A New Synthesis of Alloxazines by the Reaction of Diethyl Azodiformate with 6-Anilinouracils

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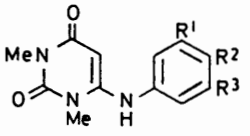
Treatment of 6-anilinouracils with diethyl azodiformate led the corresponding alloxazines (benzo[*g*]pteridine-2,4-diones). This synthesis involves initial formation of Michael-type adducts [6-anilino-5-(1,2-bisethoxycarbonylhydrazino)uracils] followed by dehydrogenative cyclization with further diethyl azodiformate.

PREVIOUS syntheses of alloxazines or isoalloxazines and/or their 5-oxides from 6-anilinopyrimidines have involved (*a*) nitrosative cyclization with various nitrosating agents,[1-3] (*b*) nitrative cyclization with potassium nitrate in acetic acid in the presence of sulphuric acid,[4] (*c*) acid-catalysed thermal cyclization of 6-anilino-5-phenylazopyrimidines,[5] (*d*) reductive cyclization of 6-anilino-5-nitrouracils with triethyl phosphite,[6] and (*e*) oxidative cyclization of 5-amino-6-anilinouracil with lead tetra-acetate.[6] We now report a convenient synthesis in which diethyl azodiformate (DAD) acts as a dehydrogenating agent as well as a nitrogen source for the direct cyclization of 6-anilinopyrimidines.[7]

Fusion of 6-anilino-1,3-dimethyluracil (1a) with 2—3 mol. equiv. of DAD at 180° for 1 h, followed by dilution

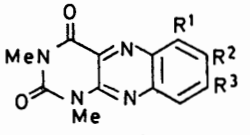
[1] H. Goldner, G. Dietz, and E. Carstens, *Annalen*, 1966, **694**, 142.
[2] F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, *Chem. and Pharm. Bull.* (*Japan*), 1972, **20**, 1832.
[3] F. Yoneda, K. Senga, and S. Nishigaki, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 260.
[4] F. Yoneda and Y. Sakuma, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 448.
[5] F. Yoneda, M. Ichiba, K. Ogiwara, and S. Nishigaki, *Chem. Comm.*, 1971, 23.
[6] E. C. Taylor, F. Sowinski, T. Yee, and F. Yoneda, *J. Amer. Chem. Soc.*, 1967, **89**, 3369.
[7] Preliminary report, F. Yoneda and S. Fukazawa, *J.C.S. Chem. Comm.*, 1972, 503.

with ether, gave 1,3-dimethylalloxazine (2a) [8] in almost quantitative yield. This reaction is equally applicable to other 6-anilinouracil derivatives [(1b—j) and (3a—d)],

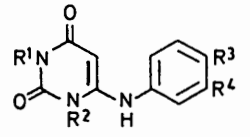


(1)

a; $R^1=R^2=R^3=H$
b; $R^1=R^3=H$, $R^2=Cl$
c; $R^1=R^2=H$, $R^3=Cl$
d; $R^2=H$, $R^1=R^3=Cl$
e; $R^1=H$, $R^2=R^3=Cl$
f; $R^1=R^3=H$, $R^2=Me$
g; $R^1=R^2=H$, $R^3=Me$
h; $R^1=H$, $R^2=R^3=Me$
i; $R^1=R^3=H$, $R^2=OMe$
j; $R^1=R^2=H$, $R^3=OMe$

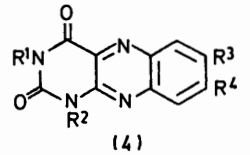


(2)

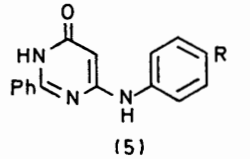


(3)

a; $R^1=R^3=R^4=H$, $R^2=Me$
b; $R^1=R^4=H$, $R^2=Me$, $R^3=Cl$
c; $R^1=Me$, $R^2=R^4=H$, $R^3=Cl$
d; $R^1=R^4=Me$, $R^2=R^3=H$

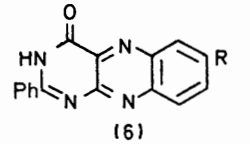


(4)

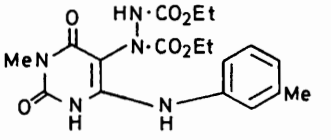


(5)

a; R=H
b; R=Cl
c; R=Br



(6)



(7)

giving excellent yields of the alloxazines (2b—j) and (4a—d). The structures of the alloxazines were determined by comparison with authentic samples prepared by alternative routes.[1,4-6] Cyclization of 6-(3-substituted anilino)uracils by this method gave exclusively the corresponding 8-substituted alloxazines, whereas the nitrosative cyclization with sodium nitrite in acetic acid gave in general mixtures of 8- and 6-substituted alloxazines (or their 5-oxides). For example, cyclization of 1,3-dimethyl-6-(*m*-toluidino)uracil (1g) with DAD gave 1,3,8-trimethylalloxazine [6] (2g) exclusively, whereas the nitrosative cyclization gave a mixture of 1,3,8-trimethylalloxazine 5-oxide and 1,3,6-trimethylalloxazine 5-oxide (82 : 18 by g.l.c.).[9] Similarly, treatment of 1,3-dimethyl-6-(3,4-xylidino)uracil (1h) with DAD gave 1,3,7,8-tetramethylalloxazine (1,3-dimethyllumichrome) [10] (2h) as the sole product, whereas the products from nitrosation were 1,3,7,8-tetramethylalloxazine 5-oxide and 1,3,6,7-tetramethylalloxazine 5-oxide (97 : 3 by g.l.c.).[9] This behaviour can be ascribed to steric hindrance by the bulky 1,2-bisethoxycarbonylhydrazino-group at C-5 of the intermediate Michael-type adduct (see later).

Although it was generally difficult to obtain the intermediate 6-anilino-5-(1,2-bisethoxycarbonylhydrazino)uracil in a high state of purity because of fast conversion into the final alloxazine, the adduct (7) was isolated in good yield from the reaction of 3-methyl-6-(3-toluidino)uracil (3d) with DAD. Attempts to cyclize (7) to 3,8-dimethylalloxazine (4d) by pyrolysis or by refluxing in solution were unsuccessful. However, treatment of (7) with further DAD at 220 °C followed by dilution with ethanol caused the separation of (4d), although in a low yield. The mother liquor contained diethyl hydrazodiformate.

This new synthesis is equally applicable to other 6-anilinopyrimidines. For example, fusion of 6-anilino-4-hydroxy-2-phenylpyrimidine (5a) and its analogues [5] (5b and c) with DAD gave the corresponding 2-phenylbenzo[*g*]pteridin-4(3*H*)-ones [5] (6a—c) in good yield.

EXPERIMENTAL

Freshly prepared diethyl azodiformate (DAD) [11] was used for all experiments.

6-Anilinouracils [(1a—j) and (3a—d)] were prepared either by exchange amination of a 6-aminouracil with the appropriate aniline hydrochloride (method **A**)[1] or by condensation of a 6-chlorouracil with an aniline (method B)[1] (Table 1). 6-Anilino-4-hydroxy-2-phenylpyrimidines [5] (5a—c) were prepared in 90—96% yield by exchange amination of 6-amino-4-hydroxy-2-phenylpyrimidine with the aniline hydrochloride.

Alloxazine Derivatives [(2a—j) *and* (4a—d)].—A mixture of a 6-anilinouracil (0.01 mol) and DAD (0.02—0.03 mol) was heated at 180 °C for 1 h, cooled, and crushed in ethanol or ether. The *product* was filtered off, washed with water, and recrystallized from acetone or dimethylformamide to give pale yellow needles (Table 2).

2-Phenylbenzo[g]*pteridin-4*(3H)*-one* (6a).—A mixture of 6-anilino-4-hydroxy-5-phenylpyrimidine (5a) (0.5 g, 0.02 mol) and DAD (1 g, 0.006 mol) was heated at 190 °C for 30 min, cooled, and treated with ether. The crystals which separated were filtered off and recrystallized from dimethylformamide to give (6a) as yellow plates (82%), identical with an authentic sample,[5] $\nu_{max.}$ (Nujol) 1 680 (CO), 1 595, 1 561, and 1 515 cm^{-1}, M^+ 274.

[8] H. Bredereck and W. Pfleiderer, *Chem. Ber.*, 1954, **87**, 1119.
[9] F. Yoneda and M. Ichiba, unpublished results.
[10] R. Kuhn and H. Rudy, *Ber.*, 1934, **67**, 1826; P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, 1960, **43**, 372.
[11] J. C. Kauer, *Org. Synth.*, Coll. Vol. IV, 1963, p. 411.

Similarly,6-(4-chloroanilino)-(5b) and 6-(4-bromoanilino)-4-hydroxy-2-phenylpyrimidine (5c) yielded the 7-chloro-(6b) and 7-bromo-(6c) benzopteridinones, respectively, in yields of 83 and 70%.

5-(1,2-*Bisethoxycarbonylhydrazino*)-3-*methyl*-6-(3-*toluidino*)*uracil* (7).—*Method A*. A mixture of 3-methyl-6-(3-toluidino)uracil (3d) (1 g, 0.004 mol) and DAD (1.2 g, 0.007 mol) was heated at 130—135 °C for 10 min, cooled, and crushed in ether. The product (7) was filtered off and washed with ethanol to give *needles* (1.4 g, 88%), m.p. 248°, $\nu_{max.}$ (Nujol) 3200 (NH), 1 739, 1 700, 1 620, 1 590, 1 520, and 1 260 cm^{-1}, M^+ 405 (Found: C, 53.2; H, 5.7; N, 17.05. $C_{18}H_{23}N_5O_6$ requires C, 53.35; H, 5.7; N, 17.3%).

Method B. A mixture of (3d) (1 g, 0.004 mol) and DAD (1.2 g, 0.007 mol) in chlorobenzene (15 ml) was refluxed for 2 h. After cooling, the crystals which separated were filtered off. Dilution of the filtrate with ether gave more crystals. Recrystallization from ethanol gave the adduct (7) (1.4 g, 88%), identical with the product prepared by method A.

TABLE 1

6-Anilinopyrimidines

Compd.	M.p. (°C)	Yield (%)	Method	Found (%) C	H	N	Formula	Required (%) C	H	N
(1a) [1]	187	75	A	62.35	5.8	18.45	$C_{12}H_{13}N_3O_2$	62.3	5.65	18.15
(1b) [1]	209	71	A	54.15	4.35	16.0	$C_{12}H_{12}ClN_3O_2$	54.25	4.55	15.8
(1c)	240	58	A	54.3	4.4	15.7	$C_{12}H_{12}ClN_3O_2$	54.25	4.55	15.8
(1d)	241	49	A	47.8	3.65	14.05	$C_{12}H_{11}Cl_2N_3O_2$	48.0	3.7	14.0
(1e)	229	52	A	48.2	3.55	13.8	$C_{12}H_{11}Cl_2N_3O_2$	48.0	3.7	14.0
(1f) [1]	240	67	A	63.6	6.4	17.4	$C_{13}H_{15}N_3O_2$	63.65	6.15	17.15
(1g) [1]	255	64	A	63.5	6.3	17.1	$C_{13}H_{15}N_3O_2$	63.65	6.15	17.15
(1h)	235	61	B	64.65	6.35	16.35	$C_{14}H_{17}N_3O_2$	64.85	6.6	16.2
(1i)	243	63	B	59.7	5.55	16.0	$C_{13}H_{15}N_3O_3$	59.75	5.8	16.1
(1j)	241	75	A	59.3	5.45	16.05	$C_{13}H_{15}N_3O_3$	59.75	5.8	16.1
(3a) [1]	308	72	A	60.9	5.3	19.45	$C_{11}H_{11}N_3O_2$	60.8	5.1	19.35
(3b)	305	60	A	52.55	4.2	16.6	$C_{11}H_{10}ClN_3O_2$	52.5	4.0	16.7
(3c)	297	58	B	52.25	4.0	16.9	$C_{11}H_{10}ClN_3O_2$	52.5	4.0	16.7
(3d)	291	60	B	62.25	5.65	18.05	$C_{12}H_{13}N_3O_2$	62.3	5.65	18.15

TABLE 2

Alloxazine derivatives

Compd.	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
(2a) [6]	247	96	59.55	4.15	23.25	$C_{12}H_{10}N_4O_2$	59.5	4.15	23.15
(2b) [1]	265	96	52.25	3.3	20.15	$C_{12}H_9ClN_4O_2$	52.1	3.3	20.25
(2c) [6]	251	95	52.2	3.3	20.05	$C_{12}H_9ClN_4O_2$	52.1	3.3	20.25
(2d)	300	87	46.3	2.65	18.0	$C_{12}H_8Cl_2N_4O_2$	46.3	2.6	18.0
(2e)	256	90	46.35	2.5	17.85	$C_{12}H_8Cl_2N_4O_2$	46.3	2.6	18.0
(2f) [1]	257	96	61.05	4.8	21.75	$C_{13}H_{12}N_4O_2$	60.95	4.7	21.85
(2g)	248	98	60.8	4.8	21.65	$C_{13}H_{12}N_4O_2$	60.95	4.7	21.85
(2h) [6]	260	99	62.25	5.2	20.55	$C_{14}H_{14}N_4O_2$	62.2	5.2	20.75
(2i)	255	93	57.5	4.4	20.65	$C_{13}H_{12}N_4O_3$	57.35	4.45	20.6
(2j)	264	98	57.25	4.5	20.8	$C_{13}H_{12}N_4O_3$	57.35	4.45	20.6
(4a) [a]	>320	85	57.7	3.55	24.3	$C_{11}H_8N_4O_2$	57.9	3.55	24.55
(4b) [1]	316	90	50.4	2.65	21.25	$C_{11}H_7ClN_4O_2$	50.3	2.7	21.35
(4c)	288	86	50.45	2.8	21.5	$C_{11}H_7ClN_4O_2$	50.3	2.7	21.35
(4d)	271	80	59.5	4.05	22.95	$C_{12}H_{10}N_4O_2$	59.5	4.15	23.15

[a] W. Pfleiderer, *Chem. Ber.*, 1956, **89**, 1148.

3,8-*Dimethylalloxazine* (4d).—A mixture of the adduct (7) (1 g, 0.0025 mol) and DAD (0.9 g, 0.005 mol) was heated at 220 °C for 5 min, then ether was adddd and the crystals were filtered off and recrystallized from ethanol to give (4d) as pale yellow needles (0.2 g, 33%).

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