SYNTHESIS OF PYRIMIDO[4,5-b][1,4,6]BENZOXADIAZOCINES, A NEW CLASS OF HETEROCYCLES

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Abstract —— The dehydrogenative cyclization of 5-(N-arylaryl-amidino)-1,3-dimethylbarbituric acids with diethyl azodicarb-oxylate afforded pyrimido[4,5-b][1,4,6]benzoxadiazocines, a new class of heterocycles.

We have previously described that the reaction of 5,7-dimethyl-2-phenyloxazolo-[5,4-d]pyrimidine-4,6(5H,7H)-dione with arylamines gives 5-(N-arylbenzamidino)-1,3-dimethylbarbituric acids (I), whose dehydrative cyclization with thionyl chloride offers a facile synthetic route to normally inaccessible 9-aryl-8-phenyl-theophyllines.[1] As part of a program directed towards the further synthetic exploitation of I, we now wish to report a simple synthesis of pyrimido[4,5-b]-[1,4,6]benzoxadiazocines, a new class of heterocycles, by the dehydrogenative cyclization of I with diethyl azodicarboxylate (DAD). The pyrimidobenzoxadiazocine system would be of medicinal interest as potential hypnotics, sedatives or psychotropics since the structure is closely related to benzodiazepine.

Treatment of the appropriate Ia-e(2.5 mmol) with DAD(100 mmol) at 160°C for 5 min, followed by dilution with ethanol caused the separation of the corresponding pyrimido[4,5-b][1,4,6]benzoxadiazocines (IIIa-e) in 42-79% yields as colorless crystals.[2] This reaction was equally applicable to other barbituric acids (If-i)[3] to give the corresponding pyrimidobenzoxadiazocines (IIIf-i) in 54-82% yields (Table).

The structure of III is isomeric with that of oxazetinopyrimidine (IV), pyrimidoxadiazine (V) or pyrimidobenzoxazepine (VI), however, the possibility of these heterocyclic systems was readily eliminated by the following spectral evidences.

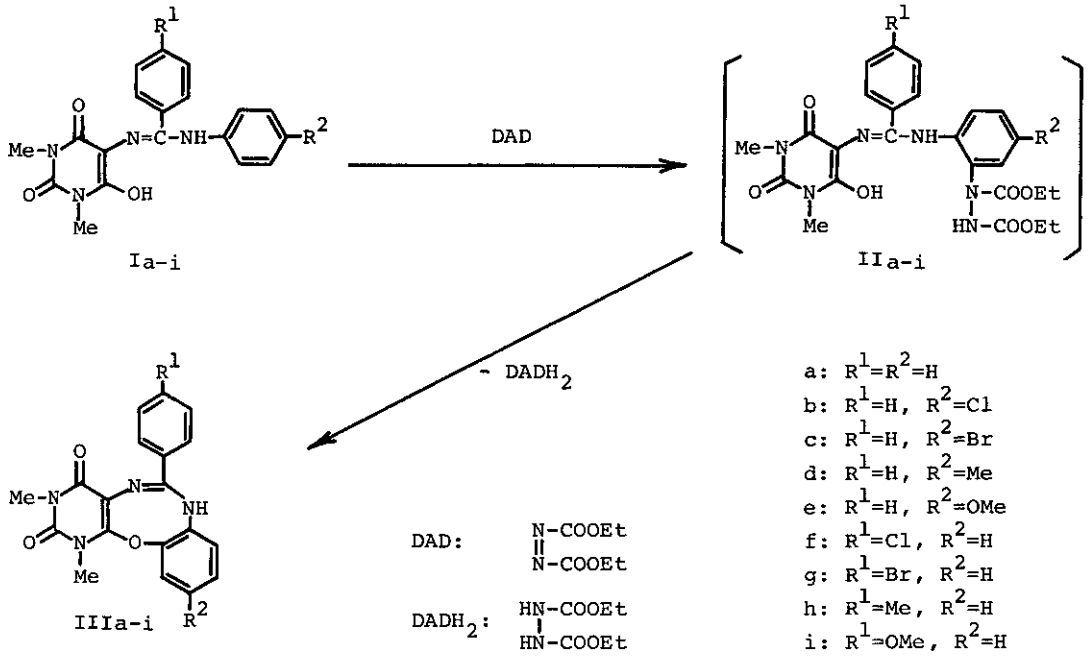
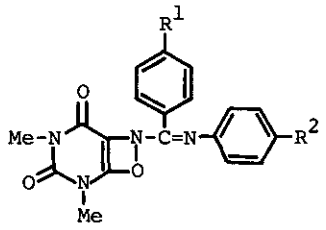


Table Pyrimido[4,5-b][1,4,6]benzoxadiazocines (III)

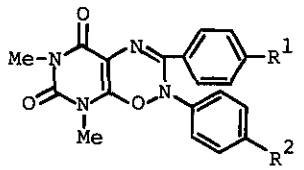
Compound[a]	Recrystn. Solvent	Mp(°C)	Yield(%)
IIIa	EtOH	251-252.5	66
IIIb	EtOH	272-273	79
IIIc	EtOH	269-270	59
IIId	EtOH	263-264	64
IIIe	EtOH	240-242	42
IIIf	EtOH	273-274	73
IIIg	EtOH-DMF	278-279	82
IIIh	EtOH	245-247	54
IIIi	EtOH-DMF	248-249	55

[a] Satisfactory analytical and spectral (IR, ^{1}H-NMR, MS) data were obtained for all compounds.

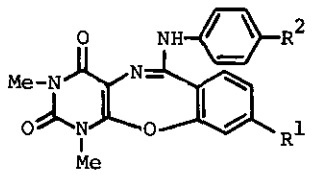
Namely, the existence of a marked secondary amino absorption band at 3350-3400 cm^{-1} in the IR spectra ruled out the structures of IV and V, while the presence of a characteristic AB and A_2B_2 splitting pattern for the compounds IIIa-e and IIIf-i, respectively, in the ^{1}H-NMR spectra excluded the structure of VI.[4] Although the structure III is tautomeric with that of III', the tautomerism is not clear at present.



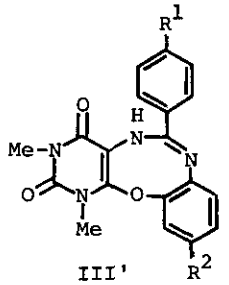
IV



V



VI



III'

The reaction of I with DAD leading to III would proceed through the initial formation of the Michael-type adduct (II)[5] and subsequent dehydrogenative cyclization accompanying the liberation of diethyl hydrazodicarboxylate ($DADH_2$), which could actually be isolated from the filtrate. The formation of II was suggested by the previous finding that the reaction of 2-aminonaphthalene with DAD gives 2-amino-1-(1,2-dicarbethoxyhydrazino)naphthalene.[6] Although several dehydrogenative cyclizations on the syntheses of heterocyclic systems have been reported, the reaction of I with DAD to give III may be the first example in which DAD has employed directly in the synthesis of 8-membered heterocycles.[7]

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. S. Nishigaki, J. Sato, K. Shimizu, and K. Senga, Chem. Pharm. Bull., 1980, 28, 1905.
2. The ^{1}H-NMR data (DMSO-d_6) for compound IIIa are as follows: δ 3.18 (s, 6H, 2 N-Me), 6.87-7.27 (m, 4H, C_6H_4), 7.33-8.00 (m, 5H, C_6H_5), 10.00 (s, 1H, NH, D_2O exchangeable).
3. These compounds were obtained by the reaction of the appropriate 2-(4-substituted phenyl)-5,7-dimethyloxazolo[5,4-d]pyrimidine-4,6(5H,7H)-diones with aniline according to the reported procedure.[1] The melting points of these compounds are as follows: If, mp 223-226°C; Ig, mp 229-230°C; Ih, mp 220-222°C, Ii, mp 217-219°C.
4. The ^{1}H-NMR data (DMSO-d_6) for compounds IIIc and IIIg are as follows:
   IIIc; δ 3.23 (s, 6H, 2 N-Me), 7.07 (d, 1H, J=2.5Hz, C_6H_3), 7.33-7.93 (m, 6H, C_6H_3 and C_6H_5), 7.77 (d, 1H, J=2.5Hz, C_6H_3), 10.17 (s, 1H, NH, D_2O exchangeable).
   IIIg; δ 3.23 (s, 6H, 2 N-Me), 6.90-7.33 (m, 4H, C_6H_4), 7.65 (d, 2H, J=3Hz, C_6H_4), 7.83 (d, 2H, J=3Hz, C_6H_4), 10.13 (s, 1H, NH, D_2O exchangeable).
5. Attempted isolation of this intermediate was unsuccessful.
6. O. Diels, Chem. Ber., 1921, 54, 213.
7. F. Yoneda, M. Higuchi, K. Mori, K. Senga, Y. Kanamori, K. Shimizu, and S. Nishigaki, Chem. Pharm. Bull., 1978, 26, 2905 and references cited therein.

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