A NOVEL SYNTHESIS OF 2,4-DIOXO-1,2,3,4-TETRAHYDRO-PYRROLO[2,3-d]PYRIMIDINE DERIVATIVES

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6-Hydrazinouracil derivatives were allowed to react with ketones or aldehydes to give 5,6-disubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-d]pyrimidine derivatives. The mechanism for the formation of these compounds is presented.

Up to now, some 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-d]pyrimidines or 7-deazaxanthines have been synthesized by J. $Davoll^{1}$, R. K. $Robins^{2}$, and E. C. Taylor³.

The authors studied a new method for the synthesis of 5,6-disubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-d]pyrimidine derivatives by heating 6-hydrazinouracil derivatives⁴) with ketones or aldehydes. Thus 6-hydrazino-1,3-dimethyluracil (Ia) was refluxed in a mixture of methyl ethyl ketone and xylene and the resulting hydrazone (IIa) was refluxed in ethyleneglycol or tetraline for 2 to 3 hours to give 1,3,5,6-tetramethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo-[2,3-d]pyrimidine (IIIa) with the evolution of ammonia (Method A). When Ia was refluxed in methyl ethyl ketone-ethyleneglycol or in methyl ethyl ketone-tetraline, IIIa could be directly obtained in a high yield without an isolation of the intermediate IIa (Method B). On heating Ia with a acidic catalyst such as ZnCl₂ or conc. H_2SO_4 , a pyrrole ring closure was unsuccessful.



In accordance with the above synthetic method, some hydrazone compounds (11b--d) and 5,6-disubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrlo[2,3-d]pyrimidines (111b--g) were also prepared.

$CH_{3} - N \rightarrow NHN = C - CH_{2}R^{1}$				$CH_{3} \xrightarrow{O}_{O} \xrightarrow{V}_{CH_{3}} \xrightarrow{N}_{R^{3}}^{R^{1}} \xrightarrow{R^{2}}$					
Compd. No.	R ¹	R ²	mp (°C)	Compd. No.	R ¹	R ²	R ³	mp (°C)	Method
IIa	CH ₃	CH ₃	132-134	IIIa	CH ₃	CH ₃	Н	>300	А,В
IIb	CHz	н	203	IIIb	CH _z	н	Н	>300	Α
IIc	C ₆ H ₅	Н	168	IIIc	C ₆ H ₅	Н	Н	287	Α
IId	н	CHz	147-148	IIId	н	CH ₃	Н	>300	Α
- <u></u>			······	IIIe	CHz	СН	CH ₃	233-234	↓ B
				IIIf	CH _z	C6H5	н	285	В
				IIIg	(CH ₂) ₄		Н	>300	В

The mechanism for the formation of the 7-deazaxanthine derivatives can be considered that a pyrrole ring closure proceeds as in the case of Fischer's indole synthesis.

$$II \longrightarrow \overset{CH_{3}-N}{\underset{CH_{3}}{\overset{V}R^{2}}} \xrightarrow{CH-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{2}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-N}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\underset{CH_{3}}{\overset{V}R^{3}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}} \xrightarrow{CH_{3}-R^{1}}{\xrightarrow{CH_{3}-R^{1}}}$$

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