SYNTHESIS OF 5-CYCLOPROPYL-6-AZAURACIL*

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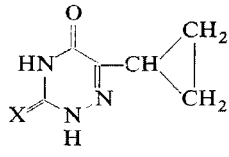
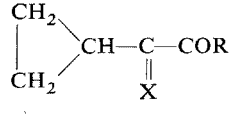
The synthesis of 5-cyclopropyl-6-azauracil (*I*) from cyclopropylglyoxylic acid thiosemicarbazone (*IV*) has been described. Cyclopropylglyoxylic acid (*II*) has been prepared by the potassium permanganate oxidation of cyclopropyl methyl ketone. The ultraviolet maximum of compound *I* is situated at longer wavelengths than that of 6-azauracil and its 5-alkyl substituted derivatives.

In spite of numerous reports on 5-alkyl-6-azauracils[1,2], no attention has been hitherto paid to analogous alicyclic derivatives of 6-azauracil. In the present paper we wish to report the synthesis of 5-cyclopropyl-6-azauracil (*I*) as the first representative of the novel series.

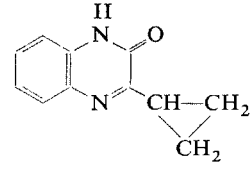
In the synthesis of compound *I*, cyclopropylglyoxylic acid (*II*) was required as the starting material. The reported[3] preparation of the acid *II* based on the reaction of the chloride of cyclopropanecarboxylic acid with methoxymethylenetriphenyl-



I; X = O
VI; X = S



II; R = OH, X = O
III; R = OCH_3, X = O
IV; R = OH, X = $NNHCSNH_2$



V

phosphorane, does not appear to be suitable for the synthesis on a larger scale. We have therefore attempted to prepare the acid *II* by the potassium permanganate oxidation of the readily accessible cyclopropyl methyl ketone analogously to the preparation of 2-methylcyclopropylglyoxylic acid from 1-(2-methylcyclopropyl)-1-propanone[4]. The tert-butylglyoxylic acid and arylglyoxylic acids have also been prepared by this method from the corresponding methyl ketones[5,6].

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Oxidation of cyclopropyl methyl ketone with potassium permanganate in an aqueous medium afforded a fair yield of the acid *II* which was isolated as the potassium salt. By reaction with diazomethane, the acid *II* was converted to the earlier reported[3] methyl ester *III*. Acid *II* was also characterised as the crystalline 3-cyclopropyl-1,2-dihydroquinoxalin-2-one (*V*).

Reaction of the acid *II* with thiosemicarbazide yielded the thiosemicarbazone *IV* which was cyclised in alkaline media with the formation of 6-cyclopropyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (*VI*). By the action of methyl iodide, compound *VI* was converted in the usual manner[1] to 5-cyclopropyl-6-azauracil (*I*). It was also attempted to prepare compound *I* in one operation from the thiosemicarbazone *IV* by the action of methyl iodide in aqueous medium, *i.e.*, analogously to the preparation of 5-methyl-6-azauracil[7,8] and 5-fluoromethyl-6-azauracil[7]. Since the yields of the final product *I* were low, the procedure was modified in such a manner that the treatment of the thiosemicarbazone *IV* with methyl iodide and the subsequent acid-catalysed hydrolysis of the intermediary 6-cyclopropyl-3-methylthio-2,5-dihydro-1,2,4-triazin-5-one (not isolated) was performed in aqueous medium of the initial pH 1 value in the presence of Zerolite FF (trifluoroacetate) ion exchange resin which binds the hydrogen iodide formed by the reaction.

The ultraviolet spectrum of compound *I* exhibits (when compared with those of 6-azauracil and its 5-alkyl derivatives) a significant shift of the absorption maximum to longer wavelengths (Table I). This shift is probably due to the conjugation effect of the cyclopropane ring which might be explained on the basis of the Bernett cyclopropane model[9] by a partial overlap of the sp^5 orbitals of the cyclopropyl group with the p_z orbital of the vicinal triazine-ring carbon atom (for the survey of reports on the conjugation effect of the cyclopropane ring see ref.[10]). The absorption maximum shift observed in comparisons of the ultraviolet spectra of variously substituted cyclopropylethylenes and isopropylethylenes[11] is of the same order of magnitude.

The polarographical behaviour of compound *I* is qualitatively identical with that of other 5-alkyl-6-azauracils[12]. The half-wave potential value of compound *I* is by 16 mV more negative than with 5-methyl-6-azauracil. This shift is of the opposite direction than it could be expected on the basis of σ^* Taft constants of the methyl and cyclopropyl group ($\sigma^*_{CH_3}$, 0·00; $\sigma^*_{c-C_3H_5}$, +0·017; *cf.*[10,13]). The more difficult polarographic reduction in the case of compound *I* might be due to the steric effect of the cyclopropyl group. Krupička and Gut[12] similarly explain the relatively high negative value of the half-wave potential in the case of 5-tert-butyl-6-azauracil.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 25°C/0·05 Torr for 8 h. Paper chromatography was performed by the descending technique on paper Whatman No 1 in the solvent systems S_1, 1-butanol–ethanol–water (4 : 1 : 5),

and S_2, 1-butanol–acetic acid–water (20 : 3 : 7). Spots were detected by viewing under ultraviolet light. The UV spectra were measured on the Unicam SP-8000 spectrophotometer. The IR spectra were recorded on the Zeiss Model UR-10 apparatus. Mass spectra were taken on a MS 902 apparatus with a double focussation. The NMR spectra were measured on a Varian HA-100 apparatus at 100 MHz using tetramethylsilane as internal standard. The pK values were measured potentiometrically at 20°C on a Beckman Model 1019 pH-meter. The thermodynamical dissociation constants were obtained by correction to the ionic strength of the solution. Polarographic measurements were performed on a LP 7 Polarograph in combination with an electron-tube recording EZ 7 millivoltmeter.

Cyclopropylglyoxylic Acid (*II*)

To a stirred mixture of cyclopropyl methyl ketone[14] (12·5 g; 0·15 mol), water (100 ml), and anhydrous sodium carbonate (0·5 g) there was added dropwise at 50°C over 36 h a solution of potassium permanganate (25 g) in water (700 ml) at such rate to keep the reaction mixture lightly purple. When the oxidation was complete, methanol was added, the mixture filtered, and the filtrate concentrated under diminished pressure at 50°C to deposit crystals of the potassium salt of the acid *II*. The recrystallisation was performed from methanol with the addition of active charcoal. Yield, 15·5 g (68%) of the potassium salt of the acid *II*, m.p. 258°C (decomp.). For $C_5H_5KO_3$ (152·2) calculated: 39·43% C, 3·31% H, 25·67% K; found: 39·59% C, 3·29% H, 25·50% K. IR spectrum (in KBr): 3089 cm^{-1} and 2990 cm^{-1} (CH of the cyclopropane ring), 1691 cm^{-1} (C=O) ketone), 1620 cm^{-1} and 1362 cm^{-1} (CO_2^-). NMR spectrum (in hexadeuteriodimethyl sulfoxide): δ 0·81 (m, 4 H, 2 CH_2 of the cyclopropyl group); 2·22 (m, 1 H, CH of the cyclopropyl group).

Methyl Cyclopropylglyoxylate (*III*; R = OCH_3, X = O)

A solution of the potassium salt of the acid *II* (2·0 g; 13 mmol) in water (20 ml) was applied to 1·5 cm × 15 cm column of Dowex 50 (H^+) ion exchange resin and the column was eluted with water (150 ml) until the effluent was neutral. The effluent was then evaporated under diminished pressure and the residual sirup treated with ethereal diazomethane until the colour of the reaction mixture remained yellow. The ether was then evaporated under diminished pressure and the residue fractionated *in vacuo* to afford 1·6 g (95%) of compound *III*, b.p. 85—90°C/12 Torr; n_D^{25} 1·4484. IR spectrum (in chloroform): 1740 cm^{-1} (C=O ester), 1713 cm^{-1} (C=O ketone). Band positions were identical with those reported in the literature[3] for compound *III*.

3-Cyclopropyl-1,2-dihydroquinoxalin-2-one (*V*)

To a solution of the potassium salt of the acid *II* (0·2 g; 1·3 mmol) in water (2 ml) there was added a solution of 1,2-phenylene diamine dihydrochloride (0·35 g; 2 mmol) in water (2 ml), the mixture kept at room temperature for 1 h, the precipitate collected with suction and crystallised from ethanol (active charcoal). Yield, 0·2 g (83%) of compound *V*, m.p. 246°C (decomp.). UV spectrum (in water): λ_{max} 227 nm and 338 nm (log ε 4·13 and 3·96), inflex 247 nm and 297 nm (log ε 3·73 and 3·75); in 0·1M-NaOH: λ_{max} 239, 292 and 348 nm (log ε 4·24, 3·47, and 3·96, resp.). IR spectrum (in KBr): 1660 (C=O), 3320, 2880 (NH), 1612, 1598, 1555, 1503, 1488, and 1431 cm^{-1} (quinoxaline ring). Mass spectrum: M^+ 186 and fragments 185, 167, 157, 143, and 132. For $C_{11}H_{10}N_2O$ (186·2) calculated: 70·95% C, 5·35% H, 15·04% N; found: 70·60% C, 5·47% H, 14·95% N.

6-Cyclopropyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (*VI*)

Cyclopropylglyoxylic acid thiosemicarbazone (*IV*). The potassium salt of the acid *II* (4·0 g 26 mmol) was deionised as described above. To the residual sirup of the free acid *II* there was then added a hot solution of the thiosemicarbazide (2·2 g; 2·4 mmol) in water (20 ml), the whole mixture kept at room temperature for 4 h, the crystalline precipitate of the thiosemicarbazone *IV* collected with suction, and dried under diminished pressure over potassium hydroxide pellets. Yield, 2·9 g (60%) of compound *IV* which was used in the next step without any purification.

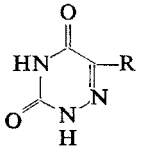
A mixture of the thiosemicarbazone *IV* (1·0 g; 5·3 mmol) and 5% aqueous sodium hydroxide (25 ml) was refluxed for 2 h and then deionised on a 1·5 cm × 15 cm column of Dowex 50 (H^+) ion exchange resin. The effluent was concentrated to deposit crystals which were recrystallised from water. Yield, 0·5 g (56%) of compound *VI*, m.p. 191–192°C (water). UV spectrum, in 0·1M-HCl: λ_{max} 219 and 272 nm (log ε 4·03 and 4·25); in 0·1M-NaOH: λ_{max} 224, 258, and 313 nm (log ε 4·27, 4·23, and 3·74, resp.). IR spectrum (in KBr): 3188, 3152, 3079 (NH); 1683 (C=O); 1225 (C=S), 1593 (triazine ring), 1023 cm^{-1} (cyclopropane ring). Mass spectrum: M^+ 169. NMR spectrum (in hexadeuteriodimethyl sulfoxide): δ 0·91 (m, 4 H, 2 CH_2, cyclopropyl), 2·14 (m, 1 H, CH, cyclopropyl), 13·03 (s, 1 H, NH). pK_1 6·54 ± 0·02. R_F values: 0·82 (in S_1) and 0·85 (in S_2). For $C_6H_7N_3OS$ (169·2) calculated: 42·59% C, 4·17% H, 24·83% N, 18·95% S; found: 42·80% C, 4·22% H, 24·57% N, 19·19% S.

5-Cyclopropyl-6-azauracil (*I*)

A. *From the thiosemicarbazone* IV. To a solution of the thiosemicarbazone *IV* (1·6 g; 8·6 mmol) in water (15 ml) there was added 10 ml of moist Zerolite FF ion exchange resin (trifluoroacetate cycle) and the whole mixture was adjusted to pH 1 by the addition of trifluoroacetic acid. Methyl iodide (1 ml) was then added, the whole stirred at 45°C for 1 h, and the excess methyl iodide

TABLE I

UV Spectra of Some Triazine Derivatives



R	0·1M-HCl		0·05M-$Na_2B_4O_7$		1M-NaOH	
	λ_{max}, nm	log ε	λ_{max} nm	log ε	λ_{max}, nm	log ε
c-C_3H_5 [a]	273	3·78	258	3·71	294	3·73
H	259	3·71	252	3·70	287	3·76
CH_3	261	3·75	251	3·71	287	3·67
C_2H_5	261	3·77	251	3·75	287	3·70
$C(CH_3)_3$	259	3·81	252	3·78	286 [b]	3·78

[a] Compound *I*; [b] measured in 3M-NaOH.

removed by distillation at ordinary pressure. The residual mixture was heated at 65°C for 6 h, the resin filtered off, and washed repeatedly with hot ethanol until the absorption at 260 nm disappeared. The filtrate and ethanolic washings were combined and concentrated under diminished pressure to deposit crystals. Yield, 0·85 g (65%) of compound *I*, m.p. 201—202°C (water). For $C_6H_7N_3O_2$ (153·2) calculated: 47·05% C, 4·61% H, 27·44% N; found: 47·20% C, 4·62% H, 27·95% N. For the UV spectrum see Table I. IR spectrum (in KBr): 3233, sh 3181, 3149, 3034 (NH), 1728, 1709, 1689 (C=O), 1589 (triazine ring), 1224 cm^{-1} (cyclopropane ring). Mass spectrum: M^+ 153. NMR spectrum (in hexadeuteriodimethyl sulfoxide): δ 0·84 (m, 4 H, 2 CH_2, cyclopropyl), 2·10 (m, 1 H, CH, cyclopropyl), 11·79 (s, 1 H, NH). Polarography: $E_{1/2}$ —1·453 *V*: : S.C.E. in the Britton–Robinson buffer solution at pH 9·2; under the same conditions, the $E_{1/2}$ value of 5-methyl-6-azauracil was —1·437 *V*/S.C.E. R_F values: 0·74 (in S_1) and 0·74 (in S_2).

B. *From the thioxo derivative* VI. A solution of compound *VI* (200 mg) in water (15 ml) was heated with methyl iodide (1 ml) under reflux for 2 h and the excess methyl iodide was removed by distillation. The residual mixture was heated at 80°C for 2 h, evaporated under diminished pressure, and the residue purified by crystallisation from water. Yield, 120 mg (66%) of compound *I*, m.p. 201—202°C, undepressed on admixture with the specimen prepared by procedure *A*. The identity was also established by UV spectra and paper chromatography in solvent systems S_1 and S_2.

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