HETEROCYCLES, Vol 15, No 2, 1981

A NEW SYNTHESIS OF PYRIMIDO[4,5-b]QUINOLINE-2,4-(1H,3H)-DIONES BY REACTION OF 6-ARYLAMINO-1,3-DIMETHYLURACILS WITH CARBON DISULFIDE

Yoshinori Tominaga, Hiroto Okuda, Mutushi Tochiki, Yoshiro Matsuda,
and Goro Kobayashi*
Faculty of Pharmaceutical Science, Nagasaki University,
Bunkyo-machi 1-14, Nagasaki 852, Japan

Abstract Reaction of 6-arylaminouracils (I) with carbon disulfide in the presence of sodium hydroxide and subsequent methylation with dimethyl sulfate gave the corresponding 1,3-dimethyl-5-methylthio-pyrimido[4,5-b]quinoline-2,4(1H,3H)-diones (II). Raney-nickel desulfurization of II afforded the corresponding 1,3-dimethylpyrimido[4,5-b]-quinoline-2,4-(1H,3H)-diones (1,3-dimethyl-5-deazaalloxazines) (VII) in good yields.

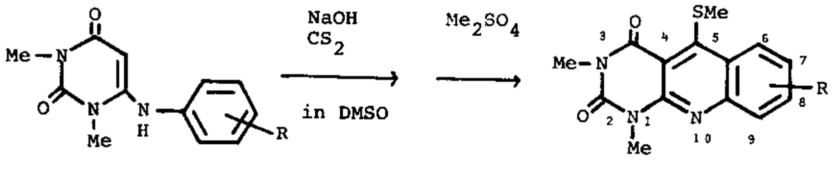
Carbon disulfide has been shown to be a useful reagent for the synthesis of various heterocyclic compounds$^{1)}$. It was previously reported that the condensation of 6-aminouracils with carbon disulfide afforded the corresponding enamino carbodithioates, methyl 9-amino-5-carbodithioates, in good yields$^{2)}$. We have investigated the application of the above reaction to the synthesis of 5-deazaalloxazines$^{3)}$. The present paper describes a new synthesis of 1,3-dimetnylthiopyrimido[4,5-b]quinoline-2,4-(1H,3H)-diones by the reaction of 6-arylamino-1,5-dimethyluracils with carbon disulfide and dimethyl sulfate.

The reaction of 6-arylamino-1,3-dimethyluracils (Ia-e) with excess carbon disulfide in the presence of sodium hydroxide and subsequent methylation with dimethyl sulfate gave the corresponding 1,3-dimethyl-5-methylthiopyrimido[4,5-b]-quinoline-2,4(1H,3H)-diones (IIa-e) in the yields indicated in Chart.

When the reaction mixture of Ia with carbon disulfide in the presence of sodium hydroxide was treated with 10% hydrochloric acid instead of dimethyl sulfate, two products ; 5,7-dimethyl-4,6-dioxo-3H,4H,6H-1,2-dithiolo[3,4-d]pyrimidine-3-thione (III) (trithione derivative), orange needles, mp 233°, and 5-mercapto-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (IV), yellow needles, mp 228°, was obtained in 33 and 21% yields, respectively. [III: IRν_{max}^{KBr}cm^{-1}: 1710, 1665(C=O); UVλ_{max}^{EtOH}nm(logε): 235(4.10), 291(4.32), 395(3.75); NMR(CF_3COOH)δ: 3.52(3H, s, N-CH_3), 3.85(3H, s, N-CH_3); Mass m/e: 246(M^+). IV: IRν_{max}^{KBr}cm^{-1}: 1695, 1620(C=O); UVλ_{max}^{EtOH}nm (logε): 239(4.51), 251(4.54), 265(4.56), 325(3.95), 394(3.84); Mass m/e: 273(M^+)]. The mechanism of the formation of IIIis thought as shown in Chart.

In the case of Ia with carbon disulfide and dimethyl sulfate, followed by treatment with sodium hydroxide, two unexpected products from those of the above reaction were obtained. These were methyl N-phenyl-N-(1,3-dimethyl-6-uracilyl)dithiocarbamate (Va), mp 193° (33%), and methyl 6-anilino-1,3-dimethyluracil-5-dithiocarboxylate (enamino carbodithioate) (VI), mp 143° (6%). The structures of Va and VI were assigned on the basis of the IR and NMR spectra and by the transformation of VI, [Va: IRν_{max}^{KBr}cm^{-1}: 1700, 1660(C=O); NMR($CDCl_3$)δ: 2.58(3H, s, S-CH_3), 3.32(3H, s, N-CH_3), 3.46(3H, s, N-CH_3), 5.78(1H, s, 5-H), 7.30-7.52(5H, m, Ph-H); VI: IRν_{max}^{EtOH} cm^{-1}: 1708, 1635(C=O); NMR($CDCl_3$)δ: 2.58(3H, s, S-CH_3), 3.10(3H, s, N-CH_3), 3.42(3H, s, N-CH_3), 7.48-7.68(5H, m, Ph-H), 14.08(1H, bs, N-H)]. Heating of VI in diphenyl ether at 250° for 20 min gave a cyclized product, IV, in 97% yield. This cyclization is a new reaction and will become of a convenient method for the preparation of quinoline derivatives. Methylation of IV with dimethyl sulfate in the presence of sodium hydroxide in dimethyl sulfoxide under a usual manner gave IIa in a good yield. On the other hand, the reaction of Ib with carbon disulfide and dimethyl sulfate in the presence of sodium hydroxide under a similar condition did not give the enamino carbodithioate type compound (VI), but afforded two products, N-carbamate (IV), colorless needles, mp 172°, and IIb in 42 and 9% yields, respectively.

Raney-nickel desulfurization of IIa-d afforded 1,3-dimethylpyrimido[4,5-b]-quinoline-2,4(1H,3H)-diones (VIIa-d) in good yields. Compound VIIa was identical with an authentic sample prepared by Yoneda's method$^{4)}$. Treatment of IIa and IIe with hydrogen peroxide in acetic acid at room temperature for 5 hr gave 5-hydroxy (or 5-oxo) derivatives (VIIIa and VIIIb) in 63 and 40% yields, respectively.

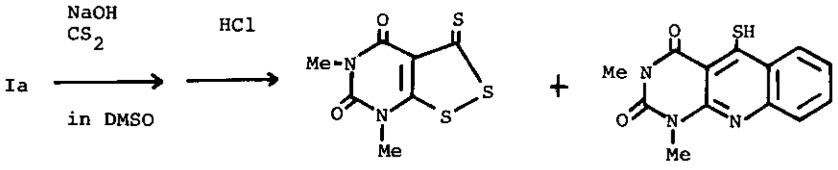


Ia-e

IIa-e

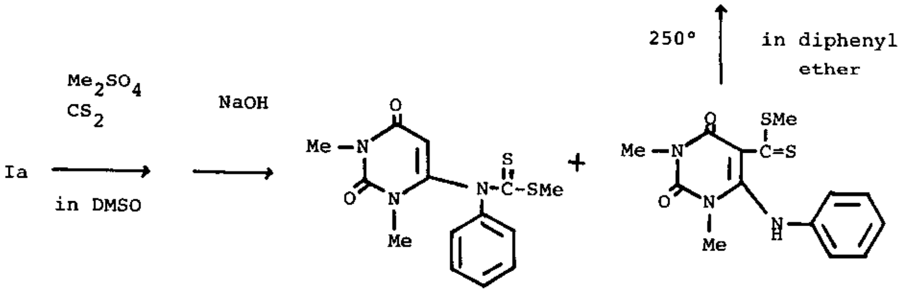
a: R=H
b: R=4-Me
c: R=4-OMe
d: R=3-OMe
e: R=2-OMe

	mp(°C)	Yield
a: R=H	166	18%
b: R=7-Me	231	25%
c: R=7-OMe	212	31%
d: R=8-OMe	218	23%
e: R=9-OMe	194	26%



III

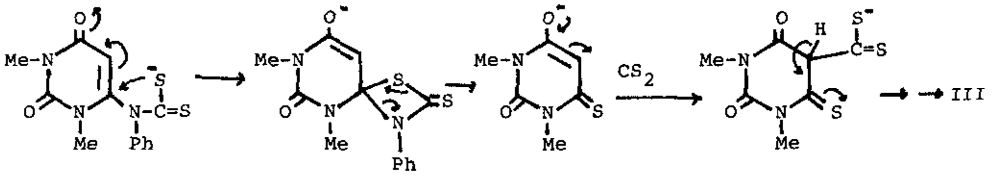
IV

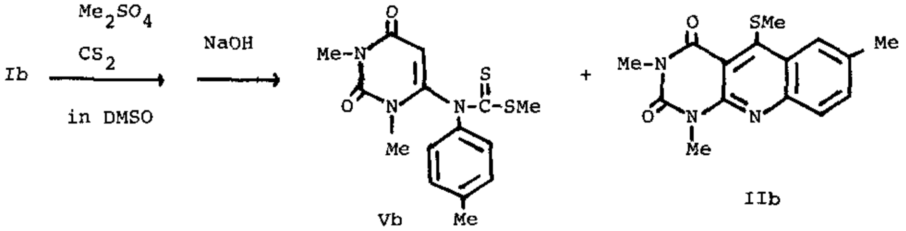


Va

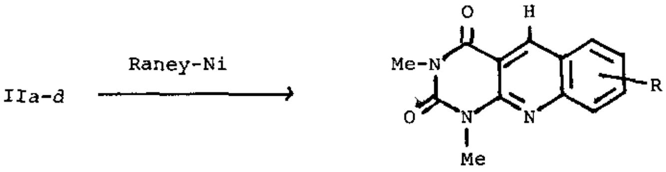
VI

$$\mathrm{IV} \xrightarrow[\text{in DMSO}]{\text{NaOH, Me}_2\text{SO}_4} \mathrm{IIa}$$



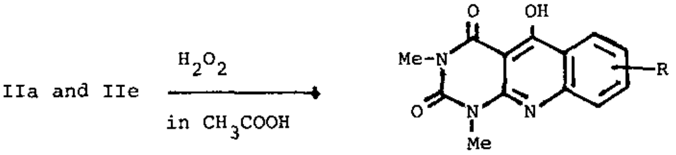


Vb IIb



VIIa-d

	mp(°C)	Yield
a: R=H	211	72% 3,4)
b: R=7-Me	228	78%
c: R=7-OMe	274	65% 3)
d: R=8-OMe	254	70% 4)



VIIIa and VIIIb

a: R=H, mp 205°, yield 63%

b: R=9-OMe, mp 168°, yield 40%

Physical Properties of Pyrimido[4,5-b]quinoline-2,4(1H,3H)-diones

IIa) IRν^{KBr}_{max}cm^{-1}: 1705, 1665(C=O). UVλ^{EtOH}_{max}nm(log ε): 220(4.33), 246(4.54), 268 (4.54), 322(3.85), 386(3.77). NMR(CDCl$_3$)δ: 2.60(3H, s, S-CH$_3$), 3.50(3H, s, N-CH$_3$), 3.78(3H, s, N-CH$_3$), 7.51(1H, dt, J=2, 8Hz, 7-H), 7.74(1H, dd, J=2, 8Hz, 9-H), 7.92(1H, dt, J=2, 8Hz, 8-H), 8.62(1H, dd, J=2, 8Hz, 6-H).

IIb) IRν^{KBr}_{max}cm^{-1}: 1705, 1660(C=O). UVλ^{EtOH}_{max}nm(log ε): 226(4.30), 254(4.55), 270 (4.58), 324(3.80), 396(3.77). NMR(CDCl$_3$)δ: 2.52(3H, s, 7-CH$_3$), 2.57(3H, s, S-CH$_3$), 3.49(3H, s, N-CH$_3$), 3.74(3H, s, N-CH$_3$), 7.58(1H, dd, J=2, 8Hz, 8-H), 7.81(1H,dt, J=2, 8Hz, 9-H), 8.39(1H, d, J=2Hz, 6-H).

IIc) IRν^{KBr}_{max}cm^{-1}: 1705, 1660(C=O). UVλ^{EtOH}_{max}nm(log ε): 224(4.32), 268(4.67), 317 (3.71), 406(3.74). NMR(CDCl$_3$)δ: 2.58(3H, s, S-CH$_3$), 3.48(3H, s, N-CH$_3$), 3.76 (3H, s, N-CH$_3$), 3.96(3H, s, O-CH$_3$), 7.53(1H, dd, J=3, 10Hz, 8-H), 7.96(1H, d, J=10Hz, 9-H), 8.02(1H, d, J=3Hz, 6-H).

IId) IRν^{KBr}_{max}cm^{-1}: 1700, 1655(C=O). UVλ^{EtOH}_{max}nm(log ε): 230(4.44), 272(4.65), 348 (4.22). NMR(CDCl$_3$)δ: 2.59(3H, s, S-CH$_3$), 3.50(3H, s, N-CH$_3$), 3.78(3H, s, N-CH$_3$), 3.99(3H, s, O-CH$_3$), 7.18(1H, dd, J=2, 9Hz, 7-H), 7.26(1H, d, J=2Hz, 9-H), 8.61(1H, d, J=9Hz, 6-H).

IIe) IRν^{KBr}_{max}cm^{-1}: 1705, 1660(C=O). UVλ^{EtOH}_{max}nm(log ε): 230(4.34), 248(4.39), 283 (4.64), 324(3.74), 400(3.65). NMR(CDCl$_3$)δ 2.61(3H, s, S-CH$_3$), 3.53(3H, s, N-CH$_3$), 3.85(3H, s, N-CH$_3$), 4.07(3H, s, O-CH$_3$), 7.19(1H, dd, J=1, 8Hz, 5-H), 7.52(1H, dd, J=8, 8Hz, 7-H), 8.23(1H, dd, J=1, 8Hz, 6-H).

VIIb) IRν^{KBr}_{max}cm^{-1}: 1700, 1655(C=O). UVλ^{EtOH}_{max}nm(log ε): 225(4.32), 246(4.56), 256 (4.66), 312(3.77), 370(3.57). NMR(CDCl$_3$)δ: 2.51(3H, s, 7-Me), 3.50(3H, s, N-CH$_3$), 3.80(3H, s, N-CH$_3$), 7.70(1H, dd, J=2, 10Hz, 8-H), 7.84(1H, d, J=2Hz, 6-H), 7.96(1H, d, J=10Hz, 9-H), 9.05(1H, s, 5-H).

REFERENCES

1) a) T.Takeshima, N.Fukuda, M.Muraoka, and T.Miyauchi, Yuki Gosei Kagaku Kyokaishi, 1973, **31**, 808: b) "Organic Compounds of Sulphur, Selenium, and Tellurium", ed. D.H.Reid, The Chemical Society, London, 1970, Vol. 1, p.187, 1973, Vol. 2, p.511, 1975, Vol. 3, p.512, 1976, Vol. 4, p.269, 1978, Vol. 5, p.177.

2) Y.Tominaga, T.Machida, H.Okuda, Y.Matsuda, and G.Kobayashi, Yakugaku Zasshi, 1979, **99**, 515.

3) K.Senga, K.Shimizu, S.Nishigaki, and F.Yoneda, Heterocycles, 1977, **6**, 1361.

4) F.Yoneda, F.Takayama, and A.Koshiro, Chem.Pharm.Bull.(Tokyo), 1979, **27**, 2507.

5) K.Bredereck and S.Humburger, Chem.Ber., 1966, **99**, 3227.

Received, 2nd August, 1980