The Photolysis and Pyrolysis of 8-Azidocaffeine (1)

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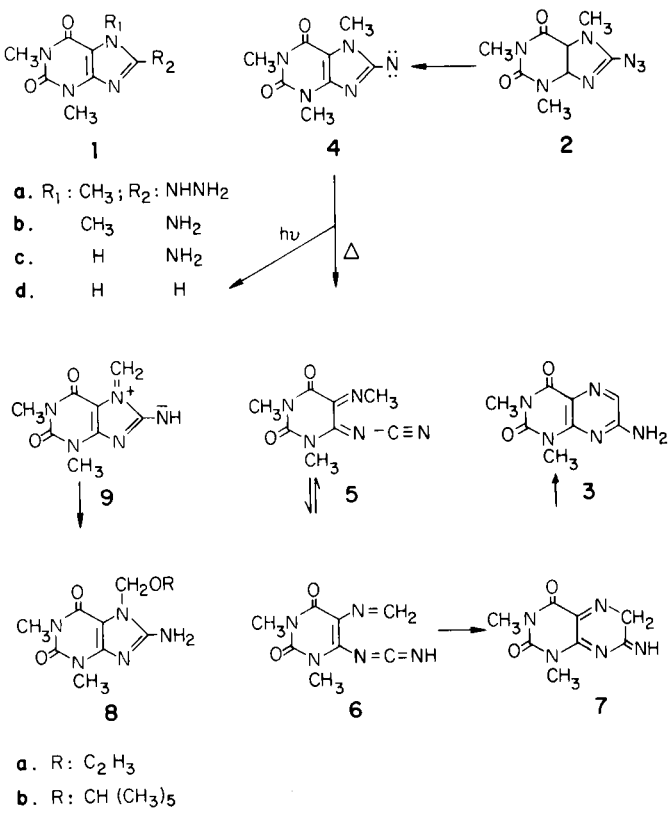
Sir:

In connection with studies on the structure of an uncharacterized, possibly dimeric, blue compound derived from 3-acetoxyxanthine (2), an attempt was made to prepare 8-triazolylxanthines from 8-azidoxanthines by reactions with enolate anions or dipoles. The azides were unstable at relatively low temperatures, and appeared to decompose before other reactions could occur. There is little information on reactions of azidopurines (3), and therefore those of the more available 8-azidocaffeine were investigated under both pyrolytic and photolytic conditions.

Diazotization of 8-hydrazinocaffeine (**1a**) (4) gave the azide (**2**) (5) (79% from ethanol); nmr (TFA): τ 6.12 [3H, s, N(7)CH_3], 6.24 [3H, s, N(3)CH_3] and 6.41 [3H, s, N(1)CH_3] (6). 8-Aminocaffeine (**1b**), previously available in poor yield (9), could be obtained quantitatively by catalytic reduction of the azide **2** with Pd/C in glacial acetic acid.

When 8-azidocaffeine (**2**) was heated in an open petri dish at 130° for 3 days, the azide absorption in the ir (2080 cm^{-1}) slowly disappeared. The pink-tinged solid obtained was dissolved in dilute ammonium hydroxide and chromatographed over Dowex-50 [H^+], 200-400 mesh, with 1 *N* hydrochloric acid, to give primarily 8-aminotheophylline (**1c**) (10) (35-41%), with some 8-aminocaffeine (**1b**) (2-4%) and theophylline (**1d**) (~ 1%). A red compound which gave rise to the pink color in the crude pyrolysis product was not eluted from the Dowex-50 column. However, chromatography of the crude material over neutral alumina, Bio-Rad AG7, 100-200 mesh, afforded a mixture of the aforementioned methylxanthine derivatives, by elution with benzene-chloroform (3:1), and the red compound (~ 1%) by further elution with chloroform. This compound was identical with a red compound that results from the oxidation of 8-hydrazinocaffeine (**1a**) with ferric chloride in hydrochloric acid, and which was previously suggested to be 8,8′-dicaffeine (4). However, from the analytical and spectroscopic data, it was identified as 8,8′-azocaffeine, m.p. > 300°; uv (chloroform) λ max 546, 504, (460), 320 and 265 nm; nmr (TFA) τ 5.42 (6H, s), 6.15 (6H, s) and 6.32 (6H, s); ms, m/e 414 (M^+) and 386 (M^+-28) (11).

When the azide **2** was heated at 130° in a covered petri dish, or in a sealed ampoule, the compound soon exploded



to give a dark brown solid, which was leeched with boiling ethanol-chloroform to leave much charred insoluble material. The soluble material was chromatographed over Dowex-50 with 1 *N* hydrochloric acid to yield 7-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine (**3**) (18-23%), m.p. > 360° (from water); nmr (TFA) τ 1.70 [1H, s, C(6)-H], 6.20 [3H, s, N(1)CH] and 6.37 [3H, s, N(3)CH_3]; uv (*p*H 1 or *p*H 13) λ max 337, 277, and 251 nm; ms: m/e 207 (M^+), 150 (M^+-57) and 122 (M^+-85) (11), and was identical with an authentic sample (12). The nmr of the pteridine **3** in DMSO-d_6 showed the amino group as a broad two proton singlet at τ 2.43. In addition, 8-aminotheophylline (12-17%) and 8-aminocaffeine (~ 1%), with trace amounts of theophylline and other unknowns were obtained.

The formation of 8-aminocaffeine and 8,8′-azocaffeine from the azide is in accord with known thermolytic pro-

ducts from other heterocyclic azides (13). However, the production of 8-aminotheophylline, which involves the loss of the elements of diazomethane, is an unusual reaction. The production of the pteridine derivative **3** during explosive decomposition presumably involves generation of the nitrene **4**, opening of the 7-8 bond to give (**5** ⇄ **6**), and recyclization *via* **7** to **3**. Conjugated nitriles, similar to structure **5**, have been invoked to explain the thermolysis products of 5-membered ring heterocyclic azides (13,14). However, there is presently no evidence to exclude a concerted process in the decomposition of the azide 2.

The irradiation of 8-azidocaffeine (**2**) (50 mg.) in dry ethanol (300 mg.) with a Hanovia 450W high pressure mercury lamp (pyrex filter) for 90 minutes gave 8-amino-7-ethoxymethyltheophylline (**8a**) (44 mg., 83%), m.p. 235-236° (from ethanol); nmr (TFA): τ 4.05 [2H, s, CH_2OEt], 6.08 [2H, q, CH_2Me], 6.27 [3H, s, N(3)CH_3], 6.43 [3H, s, N(1)CH_3] and 8.63 [3H, t, CH_3]; ms: m/e 253 (M^+) and 195 (M^+-58) (11). The nmr in DMSO-d_6 showed the 8-amino group as a broad two proton singlet at τ 2.88. Prolonged refluxing of the azide **2** in ethanol, without irradation, gave some of the ethoxymethyl derivative **8a** (15% after 3 days). The azide **2** was also irradiated in 2-propanol to give 8-amino-7-isopropoxymethyltheophylline (**8b**) (77%), m.p. 214-215° (from 2-propanol); nmr (TFA): τ 4.02 [2H, s, $CH_2OCH(Me)_2$], 5.90 [1H, m, $OCH(Me)_2$], 6.25 [3H, s, N(3)CH_3], 6.42 [3H, s, N(1)CH_3] and 8.65 [6H, d, CH_3X 2]; ms: m/e 267 (M^+) and 195 (M^+-72) (11). Photolysis of 8-azidocaffeine in alcohols should provide a useful synthetic route to 8-amino-7-alkoxymethyltheophyllines, which might be of pharmacological interest.

It is known that the irradiation of xanthine in alcohols affords 8-hydroxyalkyl derivatives, *via* attack of a hydroxyalkyl radical (15), whereas 8-alkoxy compounds are formed by nucleophilic attack by the alcohol at an 8-carbonium ion derived from 3-acetoxyxanthines (2,8). It is probable that the alkoxymethyl derivatives **8** described here are formed *via* photochemical generation of the nitrene **4**, followed by abstraction of hydride ion from the *ortho* methyl group as in **9**, and solvent attack to give **8**. However, as in the thermolytic process, a concerted mechanism cannot be excluded.

All new compounds gave satisfactory C, H, and N analyses (± 0.3%).

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