THE SYNTHESIS OF 5-CYCLOPROPYLURACIL*

I. BAŠNÁK and J. FARKAŠ

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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5-Cyclopropyl-2-thiouracil (*II*) was prepared on reaction of the sodium salt of methyl 2-cyclopropyl-2-formylacetate with thiourea. Reaction of *II* with chloroacetic acid gave 5-cyclopropyluracil (*I*). 6-Cyclopropyl-2-thiouracil (*IV*) was converted to 6-cyclopropyluracil (*III*) by the same procedure. The character of the ultraviolet spectra of compounds *I*—*IV* was discussed in connection with the conjugation effect of the cyclopropane ring.

The studies concerning the biological activity of nucleosides derived from 5-alkyluracils[1-4] led us to the preparation of uracil derivatives substituted in the position 5 with an alicyclic residue. The synthesis of 5-cyclopropyluracil (*I*) is the subject of this communication. While a series of 5-alkyluracils[5,6] and some 5-alkenyluracils[7,8] have been prepared already, among analogous alicyclic derivatives 5-cyclopentyluracil[9] and 5-(1-adamantyl)-2-thiouracil[10] only have been described.

We prepared substance *I* by a procedure[6] commonly used for the preparation of 5-alkyluracils, starting with the methyl ester of cyclopropylacetic acid. Among the methods described for the preparation of this acid[11,14] we chose Wolff's rearrangement of cyclopropyl diazomethyl ketone[15,16]. According to Turnbull[12] this rearrangement is carried out in boiling methanol under gradual addition of silver oxide. We found that under the described conditions cyclopropyl diazomethyl ketone is decomposed very slowly; after eight hours' heating in boiling methanolic solution and in the presence of a relatively large amount of silver oxide about 20% of diazoketone remained unchanged. The required methyl ester was isolated in 9% yield only, while Turnbull[12] gives a 47% yield. A substantial increase in yield was achieved by thermal decomposition[17] of cyclopropyl diazomethyl ketone in a mixture of benzyl alcohol and collidine at 155—160°C. On alkaline hydrolysis of the benzyl ester formed and subsequent reaction of the crude cyclopropylacetic acid with diazomethane we obtained the required methyl ester of cyclopropylacetic acid in a 29·5% yield. In order to control the purity methyl cyclopropylacetate was converted to cyclopropylacetoxamic acid which was found quite pure by electrophoresis. On reaction with ethyl

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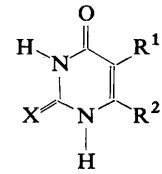

I; R^1 = cyclo-C_3H_5, R^2 = H, X = O
II; R^1 = cyclo-C_3H_5, R^2 = H, X = S
III; R^1 = H, R^2 = cyclo-C_3H_5, X = O
IV; R^1 = H, R^2 = cyclo-C_3H_5, X = S

formate and sodium hydride methyl cyclopropylacetate gave sodium salt of methyl 2-cyclopropyl-2-formylacetate which was reacted in crude state with thiourea to afford 5-cyclopropyl-2-thiouracil (*II*) from which substance *I* was prepared by reaction with chloroacetic acid.

For comparison of the physical properties we also prepared 6-cyclopropyluracil (*III*) applying the reaction of 6-cyclopropyl-2-thiouracil[18,19] (*IV*) described earlier with chloroacetic acid. The preparation of compound *III* is described in patent literature[20].

In the ultraviolet spectra of a considerable number of substances containing a cyclopropane ring adjacent to a double bond or an aromatic nucleus a bathochromic shift as high as 14 nm has been observed, which is ascribed to the conjugation ability of the cyclopropane ring[21–23]. A similar shift (2–6 nm) is also evident in the UV spectra of compounds *I*–*III*, measured in acid medium. Contrary to expectation compound *IV* displays a shift in the opposite direction. This anomalous behaviour of compound *IV* could be explained plausibly according to the analogy with Jorgenson's studies[24] concerning ultraviolet spectra of variously substituted 3-cyclopropylacrylic acid esters, as a consequence of the change in the conformation of the cyclopropane ring, *i.e.* by its deviation from the preferred "bisected" geometry[25] which permits maximum overlapping of the highest occupied molecular orbitals of the cyclopropane ring ($6a_1$ and $3b_2$) with the p_z orbitals of the double bond[26]. However, this interpretation cannot be regarded as conclusive because the work of other authors, concerning the ultraviolet spectra of cyclopropylethylenes[27] and cyclopropyl derivatives of aromatic systems[28], shows that between the cyclopropane ring conformation and its conjugation ability no evident relationship exists.

Substances *I*–*IV* did not appreciably inhibit the growth of *Escherichia coli* B even at 1000 μg/ml concentration.

EXPERIMENTAL

The melting points were determined on a Kofler block. The analytical samples were dried at 25°C/0·05 Torr for 12 hours. The ultraviolet spectra were measured on a Unicam SP/8000

spectrophotometer. The infrared spectra were measured with a Zeiss, model UR 10 spectrophotometer. The ^{1}H-NMR spectra were recorded with a Varian HA 100 instrument at 100 MHz, using tetramethylsilane as internal reference (chemical shift in p.p.m.). The mass spectra (70 eV) were measured with a MS 902 spectrometer with double focussing. Gas chromatography was carried out on a Chrom 2 instrument (Laboratorní přístroje, Prague) using a PEA-1F column at 100°C. Preparative gas chromatography was carried out on a Beckman instrument with a DEGS-4N column at 100°C and 1 atm nitrogen pressure.

Paper chromatography was carried out on paper Whatman No 1 in the following systems: S_1 1-butanol–water (25 : 4), S_2 1-butanol–formic acid–water (77 : 10 : 13). Thin-layer chromatography was carried out on Silufol UV 254 sheets in ethyl acetate (S_3). Detection was carried out under UV light. Chromatographic behaviour is expressed in R_F values.

TABLE I

Ultraviolet Spectra of 5- and 6-Substituted Derivatives of Uracil and 2-Thiouracil

Substituent	0·1M-HCl		0·1M-NaOH	
	λ_{max}, nm	log ε	λ_{max}, nm	log ε
5-cyclo-C_3H_5	268	3·95	290	3·80
5-CH_3	265[b]	3·90	290	3·74
5-C_2H_5	264[b]	3·90	289	3·75
5-i-C_3H_7	265[b]	3·85	288	3·69
5-t-C_4H_9	265[b]	3·93	289	3·86
5-cyclo-C_3H_5[a]	280	3·72	263; sh 300	4·18; 3·90
5-CH_3[a]	278[c]	4·02	260; sh 297	3·96; 3·71
5-C_2H_5[a]	277[d]	4·03	260; sh 302	3·96; 3·73
6-cyclo-C_3H_5	267	4·11	283	4·03
6-CH_3	261	3·86	280	3·72
6-cyclo-C_3H_5[a]	272	4·27	259; 300	4·27; 3·89
6-CH_3[a]	276·5[e]	4·25	259·5; sh 313	4·25; 3·71

[a] Derivatives of 2-thiouracil. [b] Values taken from ref.[5]. [c] Values from ref.[31]; at pH 1 λ_{max} 277 nm (log ε 4·28); at pH 11 λ_{max} 258 nm and 311 nm (log ε 4·22 and 3·86). [d] Values from ref.[32]: in 0·1M-HCl λ_{max} 277 nm; in 0·001M-NaOH 259 nm and 309 nm. [e] Values from ref.[33]: at pH 0 to 6 λ_{max} 215·0 nm and 276·5 nm (log ε 4·23 and 4·21); at pH 10·5 λ_{max} 233 nm, 261 nm and 307·5 nm (log ε 4·08, 4·04 and 3·89).

Cyclopropyl Diazomethyl Ketone

To an 0·6M solution of diazomethane in ether (950 ml) cyclopropanecarboxylic acid chloride[29] (33·0 g; 0·318 mol) in ether (100 ml) was added dropwise and under cooling over 3·5 hours. After addition of all the chloride the mixture was stirred at 0°C for 2 hours. Ether was distilled off at 20 Torr and 15—20°C. The distillate receiver was cooled with a mixture of solid carbon dioxide and acetone. The remaining yellow oil, cyclopropyl diazomethyl ketone (33·0 g; 95·5%),

solidified to a crystalline mass after cooling at −20°C. UV spectrum (methanol): λ_{max} 246 nm and 272 nm (log ε 3·91 and 4·05). R_F in S_3 was 0·80.

Methyl Cyclopropylacetate

Cyclopropyl diazomethyl ketone (26·0 g; 0·236 mol) was dissolved in a mixture of 50 ml of *sym*-collidine and 50 ml of benzyl alcohol. Approximately a fifth of the total volume of the mixture was put in a flask provided with a magnetic stirrer and reflux condenser and placed in a bath at 150−155°C. After several minutes a rapid decomposition of diazoketone took place the rate of which was regulated by taking the flask out of the bath for several seconds. After 15 minutes, when the evolution of nitrogen was only weak the bath temperature was increased to 160°C and the mixture was heated at this temperature for another 5 minutes. The remaining diazoketone was decomposed in portions using the same procedure. The combined fractions were diluted with ether (250 ml) after decomposition of diazoketone and the solution was extracted with three 50 ml portions of 10% sulfuric acid at 0°C. The ethereal solution was dried over anhydrous magnesium sulfate and evaporated in a vaccum at 40°C (bath temperature). Then the residue, containing benzyl alcohol and cyclopropylacetic acid benzyl ester aqueous-methanolic potassium hydroxide solution was added (prepared by dissolution of 20 g of potassium hydroxide in a mixture of 60 ml of water and 120 ml of methanol). After 12 hours' standing at room temperature methanol was distilled off *in vacuo* and the residue was extracted with ether (with five 80 ml portions). The aqueous layer was evaporated in a vaccum to a small volume, and, after cooling with ice, 20% sulfuric acid was added until the reaction was strongly acid. The mixture was then extracted with ether (seven times with 50 ml) and the extract dried over anhydrous magnesium sulfate, filtered and evaporated in a vacuum. The distillation residue was dissolved in ether (60 ml) and a 0·6M ethereal diazomethane solution was added under cooling with ice until the evolution of nitrogen ceased and the mixture remained weakly yellow. Ether and the remaining diazomethane were distilled off through a Widmer column (30 cm). Fractional distillation of the residue at atmospheric pressure gave 8·0 g of a fraction with b.p. 126−132°C; n_D^{25} 1·4165. According to gas chromatography this fraction contained 6·9% of methyl cyclopropanecarboxylate. The yield of methyl cyclopropylacetate corrected for this admixture was 29·5% (referred to starting cyclopropyl diazomethyl ketone). The fraction boiling at 126−132°C/750 Torr (200 mg) was purified by preparative gas chromatography to give methyl cyclopropanecarboxylate (identified by mass spectroscopy) and methyl cyclopropylacetate, n_D^{25} 1·4175, lit.[11] 1·4175. IR spectrum (tetrachloromethane): 3087 cm^{-1} (CH_2); 2925 cm^{-1} (CH_3); 1745 cm^{-1} (C=O); 1435 cm^{-1} (CH_3); 1020 cm^{-1} (cyclopropane ring). ^{1}H-NMR spectrum (deuteriochloroform). δ 0·04−0·66 (m, 4 H, 2 CH_2 of the cyclopropane ring); 1·04 (m, 1 H, CH of the cyclopropane ring); 2·19 (d, 2 H, CH_2CO); 3·65 (s, 3 H, CH_3). Mass spectrum: *m/e* 114 (M^+), 113, 83, 82, 59, 55 (base peak).

Electrophoresis of Cyclopropylacetoxamic Acid

Methyl cyclopropylacetate (5 mg) was converted to the corresponding hydroxamic acid with aqueous methanolic hydroxylamine solution in the described manner[30]. Electrophoresis was carried out in 0·05M triethylammonium borate (pH 6·5) at 30 Vcm^{-1} for 2 hours. After spraying with a ferric chloride solution a single spot appeared with the mobility 5·5 cm. Under the given conditions the electrophoretic mobilities of cyclopropanecarbohydroxamic acid and cyclobutanecarbohydroxamic acid were 1·6 cm and 7·0 cm respectively.

5-Cyclopropyluracil (*I*)

A mixture of compound *II* (168 mg; 1 mmol) chloroacetic acid (200 mg; 1·63 mmol) and water (2 ml) was heated in a sealed tube on a water bath for 3 hours. After 12 hours' standing at room temperature the separated compound I was filtered off under suction and crystallized from water. Yield 105 mg (70%). IR spectrum (KBr): 3200–2800 cm^{-1} (NH), 1757 cm^{-1} and 1675 cm^{-1} (C=O), 1021 cm (cyclopropane ring). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): δ 0·34–0·84 (m, 4 H, 2 CH_2 of the cyclopropane ring); 1·46 (m, 1 H, CH of the cyclopropane ring); 6·91 (broad s, 1 H, H-6); 10·46 (broad s, 1 H, NH); 11·32 (broad s, 1 H, NH). Mass spectrum *m/e* 152 (M^+), 151, 137, 109, 80, 81 (base peak), 66. For $C_7H_8N_2O_2$ (152·15) calculated: 55·24%C, 5·30% H, 18·41% N; found: 55·28% C, 5·38% H, 18·84% N. Paper chromatography: in S_1 0·59 (elongated spot), in S_2 0·59. TLC: in S_3 0·53.

5-Cyclopropyl-2-thiouracil (*II*)

A 48% suspension of sodium hydride in mineral oil (0·50 g) was added to 20 ml of ether and to this suspension ethanol (0·05 ml) was added under vigorous stirring, followed, after 5 minutes, by dropwise addition over one hour and at room temperature of a mixture of methyl cyclopropyl acetate (1·14 g; 0·01 mol), ethyl formate (1·1 g; 0·015 mol) and ether (5 ml). The mixture was stirred for 7 hours and then allowed to stand at room temperature overnight. (A sample of the reaction mixture dissolved in 0·05M-NaOH absorbed in UV light at λ_{max} 274 nm, and the absorption disappeared after acidification of the solution). Ether was evaporated *in vacuo* and a solution of 0·4 g of sodium in 30 ml of methanol and thiourea (1·32 g; 0·0175 mol) was added to the residue. After 5 hours' refluxing the mixture was cooled, diluted with water (50 ml) and neutralized by addition of Dowex 50 (H^+). Dowex was filtered off and washed with hot water until the UV absorption disappeared. The main filtrate and the wash waters were combined, filtered with a small amount of charcoal and evaporated *in vacuo* to incipient crystallization. After one hour's standing at 0°C the separated product was filtered with suction and crystallized from water. Yield of II, 0·36 g (21%, referred to methyl cyclopropylacetate). M.p. 211–212°C (water). IR spectrum (KBr): 3200–2800 cm^{-1} (NH); 1657 cm^{-1} (C=O); 1230 cm^{-1} (C=S); 1023 cm^{-1} (cyclopropane ring). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): δ 0·49–0·99 (m, 4 H, 2 CH_2 in cyclopropane ring); 1·64 (m, 1 H, CH in cyclopropane ring); 6·94 (s, 1 H, H-6); 12·15 (broad s, 2 H, 2 NH), after addition of CD_3CO_2D this signal disappears. Mass spectrum: *m/e* 168 (M^+, base peak), 153, 109, 110, 80; high resolution: M^+ 168·1264; for $C_7H_8N_2OS$ 168·1263. For $C_7H_8N_2OS$ (168·2) calculated: 49·98% C, 4·79% H, 16·65% N, 19·06% S; found: 50·30% C, 4·95% H, 16·98% N, 19·42% S. Paper chromatography: in S_1 0·82, in S_2 0·78; TLC: in S_3 0·75.

6-Cyclopropyluracil (*III*)

A mixture of compound *IV* (500 mg; 2·98 mmol), chloroacetic acid (500 mg; 4·1 mmol) and water (5 ml) was heated in a sealed tube in a boiling water bath for 8 hours. It was then allowed to stand at 8°C for 12 hours. The separated product (0·41 g) afforded after crystallization from water 0·250 mg (36%) of compound *III*. M.p. 215–224°C (decomp.), lit.[20] gives 211–217°C. IR spectrum (KBr): 3300–2800 cm^{-1} (NH); 1716 cm^{-1} and 1660 cm^{-1} (C=O); 1028 cm^{-1} (cyclopropane ring). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): δ 0·63–1·00 (m, 4 H, 2 CH_2 in cyclopropane ring); 1·58 (m, 1 H, CH in cyclopropane ring); 5·05 (s, 1 H, H-5); 10·75 (broad s, 2 H, 2 NH). Mass spectrum: *m/e* 152 (M^+, base peak), 151, 137, 109, 108, 81, 80, 68. For $C_7H_8N_2O_2$ (152·15) calculated: 55·24% C, 5·30% H, 18·41% N; found: 54·70% C, 5·37% H, 18·42% N. Paper chromatography in S_1 0·65 in S_2 0·61; TLC: in S_3 0·21.

6-Cyclopropyl-2-thiouracil (*IV*)

Compound *IV* was prepared according to Spitzmiller[18]. M.p. 234°C (water). Lit.[18,19] gives m.p. 239°C and 234°C. IR spectrum (KBr): 3200–2800 cm^{-1} (NH); 1675–1630 cm^{-1} (C=O); 1170–1180 cm^{-1} (C=S); 1024 cm^{-1} (cyclopropane ring). Mass spectrum: *m/e* 168 (M^+, base peak), 167, 109, 81, 80, 68. ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): δ 0·68–1·25 (m, 4 H, 2 CH_2 in cyclopropane ring); 1·68 (m, 1 H, CH in cyclopropane ring); 5·25 (s, 1 H, H-5); 12·08 (broad s, 1 H, NH); 12·28 (broad s, 1 H, NH). Paper chromatography: in S_1 0·78, in S_2 0·75; TLC: in S_3 0·61.

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