NUCLEIC ACID COMPONENTS AND THEIR ANALOGUES. CXXXVI.* A SIMPLE SYNTHESIS OF 6-AZACYTOSINE**

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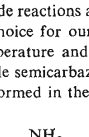
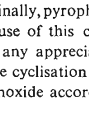
In one of the earlier papers of this Series, we have reported[1] the synthesis of 5-substituted derivatives of 6-azacytosine (5-amino-2,3-dihydro-1,2,4-triazin-3-one) (*I*). This synthesis starts from nitriles of α-keto acids which are converted to semicarbazones and the latter cyclised to 5-alkyl- and 5-aryl-6-azacytosines. This procedure could be suitable also for the preparation of 6-azacytosine itself since the known[2–4] syntheses of this compound are rather laborious. The required starting compound, nitrile of glyoxylic acid, is known, however, only in the form of some derivatives; the free nitrile is unstable under ordinary conditions and has not be hitherto prepared[5–7]. We have therefore used the following indirect route in the preparation of glyoxylic nitrile semicarbazone (*IV*) as the intermediate for the synthesis of 6-azacytosine (*I*).

Methyl glyoxylate semicarbazone (*II*) is readily accessible by reaction of chloral or chloral hydrate with semicarbazide hydrochloride in methanol[8]. Treatment of the semicarbazone *II* with ammonia afforded glyoxylic amide semicarbazone (*III*) the dehydration of which led to glyoxylic nitrile semicarbazone (*IV*). Under mild conditions (*e.g.*, with the use of thionyl chloride) the dehydration did not take place while under conditions requiring higher temperatures, there was danger of side reactions at the carbamoyl group. Finally, pyrophosphoryl chloride[9] proved to be the agent of choice for our dehydration. With the use of this chloride, the dehydration occurs at room temperature and is not accompanied by any appreciable side reactions. A good yield of the nitrile semicarbazone *IV* was obtained. The cyclisation of compound *IV* to 6-azacytosine (*I*) was performed in the presence of sodium methoxide according to the above mentioned procedure[1].



I



II, R = $COOCH_3$
III, R = $CONH_2$
IV, R = CN

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried for 8 hours at 0.1 Torr and room temperature unless stated otherwise.

Methyl Glyoxylate Semicarbazone (*II*)

Chloral hydrate (16·5 g; 0·1 mol) was added to a suspension of semicarbazide hydrochloride (11·1 g; 0·1 mol) in methanol (170 ml) and the mixture refluxed for 7 hours. Methanol (about 140 ml) was then distilled off and the residue cooled down to 5°C. The solid was collected with suction and washed with methanol till neutral. Yield, 11 g (85%) of compound *II*, m.p. 222–225°C

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(decomp.). After recrystallisation from water, the melting point was 226°C (decomp.); reported[10] for a specimen obtained by another route, m.p. 206°C (decomp.). For $C_4H_7N_3O_3$ (145·1) calculated: 33·11% C, 4·86% H, 33·08% N; found: 33·20% C, 5·01% H, 33·00% N.

Glyoxylic Amide Semicarbazone (*III*)

Methanolic ammonia (33 ml; 0·29 mol) was added to a suspension of the semicarbazone *II* (14·5 g; 0·1 mol) in methanol (150 ml) and the mixture was heated in a pressure tube for 7 hours at 100°C. The solvent was evaporated under diminished pressure and the residue was recrystallised from water to afford 8·7 g (59%) of compound *III* monohydrate, m.p. 222—224°C (decomp.); reported[11], m.p. 217—218°C (decomp.). For $C_3H_6N_4O_2.H_2O$ (148·1) calculated: 24·33% C, 5·44% H, 37·82% N; found: 24·62% C, 6·02% H, 38·06% N. Drying at 100°C/0·1 Torr for 8 hours afforded the anhydrous compound *III*. For $C_3H_6N_4O_2$ (130·1) calculated: 27·70% C, 4·65% H, 43·06% N; found: 28·02% C, 4·91% H, 42·93% N.

Glyoxylic Nitrile Semicarbazone (*IV*)

The anhydrous amide semicarbazone *III* (0·52 g; 4 mmol) was added portionwise under stirring to a solution of pyrophosphoryl chloride[12] (1·25 ml) in dioxane (7 ml). The mixture was stirred at room temperature for one hour and then treated with ice (7 g). The precipitate was collected with suction and washed with ethanol till neutral. Yield, 0·365 g (81·6%) of the product which undergoes cyclisation when heated and does not therefore melt up to 360°C. The analytical sample was recrystalised from water. For $C_3H_4N_4O$ (112·1) calculated: 32·15% C, 3·60% H, 49·98% N; found: 32·51% C, 4·00% H, 49·79% N.

6-Azacytosine (*I*)

Methanolic 1M sodium methoxide (2 ml) was added to a suspension of the nitrile semicarbazone *IV* (0·224 g; 2 mmol) in amyl alcohol (25 ml), the methanol was removed by distillation, the residual solution was refluxed for 1 hour, and evaporated to dryness under diminished pressure. The residue was dissolved in water and the solution passed through a column (15 ml) of Amberlite IRC 50 (H^+) ion exchange resin. The column was eluted with water (500 ml), the filtrates combined, and evaporated to dryness under diminished pressure. Crystallisation of the residue from water afforded 0·16 g (71·5%) of compound *I*, the R_F value and ultraviolet spectrum of which was identical with that of the authentic specimen[4].

Elemental analyses were performed in the Analytical Department (Dr J. Horáček, Head) of our Institute.

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Translated by J. Pliml.

ALKALOIDS OF THE *Papaveraceae*. XLVI.*

ALKALOIDS FROM *Glaucium fimbrilligerum* BOISS.

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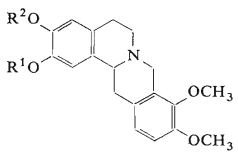
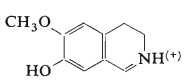
The species *Glaucium fimbrilligerum* BOISS. is an annual to biannual plant growing in Central Asia in the region of the Turkestan-highlands and Afghanistan. Alkaloids of this plant have been studied by Konovalova and coworkers[1] who isolated from its above-ground part corydine, allocryptopine and protopine, and from the root chelerythrine and sanguinarine.



Ia, $R^1 = H$, $R^2 = CH_3$
Ib, $R^1 = CH_3$, $R^2 = H$



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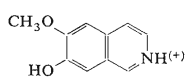

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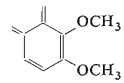

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* Part XLV: This Journal *36*, 2067 (1971).