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SYNTHESIS OF PYRIMIDINE PHOTOPRODUCTS : 6-[2'-OXO-1',2'-DIHYDROPYRIMIDIN-4'-YL]-PYRIMIDIN-2,4-DIONE (URA[6-4]PYO) AND ITS 5-METHYL-DERIVATIVE (THY[6-4]PYO)

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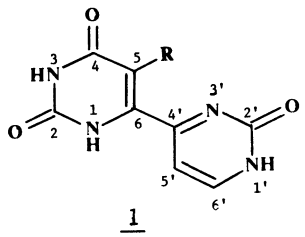
Products formed in traces by the u.v. irradiation of DNA, Thy[6-4]pyo (5-methyl-6-[2'-oxo-1',2'-dihydropyrimidin-4'-yl]-pyrimidin-2,4-dione) and Ura[6-4]pyo (6-[2'-oxo-1',2'-dihydropyrimidin-4'-yl]-pyrimidin-2,4-dione) were synthesized in excellent yield from readily available 6-acetyl-pyrimidine derivatives.

Ultraviolet irradiation of DNA produces unsymmetrical bipyrimidinyls bound at the 6- and 4'-positions, 5-methyl-6-[2'-oxo-1',2'-dihydropyrimidin-4'-yl]-pyrimidin-2,4-dione (Thy[6-4]pyo)[1] and 6-[2'-oxo-1',2'-dihydropyrimidin-4'-yl]-pyrimidin-2,4-dione (Ura[6-4]pyo)[2]. These bipyrimidinyls can be obtained by the u.v. irradiation of the appropriate nucleic acid bases, however the yields are quite low.[3] Apparently, this procedure does not supply sufficient quantities of the bipyrimidinyls for studying their possible biological importance and even chemical properties in detail, and development of synthetic methods have long been desired.[4] In this communication we wish to report the method for the synthesis of Thy[6-4]pyo and Ura[6-4]pyo.

Thy[6-4]pyo was synthesized as follows: Ethyl 3,4-dioxovalerate 4-diethylketal[5] was methylated at the 2-position with methyl iodide in methanolic sodium methoxide. Cyclization of the 2-methyl keto-ester with thiourea and the subsequent deketalization gave 6-acetyl-2-mercapto-5-methyl-pyrimidin-4-one (2a). This compound yielded the key intermediate 6-dimethylaminoethenylcarbonyl-5-methyl-2-methylthiopyrimidin-4-one (3ad) by the S-methylation followed by the reaction with dimethylformamide di t-butylacetal.[6] The vinylogous amide (3ad) was condensed with guanidine to afford 6-[2'-amino-pyrimidin-4'-yl]-5-methyl-2-methyl-thiopyrimidin-4-one (4ae). Cyclization of the compound (3ad) with other reagent, such as urea or thiourea, gave the corresponding



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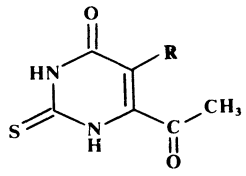

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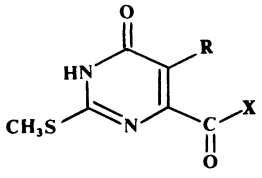

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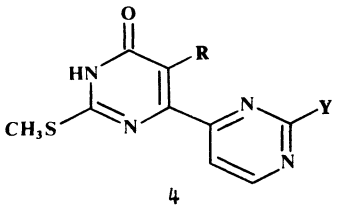

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a: R = CH_3 b: R = H

c: X = CH_3 d: X = CH=CH-NMe_2

e: Y = NH_2 f: Y = OH

bipyrimidinyl, but the yield was poorer. Nitrous acid converted the amino-bipyrimidinyl (4ae) to the 2'-oxo-derivative (4af). Hydrolysis of the methylthio-group of the dione (4af) with 6N-hydrochloric acid gave the required Thy[6-4]pyo (1a). The infrared and ultraviolet spectra of the thymine-derivative (1a) were identical with those reported in ref. 1)a). Table shows the reaction conditions of each step for the preparation of Thy[6-4]pyo.

Ura[6-4]pyo (1b) was also synthesized according to the method for Thy[6-4]pyo from 6-acetyl-2-mercaptopyrimidin-4-one (2b).[5] The reaction conditions are summerized in the Table. The synthesized Ura[6-4]pyo gave the identical infrared and ultraviolet spectra with those reported in ref. 3)b).

This simple method for the synthesis of Thy[6-4]pyo and Ura[6-4]pyo is apparently useful for the preparation of other bipyrimidinyls bound at the 6- and 4'-positions, and the application will be reported elsewhere.

TABLE

Starting Compound (mmol)	Reagent (mmol)	Solvent (ml)	Temp.	Product* (Yield %)	
2 (1)	MeI (2), K_2CO_3 (1.1)	MeOH (14)	r.t.	3ac (93)	3bc (87)
3c (1)	$HC(OBu\text{-}t)_2NMe_2$ (5)	Benzene (1.5)	60°	3ad (87)	3bd (86)
3d (0.5)	Guanidine (1)	EtOH (4)	reflux	4ae (96)	4be (92)
4e (0.5)	HNO_2 (2)	TFA and H_2O [1:1] (8)	r.t.	4af (quant.)	4bf (quant.)
4f (0.2)	6N-HCl	(4)	reflux	1a (quant.)	1b (89)

* Satisfactory spectral data (MS, NMR, IR, and UV) were obtained on the products.

Acknowledgment

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References and Notes

1) a) S.Y.Wang and A.J.Varghese, *Biochem.Biophysic.Res.Commun.*, 29, 543 (1967). b) A.J.Varghese and M.H.Patrick, *Nature*, 223, 299 (1969). c) M.H.Patrick, *Photochem.Photobiol.*, 11, 477 (1970). d) M.Ikenaga, M.H.Patrick, and J.Jagger, *Photochem.Photobiol.*, 11, 487 (1970). e) A.J.Varghese and R.S.Day III, *Photochem.Photobiol.*, 11, 511 (1970). f) M.Ikenaga and J.Jagger, *Photochem. Photobiol.*, 13, 459 (1971).

2) A.J.Varghese, *Biochemistry*, 10, 2194 (1971).

3) a) A.J.Varghese and S.Y.Wang, *Science*, 160, 186 (1968). b) M.N.Khattack and S.Y.Wang, *Science*, 163, 1341 (1969). c) D.F.Rhodes and S.Y.Wang, *Biochemistry*, 9, 4416 (1970). d) A.J.Varghese, *Biochemistry*, 10, 4283 (1971).

4) S.Y.Wang, "Photochemistry and Photobiology of Nucleic Acids" vol.1, Ed. by S.Y.Wang, Academic Press, pp. 326 (1976).

5) L.O.Ross, E.M.Acton, W.A.Skinner, L.Goodman, and B.R.Baker, *J.Org.Chem.*, 26, 3395 (1961).

6) The use of dimethylformamide dimethylacetal instead of the di t-butylacetal gave the corresponding 3-methyl-derivative.

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