$5^1,5^2$-Azinodi(2-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one) (*VII*)

A solution of the acetate *VI* (200 mg) in 30% methanolic ammonia (10 ml) was allowed to stand at room temperature for 20 hours, evaporated, and the crystalline residue triturated with methanol (3 ml) to afford 110 mg (83%) of the nucleoside *VII*, m.p. 259—260°C. The analytical sample melted at 260°C (30% aqueous methanol). For $C_{16}H_{22}N_8O_{10}$ (486·4) calculated: 39·68% C, 4·55% H, 23·05% N; found: 39·69% C, 4·74% H, 22·80% N. Paper chromatography, R_F value: at the start line in 1-butanol–water (85 : 15) and 0·21 in 2-propanol–concentrated aqueous ammonia–water (7 : 1 : 2). Ultraviolet spectrum, pH 1: λ_{max} 239 nm (ε 12·3 . 10^3), λ_{max} 351 nm (ε 25·6 . 10^3), λ_{min} 278 nm (ε 4·3 . 10^3); pH 7: λ_{max} 237 nm (ε 13·1 . 10^3), λ_{max} 350 nm (ε 24·0 . 10^3), λ_{min} 278 nm (ε 4·75 . 10^3); pH 13: λ_{max} 252 nm (ε 12·0 . 10^3), λ_{max} 388 nm (ε 21·2 . 10^3), λ_{min} 309 nm (ε 6·1 . 10^3).

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NUCLEIC ACID COMPONENTS AND THEIR ANALOGUES. CXLV.* N-SUBSTITUTION OF URACIL AND 5-BROMOOROTIC ACID

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As reported in an earlier paper[1] of this Series, the reaction of 6-azauracil and benzyl chloride in aqueous sodium hydroxide has furnished 1-benzyl-6-azauracil. Under analogous conditions, uracil (*I*) and benzyl chloride afford 1-benzyluracil (*II*). The structure of compound *II* was established by cyanoethylation to compound *II* which was identical with the specimen obtained by benzylation of 3-(2-cyanoethyl)uracil[2,3] (*IV*). Consequently, the course of benzylation

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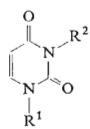
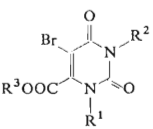
is analogous to that of 6-azauracil. Benzylation of uracil (*I*) with excess benzyl chloride leads to 1,3-dibenzyluracil (*V*). The same compound is obtained by the additional benzylation of the monobenzyl derivative *II*. Benzylation of 1-(2-cyanoethyl)uracil[2] (*VI*) in dilute aqueous sodium hydroxide leads to 3-benzyl-1-(2-cyanoethyl)uracil (*VII*). In boiling dilute ethanolic sodium ethoxide, compound *VII* is decyanoethylated under the formation of the monobenzyl derivative *VIII* which is not identical with the monobenzyl derivative *II*. On the basis of the reactions mentioned, compound *VIII* may be ascribed the structure of 3-benzyluracil. This proposal corresponds to the additional benzylation of compound *VIII* under the formation of 1,3-dibenzyluracil (*V*).





I, $R^1 = R^2 = H$
II, $R^1 = C_6H_5CH_2$, $R^2 = H$
III, $R^1 = C_6H_5CH_2$, $R^2 = CH_2CH_2CN$
IV, $R^1 = H$, $R^2 = CH_2CH_2CN$
V, $R^1 = R^2 = C_6H_5CH_2$
VI, $R^1 = CH_2CH_2CN$, $R^2 = H$

VII, $R^1 = CH_2CH_2CN$, $R^2 = C_6H_5CH_2$
VIII, $R^1 = H$, $R^2 = C_6H_5CH_2$
IX, $R^1 = R^2 = R^3 = H$
X, $R^1 = R^2 = R^3 = C_6H_5CH_2$
XI, $R^1 = R^2 = CH_2CH_2CN$, $R^3 = H$

Benzylation of 5-bromoorotic acid[4] (*IX*) with 1 mol of benzyl chloride in dilute aqueous sodium hydroxide does not lead to a pure monobenzyl derivative. Even with two mol of benzyl chloride, there is obtained a mixture of products. The pure benzyl 5-bromo-1,3-dibenzylorotate (*X*) is obtained with the use of excess benzyl chloride. In contrast to uracil[2] and 5-bromouracil[5], the attempted partial cyanoethylation of the acid *IX* in the presence of alkali failed. The carboxylate anion at position 6 contributes by its inductive effect to polarisation of the double bond at position 6—5 and to an increased interaction of the free electron pair on the nitrogen atom at position 1 with the carbonyl group at position 4; consequently, the nucleophilicity of the nitrogen atom at position 1 is decreased and the treatment of this position with acrylonitrile is not selective. The possibility of the proton removal from the nitrogen atom at position 3 and of the anion formation (necessary for a selective cyanoethylation into position 1) is simultaneously lowered. 5-Bromo-1,3-bis(2-cyanoethyl)orotic acid (*XI*) is obtained by refluxing a mixture of the acid *IX* and excess acrylonitrile in aqueous triethylamine for a longer period of time.

It has been known[4] that 5-bromoorotic acid (*IX*) does not react with 1M-NaOH even at the boiling point temperature. The attempted substitution of the bromo atom in the acid *XI* by the action of ethanolic sodium ethoxide (analogously to the treatment of 5-bromo-1,3-bis(2-cyanoethyl)-6-azauracil[5]) resulted in decyanoethylation under the formation of the acid *IX*. This finding might be explained by a decreased possibility of the nucleophilic substitution at position C-5 in view of the increased negative charge at this carbon atom ascribable to the inductive effect of the carboxylate anion of compound *XI*. The attempted ring contraction of the ester *X* on treatment with ethanolic sodium ethoxide (analogously to 5-bromo-1,3-dibenzyl-6-azauracil[5]) was also fruitless. This finding is in accordance with the earlier[5] assumption that the contraction of a six-membered ring can occur exclusively after the ring opening at position 4.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 60°C/10 Torr.

1-Benzyluracil (*II*)

A mixture of uracil (*I*; 11·2 g; 0·1 mol), water (250 ml), sodium hydroxide (10 g; 0·25 mol), and benzyl chloride (31·75 g; 0·25 mol) was heated under reflux on a steam bath for 4 hours. The reaction mixture was then cooled down to 20°C, the supernatant decanted, and the sticky residue recrystallised twice from ethanol (90 ml) to afford 15·1 g (75%) of compound *II*, m.p. 177—179°C. For $C_{11}H_{10}N_2O_2$ (202·2) calculated: 65·33% C, 4·98% H, 13·86% N; found: 65·08% C, 4·89% H, 13·71% N.

1,3-Dibenzyluracil (*V*)

A mixture of uracil (*I*; 11·2 g; 0·1 mol), water (250 ml), sodium hydroxide (20 g; 0·5 mol), and benzyl chloride (63·5 g, 0·5 mol) was heated under reflux condenser on a steam bath for 4 hours. The reaction mixture was then cooled down to 20°C, shaken with benzene (200 ml), the organic layer separated, washed with water, and evaporated under diminished pressure. The residue was dissolved in ether (150 ml) and the solution treated gradually under stirring at 0°C with light petroleum (180 ml). The precipitate was stirred for additional 3 hours and purified by reprecipitation to afford 21·3 g of compound *V*, m.p. 61—63°C. For $C_{18}H_{16}N_2O_2$ (292·3) calculated: 73·95% C, 5·52% H, 9·58% N; found: 73·71% C, 5·41% H, 9·42% N. Compound *V* (m.p. 62 to 63°C and 60—63°C, respectively) was obtained by an analogous procedure also from compounds *II* and *VIII* (yields, 77% and 79%, respectively). The melting points were without depression.

1-Benzyl-3-(2-cyanoethyl)uracil (*III*)

A. A mixture of 3-(2-cyanoethyl)uracil (*IV*; 1·65 g; 0·01 mol), water (25 ml), sodium hydroxide (0·6 g; 0·015 mol), and benzyl chloride (1·99 g; 0·015 mol) was refluxed under stirring for 4 hours, the supernatant decanted, and the sticky residue recrystallised twice from ethanol (10 ml) to afford 1·74 g (68·5%) of compound *III*, m.p. 98—100°C. For $C_{14}H_{13}N_3O_2$ (255·3) calculated: 65·87% C, 5·13% H, 16·46% N; found: 65·63% C, 5·08% H, 16·29% N.

B. A mixture of 1-benzyluracil (*II*; 2·02 g; 0·01 mol), water (10 ml), triethylamine (10 ml), and acrylonitrile (5 ml) was refluxed for 7 hours, evaporated to dryness under diminished pressure, and the residue recrystallised from ethanol (10 ml) to afford 1·78 g (69·7%) of compound *III*, m.p. 98—99°C, undepressed on admixture with the specimen obtained by procedure *A*.

3-Benzyl-1-(2-cyanoethyl)uracil (*VII*)

A mixture of 1-(2-cyanoethyl)uracil (*VI*; 3·3 g; 0·02 mol), water (80 ml), sodium hydroxide (2 g; 0·05 mol), and benzyl chloride (6·36 g; 0·05 mol) was refluxed under stirring for 4 hours and processed analogously to the preparation of compound *III*, procedure *A* to afford 3·4 g (67%) of compound *VII*, m.p. 93—95°C. For $C_{14}H_{13}N_3O_2$ (255·27) calculated: 65·87% C, 5·13% H, 16·46% N; found: 65·79% C, 5·12% H, 16·37% N.

3-Benzyluracil (*VIII*)

A mixture of 3-benzyl-1-(2-cyanoethyl)uracil (*VII*; 2·5 g; 0·01 mol) and ethanolic sodium ethoxide (prepared from 0·35 g *i.e.* 0·015 gramatom of sodium and 30 ml of ethanol) was refluxed

for 3 hours, cooled down to 20°C, adjusted with dilute (1 : 1) hydrochloric acid to pH 7, and evaporated to dryness under diminished pressure. The residue was coevaporated with ethanol (30 ml) and finally recrystallised from ethanol (10 ml) to afford 1·34 g (67%) of compound *VIII*, m.p. 180—182°C. For $C_{11}H_{10}N_2O_2$ (202·2) calculated: 65·33% C, 4·98% H, 13·86% N; found: 65·21% C, 4·78% H, 13·69% N.

Benzyl 5-Bromo-1,3-dibenzylorotate (*X*)

A mixture of 5-bromoorotic acid (*IX*; 7·05 g; 0·03 mol), water (200 ml), sodium hydroxide (4 g; 0·1 mol), and benzyl chloride (8·89 g; 0·07 mol) was heated with stirring under reflux on a steam bath for 5 hours. The mixture was cooled down to 20°C, brought to pH 7 by the addition of dilute (1 : 1) hydrochloric acid, and shaken with ether (150 ml). The ethereal layer was separated, washed with three 30 ml portions of water, dried over anhydrous sodium sulfate, and evaporated. The residue was recrystallised twice from 60% aqueous ethanol (150 ml) to afford 10·17 g (67%) of compound *X*, m.p. 98—100°C. For $C_{26}H_{21}BrN_2O_4$ (506·6) calculated: 61·89% C, 4·14% H, 15·79% Br, 5·50% N; found: 61·64% C, 4·25% H, 15·58% Br, 5·39% N.

5-Bromo-1,3-bis(2-cyanoethyl)orotic Acid (*XI*)

A mixture of the acid *IX* (4·7 g; 0·02 mol), water (20 ml), triethylamine (20 ml), and acrylonitrile (10 ml) was refluxed for 7 hours, evaporated to dryness under diminished pressure, the residue acidified to pH 2 with dilute (1 : 1) hydrochloric acid, and recrystallised twice from water (420 ml, 400 ml) to afford 5·18 g (76%) of compound *XI*, m.p. 167—168°C. For $C_{11}H_9BrN_4O_4$ (341·1) calculated: 38·72% C, 2·66% H, 23·43% Br, 16·42% N; found: 38·67% C, 2·60% H, 23·21% Br, 16·31% N.

Decyanoethylation. A mixture of the acid *XI* (3·41 g; 0·01 mol) and ethanolic sodium ethoxide (prepared from 1·38 g *i.e.* 0·06 gramatom of sodium and 50 ml of ethanol) was refluxed for 8 hours, brought to pH 7 by the addition of dilute (1 : 1) hydrochloric acid, and evaporated to dryness under diminished pressure. The residue was diluted with water (30 ml), acidified to pH 2 with dilute (1 : 1) hydrochloric acid, and filtered with active charcoal while hot. The precipitate was collected with suction and recrystallised from water (25 ml) to afford 1·84 g (78·5%) of the acid *IX*, m.p. 314—316°C, identical in every respect with the authentic specimen[4].

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