl ester (b.p. 124–126°C/98·4 kPa; n_D^{20} 1·3992) was obtained by reaction of 3,3-dimethylbutanoyl chloride[26] with methanol. Sodium bis(trimethylsilyl)amide was prepared[11] by reaction of a suspension of sodium amide in toluene (Fluka) with hexamethyldisilazane and stored as 0·3M solution in benzene. Diisopropylamine (Koch-Light) was dried by distillation from calcium hydride. The ethereal solution (0·8M) of n-butyllithium was prepared according to Gilman[27]. Ethyl formate was distilled from phosphorus pentoxide prior the reaction; ethyl acetate was dried over calcium chloride.

5-Isopropyl-2-thiouracil (*XIb*)

A mixture of methyl 3-methylbutanoate (2·0 g; 17·2 mmol) and ethyl formate (6·4 g; 86 mmol) was added dropwise in the course of 10 min to a stirred 0·3M solution of sodium bis(trimethylsilyl)amide[11] (115 ml) at room temperature. After standing for 12 h at room temperature the mixture was taken down *in vacuo* and the residue refluxed with thiourea (1·5 g; 20 mmol) in methanol (50 ml) for 5 h. The mixture was cooled, diluted with water (100 ml) and the solution was neutralized by addition of Dowex 50 (H^+). The exchange resin was filtered off and washed with aqueous methanol (1 : 1) until the eluate showed no UV absorption. The combined filtrates were decolorized with charcoal and evaporated *in vacuo*. Crystallisation from dilute acetic acid afforded 390 mg (13·3%, based on methyl 3-methylbutanoate) of the compound *XIb*, m.p. 238 to 240°C (reported[3] m.p. 238—239°C). UV spectrum (in 0·1M-HCl: λ_{max} 280 nm (log ε 4·02); (in 0·1M-NaOH): 260 nm (3·96), sh 302 nm (3·73).

5-Isopropyl-6-(2-methylpropyl)-2-thiouracil (*VIb*)

Methyl 3-methylbutanoate (3·0 g; 26 mmol) in benzene (10 ml) was added dropwise during 10 min to a stirred 1·2M benzene solution of sodium bis(trimethylsilyl)amide (25 ml) at room temperature. After stirring for 3 h at 35°C, ethyl formate (2·3 g; 31 mmol) in benzene (10 ml) was added dropwise. The mixture was set aside for 12 h at room temperature, the benzene evaporated *in vacuo* and the residue refluxed with thiourea (2·5 g; 33 mmol) and methanol (50 ml) for 5 h. The mixture was worked up as described for the compound *XIb*, affording 310 mg of the product *VIb* (10·7%, based on methyl 3-methylbutanoate); m.p. 201—203°C (methanol–water). For the UV spectrum in methanol see Table III. The mother liquor after crystallisation of *VIb* on standing for several days deposited 80 mg of a crystalline mixture of compounds, transparent in UV light. Mass spectrum of this mixture showed fragmentation pattern of 3-methylbutanamide (*m/e* 101 (M^+), 86 (M^+-15), 69, 57 (C_4H_9)) and 5-methyl-2-(1-methylethyl)-3-oxohexanamide (*m/e* 185 (M^+), 170 (M^+-15), 143 (M^+-42), 128 (M^+-57)).

5- and 5,6-Disubstituted 2-Thiouracils

An 0·8M ethereal solution of n-butyl lithium (20 mmol) was added dropwise (under nitrogen) to a stirred solution of diisopropylamine (2·1 g; 20·8 mmol) in ether (10 ml), (pre-cooled to —40°C) at temperature lower than —30°C (30—45 min). After the addition, the mixture was stirred for 30 min at —30°C, cooled to —40°C and at this temperature a solution of methyl ester of alkylacetic or cycloalkylacetic acid (20 mmol) in ether (15 ml) was added dropwise. After 20 min a solution of ethyl formate or other acylating agent was added dropwise at —30°C in the course of 20 min. The mixture was stirred for 1 h at —30°C and allowed to stand overnight at —4°C. In order to determine the yields of the β-oxo ester, 0·1 ml of the mixture was dissolved in 0·1M-NaOH (100 ml) and its absorbance measured at 275 nm. The concentration was calculated using molar extinction coefficient of methyl 2-formylbutanoate[31] as standard (λ_{max} 275·5 nm, ε 16480). The formylation of the methyl esters of the acids *XVIII*—*XX* was practically complete 1 h after addition of ethyl formate to the lithiated ester; the yields, determined by the above-described procedure, were about 80%. The yield of methyl 2-formyl-3,3-dimethylbutanoate after standing for 1 h at —4°C was 15%, after 12 h at the same temperature it rose to 35%. The ethereal solution of the formed enolate lithium salt was taken down *in vacuo* and the residue was refluxed with methanol (50 ml) and thiourea (1·5 g; 20 mmol) for 3 h. According to the solubility of the resulting 2-thiouracil in hot water, the reaction mixture was worked up using one of the following procedures:

Procedure A. The mixture was diluted with hot aqueous methanol (1 : 1; 300 ml) and neutralised with Dowex 50 (H^+) ion exchange resin. The resin was filtered off and washed with hot aqueous methanol until the filtrate showed no UV absorption. The combined filtrates were taken down *in vacuo* and the residue crystallised from hot water.

Procedure B. The mixture was taken down *in vacuo* and the residue dissolved in 10% aqueous ammonia (150 ml). The solution was extracted with ether (2× 50 ml). After removal of ammonia at 40°C *in vacuo*, the aqueous layer was acidified with hydrochloric acid (pH 4) under cooling with ice. The mixture was extracted with ethyl acetate (3× 50 ml). If the ethyl acetate extract contained any unreacted thiourea, it was washed with one portion (50 ml) of water. The combined extracts were dried over sodium sulfate, taken down *in vacuo* and the residue crystallised from aqueous methanol or ethanol. The yields, melting points, UV spectra and elemental analyses are given in Tables I, III and IV.

Methyl 2-Formyl-3-methylbutanoate (*XXII*)

Methyl 3-methylbutanoate (2·3 g; 20 mmol) was formylated using lithium diisopropylamide and ethyl formate according to the above general procedure. The ethereal solution of the formed lithium enolate was poured into ice-cold water (100 ml), the ethereal layer separated and extracted

TABLE IV

Elemental Analyses of 5-Substituted and 5,6-Disubstituted 2-Thiouracils *Ib*—*VIIIb*

Compound	Formula (mol.w.)	Calculated/Found			
		% C	% H	% N	% S
Ib	$C_8H_{10}N_2OS$	52·74	5·53	15·32	17·57
	(182·2)	53·00	5·80	15·98	17·09
IIb	$C_8H_{10}N_2OS$	52·74	5·53	15·32	17·57
	(182·2)	52·11	5·77	15·05	17·27
IIIb	$C_{11}H_{14}N_2OS$	59·43	6·35	12·60	14·42
	(222·3)	59·69	6·43	12·32	14·16
IVb	$C_8H_{12}N_2OS$	52·16	6·57	15·21	17·37
	(184·2)	52·42	6·73	15·11	17·10
Vb	$C_8H_{12}N_2OS$	52·16	6·57	15·21	17·37
	(184·2)	52·42	6·51	15·02	17·41
VIb	$C_{11}H_{18}N_2OS$	58·39	8·02	12·32	14·14
	(226·3)	58·58	8·06	12·06	13·80
VIIb	$C_8H_{10}N_2OS$	52·74	5·53	15·23	17·57
	(182·2)	52·57	5·61	15·03	17·35
VIIIb	$C_9H_{12}N_2OS$	55·09	6·17	14·28	16·30
	(196·2)	54·90	6·17	13·90	16·28

with 1M-NaOH (5×30 ml). The combined aqueous solutions were acidified with 40% sulfuric acid to pH 5 under cooling with ice and the separated oil was extracted with ether (8×40 ml). The ethereal extracts were combined, washed with a saturated sodium sulfate solution (30 ml), dried over sodium sulfate and taken down. Fractionation of the residue afforded 0·74 g (26%) of the compound *XXII*, b.p. 70–75°C/2·0 kPa. ^{1}H-NMR spectrum (in $CDCl_3$): oxo form: 1·06 (d, 6 H, $CH(CH_3)_2$, J = 7 Hz), 2·50 (m, 1 H, $CH(CH_3)_2$), 3·01 (dd, 1 H, CHCHO, J_1 = 3·6 Hz, J_2 = 7·5 Hz), 3·79 (s, 3 H, $3CO_2CH_2$), 9·72 (d, 1 H, CHO, J = 3·6 Hz); enol form: 1·10 (d, 6 H, $CH(CH_3)_2$, J = 6 Hz), 2·50 (m, 1 H, $CH(CH_3)_2$), 3·81 (s, 3 H, CO_2CH_3), 7·05 (d, broad, 1 H, =CHOH, J = 13 Hz), 11·52 (d, broad, 1 H, =CHOH, J = 13 Hz). The ratio oxo form : enol form was found to be 7 : 4 (calculated from the intensities of the ^{1}H-NMR signals). IR spectrum ($CHCl_3$): oxo form: 1740 cm^{-1} (C=O ester), 1723 cm^{-1} (C=O aldehyde); enol form: 1714 cm^{-1} (C=O ester), 1665 cm^{-1} (C=C), 2980 cm^{-1} (OH, intramolecular hydrogen bond; in CCl_4: 2930 cm^{-1}).

Methyl α-Formylcyclopropylacetate (*XXIII*)

Methyl cyclopropylacetate (2·3 g; 18·9 mmol) was formylated using the above-described procedure; yield 0·82 g (31%) of the compound *XXIII*; b.p. 65–70°C/1·6 kPa. ^{1}H-NMR spectrum (in $CDCl_3$): oxo form: 2·58 (dd, 1 H, CHCHO, J = 2·7 Hz), 3·78 (s, 3 H, CH_3), 9·74 (d, 1 H, CHO, J = 2·7 Hz); enol form: 3·82 (s, 3 H, CH_3), 7·02 (d, broad, 1 H, =CHOH, J = 12·5 Hz), 11·34 (d, 1 H, =CHOH, J = 12·5 Hz). The oxo form : enol form ratio was found to be 7 : 10 according to the intensities of ^{1}H-NMR signals. IR spectrum (in $CHCl_3$): oxo form: 1737 cm^{-1} (C=O ester), 1723 cm^{-1} (C=O aldehyde); enol form: 1714 cm^{-1} (C=O ester), 1669 cm^{-1} (C=C), 3000 cm^{-1} (OH, intramolecular hydrogen bond; in CCl_4: 2960 cm^{-1}.

5- and 5,6-Disubstituted Uracils *Ia*–*VIIIa*

The 2-thiouracils *Ib*–*VIIIb* (5 mmol) were refluxed with chloroacetic acid (2·35 g; 25 mmol) in water until the starting 2-thio compound disappeared. Sufficient amount of water (10 to 50 ml) was employed to keep the product dissolved in the hot mixture till the end of the reaction. After cooling, the separated product was filtered, washed with water and crystallised. Yields of the products, their elemental analyses and UV spectra are given in Tables II and V.

Cyclobutanecarboxylic Acid

Cyclopentanone (126 g; 1·5 mol) was oxidised with hydrogen peroxide in tert-butyl alcohol according to the described method[32]. The isolation procedure was modified as follows. After removal of the separated selenium by filtration the reaction mixture was taken down *in vacuo* and the residue dissolved in 10% sodium carbonate solution (400 ml). The solution was filtered with charcoal and celite and the filtrate extracted with ether (100 ml). A saturated aqueous solution of potassium permanganate was gradually added to the aqueous layer till the pink colour of the mixture persisted for 5 min. The excess potassium permanganate was destroyed by reduction with methanol, the mixture warmed to 50°C and the manganese oxide filtered and washed with water. The combined filtrates were concentrated *in vacuo* to 100 ml, cooled with ice and acidified with 15% hydrochloric acid to pH 4. The mixture was extracted with ether (7 . 100 ml), the ethereal extracts were combined, dried over sodium sulfate and the ether was evaporated under atmospheric presure. Fractionation of the residue afforded 23·0 g (15·3%) of cyclobutanecarboxylic acid, b.p. 95–110°C/0·53 kPa. A sample of the product was transformed by treatment with diazomethane into the methyl ester which was homogeneous according to gas–liquid chromatography (poly(ethylene glycol adipate) column, 80°C).

Methyl Cyclobutylacetate

Cyclobutyl diazomethyl ketone[22] was prepared by the procedure described previously for the analogous cyclopropane derivative[8]. B.p. 80–85°C/2·7 kPa, n_D^{20} 1·5180. ^{1}H-NMR spectrum (in $CDCl_3$): 2·15 (m, 6 H, —$(CH_2)_3$—), 3·13 (m, 1 H, $CH(CH_2)_3$), 5·15 (s, 1 H, CHN_2). UV spectrum (in methanol): λ_{max} 246 nm and 272 nm (log ε 3·91 and 4·05, respectively).

To a stirred boiling solution of cyclobutyl diazomethyl ketone (6·5 g; 52·4 mmol) in methanol (35 ml) was added a 10% solution of silver benzoate in triethylamine in 0·5 ml portions. Each new portion of the catalyst was added only when the nitrogen evolution nearly ceased, the total amount of the silver benzoate solution employed being 20 ml. The course of the diazo ketone decomposition was monitored by thin-layer chromatography (benzene–ethyl acetate 5 : 1). After the starting compound had disappeared the mixture was refluxed for 20 min, filtered and treated with an aqueous sodium hydroxide solution (9·0 g of NaOH in 250 ml of water). After standing at room temperature for 12 h the mixture was boiled for 10 min, filtered and taken down *in vacuo*. The residue was dissolved in water (30 ml) and extracted with ether (3 . 30 ml). The aqueous layer was acidified with 20% sulfuric acid under cooling with ice, extracted with ether (7 . 30 ml), the ethereal extracts were dried over sodium sulfate, taken down and the residue

TABLE V

Yields, Melting Points and Elemental Analyses of 5-Substituted and 5,6-Disubstituted Uracils *Ia–VIIIa*

Compound Yield, %	M.p., °C solvent	Formula (mol.w.)	Calculated/Found % C	 % H	 % N
Ia	253	$C_8H_{10}N_2O_2$	57·82	6·07	16·86
66	methanol	(166·2)	57·78	5·98	16·68
IIa	264–269	$C_8H_{10}N_2O_2$	57·82	6·07	16·86
72	methanol	(166·2)	57·73	6·03	16·89
IIIa	241–242	$C_{11}H_{14}N_2O_2$	64·05	6·84	13·58
88	ethanol	(206·2)	63·67	6·29	13·86
IVa	289–292[a]	$C_8H_{12}N_2O_2$	57·13	7·19	16·66
91	methanol	(168·2)	57·48	7·42	16·48
Va	250–251	$C_8H_{12}N_2O_2$	57·13	7·19	16·66
60	methanol–water	(168·2)	57·12	7·20	16·80
VIa	241–242	$C_{11}H_{18}N_2O_2$	62·83	8·63	13·32
80	methanol–water	(210·3)	62·46	8·21	13·58
VIIa	325 (dec.)	$C_8H_{10}N_2O_2$	57·82	6·07	16·86
83·5	ethanol–water	(166·2)	57·95	6·31	16·66
VIIIa	294–295[b]	$C_9H_{12}N_2O_2$	59·98	6·71	15·55
86	dimethylformamide	(180·2)	59·80	6·85	15·42

[a] Ref.[30] 289–292°C; [b] ref.[29] 327°C.

treated with ethereal solution of diazomethane till the yellow coloration persisted. After evaporation of the solvent (Vigreux column) the residue was fractionated, yielding 4·0 g of a fraction, b.p. 140–145°C/98·4 kPa, containing methyl cyclobutylacetate which was 90% pure according to gas–liquid chromatography on poly(ethylene glycol adipate) at 100°C. The peaks of the impurities (7·5% and 2·5%) had shorter retention times. The yield of methyl cyclobutylacetate, calculated for the pure compound, was 53·7%. An analytical sample, obtained by redistillation at atmospheric pressure, was shown by gas–liquid chromatography (poly(ethylene glycol), 80°C) to be 96·3% pure; n_D^{20} 1·4279. ^{1}H-NMR spectrum (60 MHz, $CDCl_3$): 2·46 (s, 2 H, $CH_2CO_2CH_3$), 3·62 (s, CH_3O); IR spectrum (CCl_4): 1 730 cm^{-1} (C=O), 2981 cm^{-1} (CH_2 in cyclobutane), 2902 cm^{-1} (CH_2 in cyclobutane), 917 cm^{-1} (cyclobutane ring skeletal vibration). For $C_7H_{12}O_2$ (128·2) calculated: 65·59% C, 9·44% H; found: 65·51% C, 9·74% H.

Thermal decomposition of cyclobutyl diazomethyl ketone in a collidine–benzyl alcohol mixture under conditions described for the decomposition of cyclopropyl diazomethyl ketone[8] afforded only a 12% yield of methyl cyclobutylacetate.

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