New Synthesis of Purines by the Reaction of Diethyl Azodicarboxylate with 6-Alkylaminouracils

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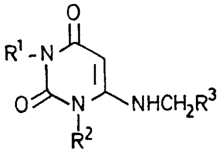
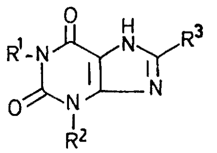
Summary Treatment of 6-alkylamino-uracils with excess of diethyl azodicarboxylate gave the respective xanthine derivatives; reaction of 6-amino-5-(1,2-diethoxycarbonylhydrazino)-1,3-dimethyluracil with aryl aldehydes also gave the corresponding xanthine derivatives.

WE report a new synthesis of purines in which diethyl azodicarboxylate (DAD) acts as a dehydrogenation reagent as well as a nitrogen source for the direct cyclization of 6-*N*-benzyl- and 6-*N*-alkyl-aminouracils.

Fusion of compound (I)[1] with 3 equiv. of DAD at 170—

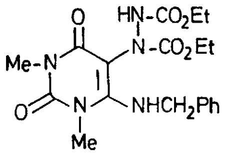
180° for 2 h, followed by dilution with ethanol gave a good yield of 8-phenyltheophylline (VI).[1] The reaction is equally applicable to other alkylamino-uracils[1] to give the corresponding xanthines[1] (see Table 1).



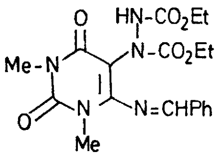


(I) $R^1 = R^2 = Me$, $R^3 = Ph$
(II) $R^1 = Me$, $R^2 = H$, $R^3 = Ph$
(III) $R^1 = H$, $R^2 = Me$, $R^3 = Ph$
(IV) $R^1 = R^2 = Me$, $R^3 = Et$
(V) $R^1 = R^2 = Me$, $R^3 = Pr^n$

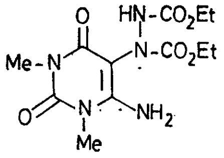
(VI) $R^1 = R^2 = Me$, $R^3 = Ph$
(VII) $R^1 = Me$, $R^2 = H$, $R^3 = Ph$
(VIII) $R^1 = H$, $R^2 = Me$, $R^3 = Ph$
(IX) $R^1 = R^2 = Me$, $R^3 = Et$
(X) $R^1 = R^2 = Me$, $R^3 = Pr^n$
(XIV) $R^1 = R^2 = Me$, $R^3 = p$-ClC$_6$H$_4$
(XV) $R^1 = R^2 = Me$, $R^3 = p$-MeOC$_6$H$_4$
(XVI) $R^1 = R^2 = Me$, $R^3 = p$-NO$_2$C$_6$H$_4$
(XVII) $R^1 = R^2 = Me$, $R^3 = 3,4$-Cl$_2$C$_6$H$_3$
(XVIII) $R^1 = R^2 = Me$, $R^3 = 3,4$-CH$_2$O$_2$-C$_6$H$_3$



(XI)



(XII)



(XIII)

Treatment of (I) with 1 equiv. of DAD under the same conditions gave the Michael-type adduct (XI), m.p. 156°,† which did not form the desired purine upon thermolysis under any conditions. However, treatment of (XI) with further DAD at 170—180° gave 8-phenyltheophylline as expected, although in less satisfactory yield (*ca.* 40%). DAD probably abstracted two hydrogen atoms from (XI) to give the uracil (XII), which cyclized immediately to a purine.

TABLE 1

Purine formation by reaction of 6-*N*-benzyl- and 6-*N*-alkyl-aminouracils with DAD for 2 h [3h for (V)]

Starting material	Temp/°C	Product	Yield/%
(I)	180	(VI)	71
(II)	180	(VII)	68
(III)	180	(VIII)	83
(IV)	190	(IX)	50
(V)	200	(X)	30

TABLE 2

Purine formation by reaction of compound (XIII) with aryl aldehydes

Aryl aldehyde	Product	Yield / %
Benzaldehyde[a]	(VI)	72
p-Chlorobenzaldehyde[a] ..	(XIV)	78
p-Anisaldehyde[a]	(XV)	65
p-Nitrobenzaldehyde[b]	(XVI)	61
3,4-Dichlorobenzaldehyde[c] ..	(XVII)	81
Piperonal[a]	(XVIII)	73

[a] 170 °C for 4 h. [b] 180°C for 5 h. [c] 180 °C for 3·5 h.

To confirm this, we have examined the condensation of the uracil (XIII)[2] with aryl aldehydes, which should presumably give intermediates of type (XII). Thus heating (XIII) with several aryl aldehydes at 170—180° for *ca.* 4 h, followed by dilution with ethanol caused the separation of the corresponding purines, although the intermediate (XII was not detected (see Table 2).

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† Satisfactory analytical and spectral data were obtained for all products.

[1] H. Goldner, G. Dietz, and E. Carstens, *Annalen*, 1966, **691**, 142.
[2] E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, 1968, **90**, 1374.