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A PHOTO-REARRANGEMENT OF 5-DIAZOURACIL.A CONVENIENT SYNTHESIS OF 2-OXO-4-IMIDAZOLINE-4-CARBOXYLIC ACID DERIVATIVES.[1]

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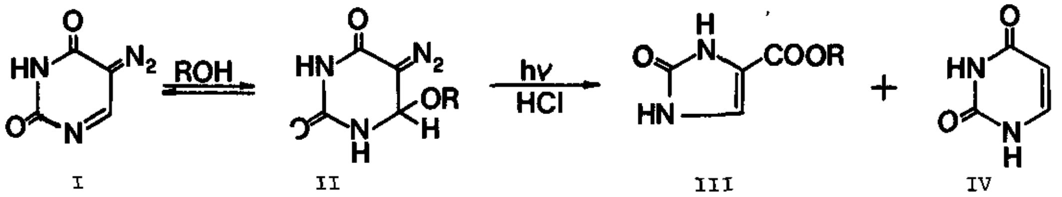
Abstract - A photochemical transformation of 5-diazouracil alcohol adducts into 2-oxo-4-imidazoline-4-carboxylates under strongly acidic conditions is described.

In the past, 2-oxo-4-imidazoline-4-carboxylic acid derivatives have been synthesized by the condensation of urea and urea derivatives with tartaric acid in fuming sulphuric acid[2] and by conversion of 5-fluorouracil derivatives in aqueous alkaline solutions[3].

On the other hand, 5-diazouracil has attracted a considerable interest because of its bactericidal[4-6] and cancerostatic activity[7,8]. Recently, the structures of 5-diazouracil, 5-diazouracil hydrate and 5-diazouracil methanol adduct and related derivatives have been reinvestigated[9-12] and some of them confirmed by X-ray analysis[13]. Conversions of 5-diazouracil into 1,2,3-triazole-4-carboxylic acid derivatives have been reported[12,14]. However, the transformation of 5-diazouracil into 2-oxo-4-imidazoline-4-carboxylic acid derivatives has not been reported so far, in spite of the fact that several other, less attractive, heterocyclic α-diazo ketones have been converted into the corresponding carboxylic acid derivatives since the Süss's first report[15,16], most probably because of the great stability of 5-diazouracil alcohol adducts under photochemical reaction conditions in neutral solutions.

In continuation of our studies on the transformation of heterocyclic α-diazo ketones[17,18] we wish to report a ring contraction of 5-diazouracil into 2-oxo-4-imidazoline-4-carboxylates under photochemical conditions in strongly acidic solutions, according to the Scheme.



R=H, alkyl

Scheme

When a suspension of 5-diazouracil (I) (200 mg) or 5-diazouracil hydrate (II, R=H) (200 mg) in an alcohol (20 ml) was irradiated at 254 nm in a Rayonet photochemical reactor RPR 100, the corresponding 5-diazouracil alcohol adducts (II, R=alkyl) were formed within one hour. This transformation is a thermal one, and can be followed by observing the shifting of the diazo peak in IR spectrum from ν_{N_2} = 2150 cm^{-1} for I or ν_{N_2} = 2120 cm^{-1} for II (R=H) to ν_{N_2} = 2100 cm^{-1} for II (R=alkyl). Since these adducts are insoluble in alcohol, they were isolated by filtration and characterized. The details are summarized in Table I.

Table I. 5-Diazouracil alcohol adducts (II, R=alkyl)

R	Yield[a] (%)	m.p.	Molecular formula[b]	I.R. ν_{N_2} /cm^{-1}/	^{1}H-NMR (d_6-DMSO) τ (ppm)			
					H_6	R	NH	J/Hz/
CH_3	86	195[c]	$C_5H_6N_4O_3$		4,20 (d)	6,75 (s)	1,20 (d) 0,3 (broad)	J_{H_6NH}=3,5
i-C_3H_7	85	169	$C_7H_{10}N_4O_3$	2100	4,15 (d)	6,1 /m,$C\underline{H}(CH_3)_2$/ 8,9 /d,$CH(C\underline{H}_3)_2$/	1,3 (d) 0,3 (broad)	J_{H_6NH}=3,5 J_{CHCH_3}=6,0
n-Bu	64	136	$C_8H_{12}N_4O_3$	2100	4,20 (d)	6,5 /t,$C\underline{H}_2(CH_2)_2CH_3$/ 8,6 /m,$CH_2(C\underline{H}_2)_2CH_3$/ 9,1 /t,$(CH_2)C\underline{H}_3$/	1,3 (d) 0,1 (broad)	J_{H_6NH}=3,5 $J_{CH_2CH_2}$=6,0 $J_{CH_2CH_3}$=6,0

a) yields of purified products are given

b) satisfactory analyses (C,H,N) were obtained for all compounds

c) Lit.[9] 198°;

By further irradiation of 5-diazouracil alcohol adducts (II,R=alkyl) elimination of nitrogen was taking place and 2-oxo-4-imidazoline-4-carboxylates (III,R=alkyl) were formed. This transformation was slow in neutral solutions. After 20 hours of irradiation only about 10-15% of the starting material was converted, yielding a mixture of the corresponding ester III and uracil (IV). On the other hand, the conversion proceeds smoothly to completion in 4-5 hours in a solution saturated with dry hydrogen chloride. The reactions were followed and the products separated by T.L.C. (Merck DC-Fertigplatten Kieselgel 60 F254 and a mixture of chloroform and methanol 6:1 as solvent was used). Besides the rearranged products (III, R=alkyl), 1-3 % of uracil (IV) as the protodediazonization product was also isolated.[19] An analogous irradiation of 5-diazouracil hydrate (II, R=H) in concentrated aqueous hydrochloric acid afforded 2-oxo-4-imidazoline-4-carboxylic acid (III,R=H). The experimental details are summarized in Table II.

Table II. 2-Oxo-4-imidazoline-4-carboxylic acid derivatives(III)

R	Yield[a] /%/	m.p.	Molecular formula[b] m/e M$^+$	I.R. $\nu_{C=O}$ /cm^{-1}/	^{1}H-NMR (d_6-DMSO) τ(ppm)			
					H_5	R	NH	J/Hz/
H	65	270[c]	$C_4H_4N_2O_3$ 128					
CH_3	53	280	$C_5H_6N_2O_3$ 142	1740 1670	(d)			
CH_2CH_3	48	258[e]	$C_6H_8N_2O_3$ 156	1750 1670	2,95(d)	$6,20(q,C\underline{H}_2CH_3)$ $8,75(t,CH_2C\underline{H}_3)$	-0,5 -1,2	$J_{H_5NH}=5,0$ $J_{CH_2CH_3}=6,0$
n-C_3H_7	40	256	$C_7H_{10}N_2O_3$ 170	1750 1670	2,9(d)	$6,20(t,C\underline{H}_2CH_2CH_3)$ $8,35(m,CH_2C\underline{H}_2CH_3)$ $9.05(t,CH_2CH_2C\underline{H}_3)$	-1,5 -2,3	$J_{H_5NH}=5,0$ $J_{CH_2CH_2}=6,0$ $J_{CH_2CH_3}=6,0$
i-C_3H_7	45	248	$C_7H_{10}N_2O_3$ 170	1740 1670	2,85(s)	$5,7/m,C\underline{H}(CH_3)_2/$ $8,85/d,CH(C\underline{H}_3)_2/$	-0,45 -1,1	$J_{CHCH_3}=6,0$
n-C_4H_9	35	236	$C_8H_{12}N_2O_3$ 184	1740	2,95(s)	$6,20/t,C\underline{H}_2(CH_2)_2CH_3/$ $8,50/m,CH_2(C\underline{H}_2)_2CH_3/$ $9,07/t,(CH_2)_3C\underline{H}_3/$	-0,4 -1,0	$J_{H_5NH}=5,0$ $J_{CH_2CH_2}=6,0$ $J_{CH_2CH_3}=6,0$

a) Yields of purified products are given

b) satisfactory analyses (C,H,N) were obtained for all compounds

c) Lit.[2] 261; d) NMR spectrum is identical with that reported in the Lit.[3]

e) Lit.[2] 255°;

The transformation is supposed to be a photo Wolff rearrangement[20] and represents a convenient one step synthesis of 2-oxo-4-imidazoline-4-carboxylates.

REFERENCES AND NOTES

1 Presented in part at the VIth Symposium on Chemistry of Heterocyclic Compounds, Brno, Czechoslovakia, July, 4-7, 1978.

2 G.E.Hilbert, J.Amer.Chem.Soc., 1932, 54, 3413

3 B.A.Otter, E.A.Falco, and J.J.Fox, J.Org.Chem., 1968, 33, 3593.

4 T.H.Weisman and L.E.Loveless, Proc.Soc.Exp.Biol.Med., 1954, 86, 268.

5 E.Previc and S.Richardson, J.Bacteriol., 1969, 97, 416.

6 E.E.Hunt and R.F.Pitillo, Appl.Microbiol., 1968, 16, 1792.

7 J.R.Bateman, E.M.Jacobs, A.A.Marsh, and J.L.Steinfield, Cancer Chemother., Rep., 1964, No.14, 27.

8 A.Goldin, H.B.Wood, and R.R.Engle, Cancer Chemother.Rep., Suppl. 1, 1969, (Part 2), 1.

9 T.C.Thurber and L.B.Townsend, J.Heterocyclic Chem., 1972, 9, 629.

10 T.C.Thurber and L.B.Townsend, J.Heterocyclic Chem., 1975, 12, 711.

11 T.C.Thurber and L.B.Townsend, J.Amer.Chem.Soc., 1973, 95, 3081.

12 T.C.Thurber and L.B.Townsend, J.Org.Chem., 1976, 41, 1041, and references cited therein.

13 D.J.Abraham, T.C.Cochran, and R.D.Rosenstein, J.Amer.Chem.Soc., 1971, 93,6279.

14 S.Romani and W.Klötzer, J.Heterocyclic Chem., 1978, 15, 1349.

15 O.Süs, Ann., 1953, 579, 135.

16 For a review see: M.Tišler and B.Stanovnik, Heterocycles, 1976, 4, 1115.

17 B.Stanovnik, M.Tišler, and J.T.Carlock, Synthesis, 1976, 754.

18 J.T.Carlock, J.S.Bradshaw, B.Stanovnik, and M.Tišler, J.Org.Chem., 1977, 42 1883.

19 When an aqueous solution of hydrochloric acid was used instead of dry hydrogen chloride in these experiments,a mixture of the corresponding ester (III,R=alkyl),acid (III,R=H) and traces of uracil (IV) was isolated. The ratio between the ester (III,R=alkyl) and the acid (III,R=H) was dependent on the amount of water present in the irradiated solution.

20 For reviews of the Wolff rearrangement see: W.Kirmse, "Carbene, Carbenoide und Carbenanaloge", Verlag Chemie, Weinheim 1969, p. 166; M.Jones and R.A.Moss, "Carbenes", J.Wiley, New York, N.Y. 1973, p. 173.

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