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SYNTHESIS OF XANTHINES BY THE REACTION OF 6-AMINO-5-ARYLAZOURACILS OR 5-ARYLAZOBARBITURIC ACIDS WITH ALKYLAMINES

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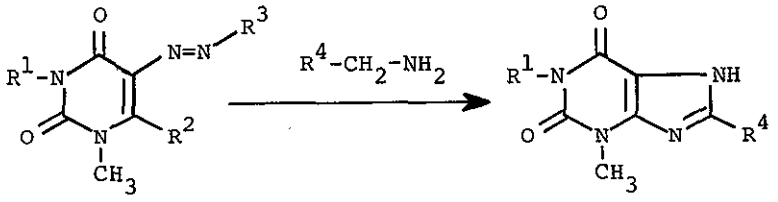
Treatment of 6-amino-5-arylazouracils or 5-arylazobarbituric acids with alkylamines offers a convenient synthetic method of xanthines.

6-Amino-5-nitrosopyrimidines have received considerable recent attention as versatile synthetic intermediates in the synthesis of purines.[1,2] On the other hand, the direct synthesis of purines using 5-arylazo analogs in place of the above 6-amino-5-nitrosopyrimidines still remains to be studied, although a few synthetic procedures have been developed. These procedures involve the condensations of 6-amino-5-arylazopyrimidines with aryl aldehydes and amide acetals.[3] We now report a simple synthesis of xanthines by the condensation of 6-amino-5-arylazouracils or 5-arylazobarbituric acids with alkylamines.

Fusion of 6-amino-1,3-dimethyl-5-phenylazouracil (Ia) with excess benzylamine at 230° gave 8-phenyltheophylline (IIa). Similarly, other 6-amino-5-arylazouracils (Ib-e) having a substituent

in the arylazo-group were used for the condensation with benzylamine in order to examine the influence of the substituent upon the yields. The results are summarized in Table. The table shows that the presence of an electron-withdrawing substituent in the arylazo-group had no significant effect on the yields of IIa. Other xanthine derivatives were also obtained by the condensation of 6-amino-5-arylazouracils with an appropriate amine (Table).



(Ia) $R^1=CH_3$, $R^2=NH_2$, $R^3=C_6H_5$
(Ib) $R^1=CH_3$, $R^2=NH_2$, $R^3=\underline{m}\text{-}CH_3\text{-}C_6H_4$
(Ic) $R^1=CH_3$, $R^2=NH_2$, $R^3=\underline{m}\text{-}Cl\text{-}C_6H_4$
(Id) $R^1=CH_3$, $R^2=NH_2$, $R^3=\underline{p}\text{-}Cl\text{-}C_6H_4$
(Ie) $R^1=CH_3$, $R^2=NH_2$, $R^3=\underline{p}\text{-}NO_2\text{-}C_6H_4$
(If) $R^1=H$, $R^2=NH_2$, $R^3=C_6H_5$
(Ig) $R^1=CH_3$, $R^2=OH$, $R^3=C_6H_5$
(Ih) $R^1=CH_3$, $R^2=OH$, $R^3=\underline{p}\text{-}Cl\text{-}C_6H_4$

(IIa) $R^1=CH_3$, $R^4=C_6H_5$
(IIb) $R^1=CH_3$, $R^4=C_6H_5\text{-}CH_2$
(IIc) $R^1=H$, $R^4=C_6H_5$

This reaction may be initiated by the transamination of I by alkylamines, which is facilitated in the presence of the arylazo-group. It is possible that the preformed 6-alkylamino-5-arylazouracils cause intramolecular cyclization to give xanthines. In fact, some success of cyclization of this type has been reported with 6-alkylamino-5-arylazouracils.[4]

Treatment of 1,3-dimethyl-5-phenylazobarbituric acid (Ig) with

benzylamine under the same conditions gave also IIa in almost the same yield. The reaction of 5-(p-chlorophenyl)azo-1,3-dimethylbarbituric acid (Ih) with 2-phenethylamine yielded 8-benzyltheophylline (IIb), albeit in poor yield.

TABLE Formation of 8-Substituted Theophyllines

5-Arylazopyrimidine	Amine	Reaction Conditions Temp (°C)	Time (min)	Product	Yield (%)
Ia	Benzylamine	230	10	IIa	51
Ib	Benzylamine	230	7	IIa	56
Ic	Benzylamine	230	5	IIa	82
Id	Benzylamine	230	8	IIa	63
Ie	Benzylamine	230	5	IIa	50
Ig	Benzylamine	230	5	IIa	53
Ia	2-Phenethylamine	240	15	IIb	22
Id	2-Phenethylamine	250	8	IIb	44
Ih	2-Phenethylamine	240	15	IIb	10
If	Benzylamine	240	5	IIc	40

EXPERIMENTAL

The starting materials (Ia-h) were prepared by the known procedure.[5]

8-Phenyltheophylline (IIa).[6] —— Method A. A mixture of 6-amino-1,3-dimethyl-5-phenylazouracil (Ia) (0.5 g, 0.0019 mol) and benzylamine (0.5 g, 0.0047 mol) was fused at 230° for 10 min. The reaction mass was triturated in ethanol, collected and washed with ether. Recrystallization from dimethylformamide gave colorless prisms of IIa (0.25 g, 51%), m.p. > 360°.

Method B. A mixture of 1,3-dimethyl-5-phenylazobarbituric

acid (Ig) (0.5 g, 0.0019 mol) and benzylamine (0.5 g, 0.0047 mol) was fused at 230° for 5 min. The crystals thus separated were collected and recrystallized from dimethylformamide to give colorless prisms of IIa (0.26 g, 53%), m.p. > 360°.

3-Methyl-8-phenylxanthine (IIc).[6] —— A mixture of 6-amino-1-methyl-5-phenylazouracil (If) (0.5 g, 0.002 mol) and benzylamine (0.5 g, 0.0047 mol) was fused at 240° for 5 min. The reaction mass was treated as above to give colorless prisms of IIc (0.2 g, 40%), m.p. > 360°.

8-Benzyltheophylline (IIb).[6] —— A mixture of 6-amino-5-(p-chlorophenyl)azo-1,3-dimethyluracil (Id) (0.5 g, 0.0017 mol) and 2-phenethylamine (0.4 g, 0.0033 mol) was fused at 250° for 8 min. The reaction mass was triturated in a mixture of ethanol and ether, collected and recrystallized from ethanol to give colorless needles of IIb (0.2 g, 44%), m.p. 295°. Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.34; H, 5.29; N, 20.55.

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