The preparations to be evaluated were administered orally to groups of six male Füllinsdorf rats of body weight range 160-200 g after the animals had fasted overnight. Compounds were dissolved or suspended in water by mixing in a mortar with 1 or 2 drops of Tween 80. Rats were dosed on a milligram per kilogram basis 1 h before measuring the thickness of both hind paws and the subplantar injection of 0.05 mL of carrageenan (Kraft Foods, lot 3F1.11), 1% w/v, in physiological saline. Three hours later the ensuing swelling was measured, and the percent inhibition of the edema formation was calculated by considering the edema in the control animals to be 100%. Paw thickness was measured using the anvil and pin AASE Antiinflammatory Screening Equipment (Roche, Basle) thickness-measuring transducer.

**Passive Paw Anaphylaxis Test for Inhibitors of Immediate Hypersensitivity.**<sup>28</sup> Sera containing heat-labile homocytotropic antibodies for use in passive paw anaphylaxis (PPA) were raised in 150–200 g female brown Norway rats. Each rat was injected intraperitoneally with 0.5 mL of *Bordetella pertussis* vaccine (Commonwealth Serum Laboratories, Melbourne) containing  $2 \times 10^{10}$  organisms and intramuscularly with 2 mg of crystalline ovalbumin (OA) (Sigma, St. Louis, Grade VI, lot 67C-8035) in 0.5 mL of physiological saline.<sup>29</sup> Eleven days later, animals were bled and sera were recovered and tested for activity in passive cutaneous anaphylaxis (PCA) experiments in rats.<sup>30</sup> For PPA studies, groups of six to eight Oxford Hooded [HO (PVG/C)] rats of approximately 200 g were used. Following the measurement of the thickness of both hind paws, rats were given subplantar injections in each paw of 0.05 mL of a suitable dilution or rat anti-OA serum. Two hours later, animals were injected iv in the tail with 0.3 mL of a 1% w/v solution of OA in physiological saline. Fifteen minutes after antigen challenge, paw swelling was measured using the AASE thickness-measuring transducer. Paws of control animals were injected with diluted antiserum, but these rats were not challenged with antigen before paw thicknesses were read. The mean increase in paw thickness in the antigen-challenged rats was obtained by deducting the mean figure obtained from control animals sensitized with diluted antiserum. Three other groups of control animals used in PPA studies were injected in the hind paws with saline, serum from immunized rats, or serum from rats injected with OA and B. pertussis but which gave a PCA titre of 0. Percent inhibition of the immediate allergic reaction was calculated by considering the swelling in the control paws to be 100%. Compounds tested for inhibition of PPA were given iv 5 min before antigen challenge.

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## Inhibition of Separated Forms of Cyclic Nucleotide Phosphodiesterase from Pig Coronary Arteries by 1,3-Disubstituted and 1,3,8-Trisubstituted Xanthines

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A series of xanthines with varied substituents in the 1, 3, and 8 positions were prepared in an attempt to understand the structure-activity relationship for alkylxanthines as inhibitors of two different forms of cyclic nucleotide phosphodiesterase. Polar substituents on the 1 or 3 position of the xanthine reduced the potency of the xanthines to inhibit both the calmodulin-sensitive and the "cyclic AMP specific" forms of phosphodiesterase. Polar substituents on the 8 position of the xanthine, other than a carboxylic acid, increased the potency to inhibit the calmodulin-sensitive form of phosphodiesterase, if they were capable of donating electrons to the xanthine nucleus. On the other hand, any substituent in the 8 position larger than H reduced the potency of the xanthines to inhibit the cyclic AMP specific form of phosphodiesterase. Topographical maps of the active sites of the two forms of phosphodiesterase are presented in summary.

Alkylxanthines (theophylline, caffeine, and 1-methyl-3-isobutylxanthine) are well known as inhibitors of cyclic nucleotide phosphodiesterase activity. We have demonstrated that modification of the xanthine structure can give rise to compounds that inhibit relatively selectively one of the two forms of phosphodiesterase found in pig coronary arteries (peak I and peak II).<sup>2,3</sup> These enzymes appear to be representative of two of the major forms of phosphodiesterase, the calmodulin-sensitive form (peak I) and the "cyclic AMP specific" form (peak II), both of which are found in most mammalian cells. The cyclic

AMP specific form is characterized by its relative specificity for cyclic AMP as substrate and by its apparent negative cooperativity. The activity of this form of phosphodiesterase is not altered by calmodulin. The calmodulin-sensitive form has a lower apparent  $K_m$  for cyclic GMP (~1-3  $\mu$ M) than for cyclic AMP (~50-100  $\mu$ M). The  $V_{\text{max}}$  of this form of phosphodiesterase with cyclic AMP as substrate, however, is about 2-fold greater than is the  $V_{max}$  with cyclic GMP as substrate. Because of the lower  $K_m$  for cyclic GMP, this enzyme has been considered to be the cyclic GMP phosphodiesterase; indeed, this form seems to be almost solely responsible for cyclic GMP hydrolysis in pig coronary arteries. That is not to say, however, that the calmodulin-sensitive enzyme can not participate in the regulation of intracellular levels of cyclic AMP. At least in pig coronary arteries, total cyclic AMP phosphodiesterase activity at 1  $\mu$ M substrate concentration is about equally divided between the calmo-

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dulin-sensitive form and the cyclic AMP specific form. Thus, the calmodulin-sensitive form could contribute to cyclic AMP regulation, but whether it does or not in intact cells is not clear.

We have shown that these two enzyme forms also differ in their susceptibilities to inhibition by xanthines with varied alkyl substituents.<sup>2,3</sup> Both forms appear to require the intact bicyclic ring system of xanthine<sup>2,4</sup> and both are more potently inhibited by 1-methyl-3-isobutylxanthine (MIX) than by theophylline. It was shown, however, that alkyl or aralkyl substitution in the 7 position<sup>2</sup> or alkyl substitution in the 8 position<sup>3</sup> of MIX gave compounds which were up to 35 times more potent as inhibitors of the calmodulin-sensitive form than of the cyclic AMP specific form. Conversely, substitution of larger alkyl groups for methyl in the 1 position of MIX gave compounds up to 5 times more potent as inhibitors of the cyclic AMP specific form than of the calmodulin-sensitive form. In this report, we present the results of structural modification of the xanthine nucleus in which the 1, 3, and 8 positions are substituted with various functionalities other than simple hydrocarbon groups. The agents were designed to extend the structure-activity relationships (SAR) of the xanthines as phosphodiesterase inhibitors and, at the same time, to obtain xanthines that are soluble enough in aqueous buffers to permit biological studies in the absence of organic solvents.

## **Results and Discussion**

Theophylline has long been recognized as a phosphodiesterase inhibitor and is still often used in biological studies despite the commercial availability of more potent agents such as 1-methyl-3-isobutylxanthine and papaverine. With few exceptions, the xanthines listed in Table I are more potent than theophylline as inhibitors of either peak I (calmodulin sensitive) or peak II (cyclic AMP specific) activity. At least in part, this increased activity is attributable in substitution of isobutyl for methyl in the 3 position. Increased activity also results from allyl (14), methallyl (15), isoamyl,<sup>3</sup> or benzyl<sup>3</sup> substitution in this position. This increased potency appears to be due to hydrophobic binding, since the more polar hydroxyethyl (12) and acetoxyethyl (13) groups reduce potency to inhibit both peak I and peak II activities.

We have reported<sup>3</sup> that for potent inhibition of either peak I or peak II activities, alkyl substituents rather than hydrogen are required at the 1 position. Potency to inhibit peak I activity is, however, reduced by substituting isoamyl or isobutyl for the 1-methyl group of MIX (Table I, compare IIX with MIX), and substitution of a carboxylic acid (10) in this position greatly reduces potency against either peak of activity. Conversion of 10 to the more lipophilic methyl ester (11) partially restores potency to inhibit both enzyme forms but presumably is still too polar to be well accomodated by the site which receives the isoamyl group of IIX.

We have also reported<sup>3</sup> that alkyl substitution in the 8 position of MIX reduces potency to inhibit peak II activity but does not affect potency against peak I. An electronwithdrawing group (such as trifluoromethyl), however, reduces potency against both peaks of activity. As shown in Table I, the 8-(methylamino) (5) and 8-(dimethylamino) (6) functions both increased the potency of the MIX moiety to inhibit peak I and reduced the potency of the MIX moiety to inhibit peak II. These compounds (5 and 6) are, however, quite insoluble in aqueous buffers and, in fact, are very poorly soluble in strong acid. Their usefulness is therefore limited, despite the fact that they are more than 50-fold more potent as inhibitors of peak I than as inhibitors of peak II activity. The lack of basic character of the amino group (i.e., lack of electron density on the nitrogen) and the increased potency to inhibit peak I activity indicate that electron-donating groups in this position increase potency against peak I. The carboxylic acid function (7) is the only 8-substituent that greatly reduces the potency of the 1-methyl-3-isobutylxanthine moiety to inhibit peak I phosphodiesterase activity. Potency against peak I is almost completely restored by conversion to the methyl ester (8). Thus, even relatively polar 8-substituents are well tolerated by peak I if they are not electron withdrawing, while any 8-substitution greatly reduces potency against peak II.

The data presented here and elsewhere<sup>2,3</sup> can be summarized in the following manner. (1) Nonpolar substitution larger than methyl in the 3 position of the xanthine nucleus enhances potency against either peak of activity. It would appear from these data that the 3-substituent of the xanthine binds to a lipophilic site on both peak I and peak II. (2) Some substituent other than hydrogen is required at position 1 of the xanthine, and the size of this substituent has a great influence upon the potency of the xanthine to inhibit peak I but not peak II activity.<sup>3</sup> The most straightforward interpretation of these data is that the site that accomodates the 1-substituent on the active site of peak I is limited in size, but the corresponding site on peak II can accomodate larger groups. The 1-substituent does not appear to contribute to the binding to peak II per se, because IIX and MIX are equipotent inhibitors of peak II activity. The sites on peak I and peak II apparently can not tolerate polarity, however, since 10 and 11 are poor inhibitors of either activity. (3) The sites on the two enzyme forms to which the xanthines bind apparently differ in their ability to tolerate bulk in the 8 position of the xanthine. Increased bulk in the 8 position and in the nearby 7 position<sup>2</sup> is well tolerated by the site of peak I, but the site on peak II cannot tolerate bulk in the 8 position. Substitution of groups ranging in size from methyl to tert-butyl<sup>3</sup> or carbomethoxyethyl (8) onto the 8 position of the MIX molecule has little effect on the potency to inhibit peak I activity, whereas any of these substitutions drastically reduces the potency to inhibit peak II activity. In addition to the steric aspect of the 8-substituent, 8-substituents that withdraw electrons from the xanthine reduce the potency of the xanthine to inhibit either enzyme form.<sup>3</sup> In contrast, agents that can donate electrons to the xanthine nucleus (5 and 6) increase the potency of the xanthine to inhibit peak I activity. The nature of this electronic effect on potency cannot be discerned from these data but may be related to alteration of hydrogen bonding, ring dipoles, or any combination of these and other parameters.

Using these generalizations and making a number of assumptions concerning the interaction of the two isozymes with their preferred cyclic nucleotide substrates, we have formulated working models of the active sites for peak I and peak II phosphodiesterases. The more potent xanthines are competitive inhibitors of cGMP hydrolysis by peak I phosphodiesterase activity (data not shown). Peak II activity, however, does not obey Michaelis-Menten kinetics and gives apparently negatively cooperative kinetic plots. For this reason, neither  $K_i$  values nor the type of inhibition can be determined by currently available methods. Nonetheless, it is reasonable to assume that the xanthines also bind to the hydrolytic site of peak II

<sup>(4)</sup> Buchman, R.; Heinstein, P. F.; Wells, J. N. J. Med. Chem. 1974, 17, 1168.

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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4 CH,	4 CH, CH, CH,CHCH, CH,CI, CH,CI 106-5 EtOH b C <sub>1</sub> ,H <sub>1</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 8.9 ± 2 28% ± 4 5 CH, CH,CHCH, NHCH, 265-267 EtOH c C <sub>1</sub> ,H <sub>1</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.2 ± 0.1 39% ± 7 6 CH, CHCH, NHCH, 265-267 EtOH c C <sub>1</sub> ,H <sub>1</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.2 ± 0.1 39% ± 7 7 CH, CH,CHCH, CH,J, NHCH, 265-267 EtOH d C <sub>1</sub> ,H <sub>1</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.2 ± 0.1 39% ± 7 8 CH, CH,CHCH, CH,J, NHCH, 270-272 EtOH 35 C <sub>1</sub> ,H <sub>1</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.5 ± 0.2 33% ± 3 9 CH, CH,CHCH, CH,J, NHCH, 270-272 EtOH d C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.5 ± 0.2 33% ± 3 10 CH,CH,H CH,J, CH,CH,J H 216-217 EtOH e C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.5 ± 3 11 CH,CO,CH, CH,CH,J H 216-217 EtOH e C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.1 ± 1 29% ± 1 12 CH, CH,CH,J H 216-217 EtOH e C C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.1 ± 1 29% ± 1 13 CH, CH,CH,J H 216-217 EtOH e C C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.1 ± 1 29% ± 1 14 CH, CH,CH,J H 216-217 EtOH e C C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, H 1.2 ± 30% ± 1 15 CH, CH,CH,J H 216-217 EtOH e C C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, C H 26% ± 2 4,0% ± 1 16 CH,CH,J,CH,J H 216-211 EtOH e C C <sub>1</sub> ,H <sub>2</sub> ,N <sub>1</sub> O <sub>1</sub> C, C H 26% ± 5 1.0% ± 1 17 (1-methyl-3:soolutyl-3-sachthine) 16 CH,CH,H,O,C C,H 26% ± 5 1.0% ± 1 17 (1-methyl-3:soolutyl-3-sachthine) 16 CH,CH,H,O,C C,H 26% ± 5 1.0% ± 1 17 (1-methyl-3:soolutyl-3-sachthine) <sup>4</sup> 18 CH,N <sub>1</sub> O <sub>1</sub> C, C,H,N <sub>1</sub> O <sub>1</sub> C,H,N 26,H,NO1 E,C,H,N 26,H,NO1 E,C,H,N 26,H,NO1 E,C,H,NO1 E,C	4 CH,	e	CH,	CH <sub>2</sub> CH(CH <sub>3</sub> ),	CH <sub>2</sub> OH	216 - 217	$H_2O$	34	C., H., N, O,	C, H	$9.4 \pm 2$	$283 \pm 18$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4	CH3	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CI	105- 106 5	EtOH	9	C <sub>11</sub> H <sub>15</sub> CIN <sub>4</sub> O <sub>2</sub>	С, Н	<b>8.9</b> ± 2	$28\% \pm 4$
6 CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> (CH <sub>3</sub> ), N(CH <sub>3</sub> ), N(C <sub>3</sub> ), N(C <sub>3</sub> ), N(CH <sub>3</sub> ), N(CCH <sub>3</sub> ), N(CH <sub>3</sub> ),	6 CH <sub>3</sub> CH <sub>4</sub> CH(CH <sub>3</sub> ), N(CH <sub>3</sub> ), N(CH <sub>3</sub> ), 284-285 EtOH d C <sub>1</sub> H <sub>10</sub> N/O <sub>1</sub> C, H 1.6 ± 0.2 33% ± 3 dec CH <sub>4</sub> CH(CH <sub>3</sub> ), C(H,CH <sub>3</sub> ), C(H,CH <sub>4</sub> ), C(H,CH <sub></sub>	6 CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> (CH), N(CH) <sub>3</sub> , N(CH) <sub>3</sub> , 284–285 EtOH d C <sub>1</sub> H <sub>10</sub> N <sub>3</sub> O, C, H 1.6 ± 0.2 33% ± 3 dec 7 CH, CH(CH) <sub>3</sub> , CH,CH(CH) <sub>3</sub> , CH,CH <sub>3</sub> OO,H 270–272 EtOH 35 C <sub>3</sub> H <sub>10</sub> N <sub>3</sub> O, C, H 45 ± 8 12% ± 3 30% ± 4 9 CH,CO,CH, CH,CH(CH) <sub>3</sub> , CH,CH,CO,CH, 172–173 MeOH e C <sub>1</sub> H <sub>20</sub> N <sub>4</sub> O, C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, CH,CH,OH, H 172–174 EEOH 66 C <sub>1</sub> H <sub>20</sub> N <sub>4</sub> O, C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, CH,CH,OH, H 276–174 EEOH 22 C <sub>4</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, CH,CH,OH, H 272–174 EEOH 22 C <sub>4</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, CH,CH,OH, H 276–174 EEOH 22 C <sub>4</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, CH,CH,OH, H 278–174 EEOH 22 C <sub>4</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, CH,CH,OH, H 278–174 EEOH 22 C <sub>4</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, H 216–CH, H 236, 0 C, H 24% ± 2 1.9% ± 1 11 CH,CO,CH, H 217, CH,CH,OH,OH 13 isobuty18-azarathine) <sup>4</sup> (CH,CH) CH,CH, H 210–211 EROH 73 C <sub>6</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 5 2.7% ± 5 1.16% CH,CH,OH 13 isobuty18-azarathine) <sup>4</sup> (CH,CH) CH,CH, H 210–211 EROH 73 C <sub>6</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 5 1.0% ± 1 10 ± 3 10 ± 3 10 ± 3 10 ± 6 1.17 (1-methy1-3 isobuty18-azarathine) <sup>4</sup> (CH,CH) CH, H 210–211 EROH 73 C <sub>6</sub> H <sub>10</sub> N <sub>4</sub> O, C, H 24% ± 5 1.0% ± 1 10 ± 3 10 ± 6 1.17 (1-methy1-3 isobuty18-azarathine) <sup>4</sup> (CH,CH) CH,CH 14 100,0 C, H 10 0,0 C, H 20,0 C, H 10 0,0 C	6 CH <sup>3</sup> , CH <sup>3</sup> (CH <sup>3</sup> ), N(CH <sup>3</sup> ), N(CH <sup>3</sup> ), N(CH <sup>3</sup> ), 284-285 EtOH d C <sup>1</sup> H <sub>0</sub> N <sub>0</sub> O <sup>3</sup> , C, H 1.6 ± 0.2 33% \pm 3 dec C <sup>1</sup> H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 45 \pm 8 12% \pm 3 30% \pm 4 9 CH <sup>3</sup> , CH <sub>2</sub> CH(CH <sup>3</sup> ), CH <sub>2</sub> CH(CH <sup>3</sup> ), CH <sub>2</sub> CH <sub>2</sub> OO <sub>4</sub> H 206 + C C <sub>1</sub> H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 45 \pm 8 12% \pm 3 9 CH <sup>3</sup> , CH <sub>2</sub> CH(CH <sup>3</sup> ), CH <sub>2</sub> CH(CH <sup>3</sup> ), CH <sub>2</sub> CH <sub>2</sub> OO <sub>4</sub> H 206 + C C <sub>1</sub> H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 45 \pm 8 12% \pm 3 30% \pm 4 10 CH <sup>3</sup> , CH <sub>2</sub> CH(CH <sup>3</sup> ), H 216-217 EtOH 60 C <sub>1</sub> H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 24% \pm 2 1.9% \pm 1 11 CH <sub>2</sub> CO <sub>4</sub> H, CH <sub>2</sub> CH(CH <sup>3</sup> ), H 216-217 EtOH 70 C, H 216 ± 1.92 33% \pm 2 13 CH <sup>3</sup> , CH <sub>2</sub> CH(CH <sup>3</sup> ), H 216-217 EtOH 60 C <sub>1</sub> H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 24% \pm 2 1.9% \pm 1 12 CH <sup>3</sup> , CH <sub>2</sub> CH(CH <sup>3</sup> ), H 226 dec EtOH 73 C, H, NO <sup>4</sup> , C, H 26% \pm 2 40% \pm 1 13 CH <sup>3</sup> , CH <sub>2</sub> CH <sub>2</sub> CH <sup>4</sup> , H 2172-174 EtoH 73 C, H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 26% \pm 2 40% \pm 1 13 CH <sup>3</sup> , CH <sub>2</sub> CH <sub>2</sub> CH <sup>4</sup> , H 216-211 EtOH 73 C, H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 26% \pm 2 40% \pm 1 13 CH <sup>3</sup> , CH <sub>2</sub> CH <sub>2</sub> CH <sup>4</sup> , H 216-211 EtOH 73 C, H <sub>0</sub> N <sub>0</sub> O <sup>4</sup> , C, H 26% \pm 5 1.0% \pm 1 13 CH <sup>3</sup> , CH <sub>2</sub> CH <sub>2</sub> CH <sup>4</sup> , H 216-211 EtOH 73 C, H <sub>1</sub> N <sub>1</sub> O <sup>4</sup> , C, H, 26% \pm 5 1.0% \pm 1 16 CH <sub>1</sub> CH(CH(CH) <sup>3</sup> ) CH <sub>2</sub> CH <sup>4</sup> , H 213-215 EtOH 60 C <sub>1</sub> H <sub>1</sub> N <sub>1</sub> O <sup>4</sup> , C, H, N 38% \pm 4 42% \pm 5 1.0% \pm 1 17 (1-methyl-3-isobutyl*azaxanthine) <sup>k</sup> 160+170 EtoH 1600+170 EtoH 160+170 EtoH 170 Et	ß	CH,	CH,CH(CH,),	NHCH	265-267	EtOH	ల	CH.,N,O,	C, H	$1.2 \pm 0.1$	<b>39%</b> ± 7
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	9	CH <sub>3</sub>	CH <sup>2</sup> CH(CH <sub>3</sub> ) <sup>2</sup>	N(CH <sub>3</sub> ) <sub>2</sub>	284-285	EtOH	q	C <sub>12</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub>	C, H	$1.6 \pm 0.2$	$33\% \pm 3$
7 CH,	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	7         CH,         CH,         CH, CHC(H),         CH,CHC(H),         CH,CHC(H),         CH,CHC(H),         CH,CHC(H),         CH,CHC(H),         CH,CHC(H), $172-173$ BCOH $65$ C <sub>1</sub> H <sub>1</sub> M,O,         C, H $45 \pm 8$ $122\% \pm 3$ $30\% \pm 3$ 9         CH,         CH,CHC(H),         CH,CHC(H),         CH,CHC(H),         CH,CHC(H), $96$ C, $111$ $112-17$ $216-217$ $BCOH$ $60$ C,H,M,O,         C,H $24\% \pm 2$ $119\% \pm 1$ 11         CH,CH(CH),         CH,CHC(H),         H $172-174$ $benzene$ $f$ $C_1H_1M,O_0$ C,H $24\% \pm 2$ $119\% \pm 1$ 11         CH,CHOH         H $172-174$ $benzene$ $f$ $C_1H_1M,O_0$ C,H $24\% \pm 2$ $119\% \pm 1$ 11         CH,CHOH         H $172-174$ $benzene$ $f$ $C_1H_1M,O_0$ C,H $24\% \pm 2$ $119\% \pm 5$ 12         CH,         CH,CHOH         H $172-174$ $benzene$ $f$ $C_1H_1M,O_0$ $C,H$ $24\% \pm 3$ $36 \pm 3$ $36 \pm 3$ <td><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></td> <td></td> <td></td> <td></td> <td></td> <td>dec</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					dec						
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	8 CH, CH, CH, CH, CH, CH, CD, CH, 172-173 MeOH e C, H, M, Q, C, H 9.8 ± 3 30% ± 4 9 CH, CH, CH, CH, CH, CH, CH, CH, CO, CH, 172-173 MeOH e C, H, M, N, Q, C, H 11 ± 1 29% ± 3 10 CH, CO, H CH, CH, J, H 266% ± 2 1.9% ± 1 11 CH, CO, CH, CH, CH, J, H 266% ± 2 1.9% ± 1 12 CH, CO, CH, 216-217 EtOH 65 C, H, M, N, Q, C, H 266% ± 2 1.9% ± 1 13 CH, CH, CO, CH, H 172-174 benzene $f$ C, H, M, N, Q, C, H 266% ± 2 1.9% ± 1 14 CH, CO, CH, CH, J, H 266% ± 2 1.9% ± 1 15 CH, CH, CH, J, CH, CH, J H 268 dec EtOH 73 C, H, M, Q, C, H 286% ± 5 2.7% ± 5 15 CH, CH, CH, CH, J H 210-211 EtOH 73 C, H, M, Q, C, H 28% ± 4 428% ± 5 1.0% ± 1 16 CH, CH, CH, J = CH, H 213-215 EtOH 69 C, H, M, Q, C, H 28% ± 4 428% ± 5 1.0% ± 1 16 CH, CH, CH, J = CH, H 213-215 EtOH 69 C, H, M, Q, C, H 38% ± 4 428% ± 5 1.0% ± 1 17 (1-methyl-3-isobutyl's anaxanihre) 16 CH, CH, CH, J = CH, H 213-215 EtOH 69 C, H, M, Q, C, H 38% ± 4 428% ± 5 1.0% ± 1 17 (1-methyl-3-isobutyl's anaxanihre) 17 (1-methyl-3-isobutyl's anaxanihre) 18 (1-methyl-3-isobutyl's anaxanihre) 18 (1-methyl-3-isobutyl's anaxanihre) 18 (1-methyl-3-isobutyl's anaxanihre) 18 (1-methyl-3-isobutyl's anaxanihre) 17 (1-methyl-3-isobutyl's anaxanihre) 18 (1-methyl-3-isobutyl's anaxanihre) 19 (1-methyl-3-isobutyl's anaxan	8 CH <sub>3</sub> CH <sub>3</sub> CH <sub>4</sub> (CH,), CH <sub>2</sub> (H,CH,), CH <sub>2</sub> (H,CO,CH, 172-173 MeOH $e$ C <sub>11</sub> H <sub>2</sub> N <sub>2</sub> O, C, H 11±1 298±3 305±4 9 CH, CH,CH(CH,), CH,CH,CH,CH,CH,CH,CH,CH,CH,CH,CH,	7	CH	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H	270-272	EtOH	35	C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub>	C, H	$45 \pm 8$	$12\% \pm 3$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	9 CH <sub>3</sub> CH <sub>3</sub> CH <sub>4</sub> CH(CH <sub>3</sub> ), CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH 216-217 EtOH 60 C <sub>13</sub> H <sub>2</sub> N <sub>4</sub> O <sub>3</sub> C <sub>1</sub> H 11±1 29%±3 10 CH <sub>2</sub> CO <sub>2</sub> H CH <sub>2</sub> CH(CH <sub>3</sub> ), H 212-174 benzene $f$ C <sub>12</sub> H <sub>4</sub> N <sub>4</sub> O <sub>3</sub> C <sub>1</sub> H 2.4% ± 2 1.9%±1 11 CH <sub>2</sub> CO <sub>2</sub> CH, CH <sub>2</sub> CH(CH <sub>3</sub> ), H 172-174 benzene $f$ C <sub>12</sub> H <sub>4</sub> N <sub>4</sub> O <sub>3</sub> C <sub>1</sub> H 2.4% ± 2 1.9%±1 12 CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> D H 256% ± 2 4.0% ± 1 13 CH <sub>3</sub> CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> D CH <sub>3</sub> D H 256% ± 2 1.9% ± 1 14 CH <sub>3</sub> CH <sub>3</sub> CH <sub>2</sub> D CH <sub>3</sub> D H 2122174 benzene $f$ C <sub>12</sub> H <sub>4</sub> N <sub>4</sub> O <sub>3</sub> C <sub>1</sub> H 25% ± 5 2.7% ± 5 14 CH <sub>3</sub> CH <sub>3</sub> D CH <sub>3</sub> D CH <sub>3</sub> D CH <sub>3</sub> H 200 H 73 C <sub>3</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> C <sub>1</sub> H 23% ± 5 2.7% ± 5 14 CH <sub>3</sub> CH <sub>4</sub> CH(CH <sub>3</sub> ) CH <sub>2</sub> CH <sub>2</sub> D CH <sub>3</sub> H 210-211 EtOH 73 C <sub>4</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> C <sub>1</sub> H 23% ± 5 1.0% ± 1 15 CH <sub>3</sub> CH <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> H 210-211 EtOH 73 C <sub>4</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> C <sub>1</sub> H 25 ± 3 36 ± 3 16 CH <sub>4</sub> CH <sub>4</sub> CH <sub>3</sub> D CH <sub>3</sub> D CH <sub>3</sub> H 200 H 73 C <sub>6</sub> H <sub>10</sub> N <sub>3</sub> O <sub>3</sub> C <sub>1</sub> H 25 ± 3 10 ± 3 16 CH <sub>4</sub> CH <sub>3</sub> D CH <sub>3</sub> D CH <sub>3</sub> D CH <sub>3</sub> H 10 2 213-215 EtOH 69 C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub> C <sub>1</sub> H 25 ± 3 10 ± 3 16 CH <sub>4</sub> CH <sub>4</sub> D CH <sub>4</sub> D COCH <sub>3</sub> H 15 CH <sub>3</sub> H 15 CH <sub>1</sub> H 15 CH <sub>1</sub> H 15 CH <sub>1</sub> 15 ± 2 1.0% ± 1 17 (1-methyl-3-isobutylxanthine) <sup>k</sup> 15 - 15 1.00 ± 9 110 ± 9 100 ± 6 theophylline <sup>a</sup> Yield from 1.3-disubstituted 5-nitroso-6-aminouracil <sup>b</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl+8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared	9 CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> (C(CH <sub>3</sub> ) <sup>1</sup> CH <sub>2</sub> (CH <sub>3</sub> ) <sup>1</sup> H CH <sub>2</sub> (CH <sub>2</sub> ) <sup>1</sup> H CH <sub>2</sub> (CH <sub>3</sub> ) <sup>1</sup> H CH <sub>2</sub> CH <sub>2</sub> (H) N/O <sub>4</sub> C H 43% ± 5 13% \pm 5 1	9 CH, 10 CH,CO,H CH,CH,J, CH,CH,OH 216-217 BtOH 60 C, H,M,Q, C, H 11±1 295±3 11 CH,CO,CH, CH,CH,J, H 172-174 65 C, H,M,Q, C, H 24%±2 19%±5 12 CH, 12 CH, 12 CH, 13 CH, CO,CH, CH,OCOCH, H 172-174 EAOH 22 C, H,M,Q, C, H 30%±1 23%±5 14 CH, 15 CH, 16 CH,CH,J, CH,COCCH, H 217-198 EtOH 22 C, H,M,Q, C, H 30%±1 23%±5 16 CH,CH,J,CCH,J CH,J 1 173 C, H,M,Q, C, H 24%±5 106 16 CH,CH,J 2000CH, H 213-211 EtOH 73 C, H,M,Q, C, H 265±3 365±3 16 CH,CH,J 2000CH, H 213-215 EtOH 69 C, H,M,Q, C, H 265±3 365±3 16 CH,CH,J 2000CH,J 2000CH, H 213-215 EtOH 69 C, H,M,Q, C, H 265±3 365±5 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 18 CH, 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 18 CH, 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 18 CH, 17 (1-methyl-3-isobutyl-8-azaranhine) <sup>k</sup> 18 CH, 10 (1-methyl-3-isobutyl-8-bromoxanhine) <sup>k</sup> 18 CH, 10 (1-methyl-3-isobutyl-8-bromoxanhine <sup>k</sup> 17 (1-methyl-3-isobutyl-8-bromoxanhine) <sup>k</sup> 17 (1-methyl-3-isobutyl-8-bromoxanhine <sup>k</sup> for 10 in 68% yield. <sup><i>e</i></sup> Prepared from 10 in 68% yield. <sup><i>e</i></sup> Prepared from 12 in 83% yield. <sup><i>h</i></sup> Structure stabilished by hydrogenation to MIX. <sup><i>f</i></sup> Structure extabilished by hydrogenation to MIX. <sup><i>f</i></sup> Structur	œ	CH	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	172-173	MeOH	в	C <sub>14</sub> H <sub>20</sub> N <sub>4</sub> O <sub>4</sub>	C, H	$9.8 \pm 3$	$30\% \pm 4$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	6	CH	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	216-217	EtOH	60	C13H20NO3	C, H	11±1	$29\% \pm 3$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	11 $CH_2CO_2CH_3$ $CH_2CH(CH_3)_1$ $H$ $172^{-174}$ benzene $f$ $C_{14}H_{0}N_{0}O_{1}$ $C, H$ $26\% \pm 2$ $40\% \pm 1$ 12 $CH_3$ $CH_3CH_2OH_4$ $H$ $H$ $22$ $C_8H_{10}N_{0}O_{3}$ $C, H$ $30\% \pm 1$ $23\% \pm 5$ 13 $CH_3$ $CH_3$ $CH_2CH_2OCCH_3$ $H$ $H$ $22$ $C_8H_{10}N_{1}O_{3}$ $C, H$ $43\% \pm 5$ $27\% \pm 5$ 14 $CH_3$ $CH_3$ $CH_2CH_2OCCH_3$ $H$ $H$ $210^{-211}$ $EtOH$ $73$ $C_9H_{10}N_{1}O_{3}$ $C, H$ $23\% \pm 5$ $27\% \pm 5$ 15 $CH_3$ $CH_3$ $CH_2CH_3$ $H$ $210^{-211}$ $EtOH$ $73$ $C_9H_{10}N_{2}O_{3}$ $C, H$ $23\% \pm 5$ $27\% \pm 5$ 16 $CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$ $10^{-2}$ $38\% \pm 4$ $42\% \pm 2$ 15 $CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$ $10^{-2}$ $10^{-2}$ $10\% \pm 1$ 15 $CH_3$ $CH_3$ $CH_3$ $CH_3$ $10^{-2}$ $10\% \pm 1$ $10\% \pm 2$ 16 $CH_3$ $10^{-2}$ $10^{-2}$ $10^{-2}$ $10\% \pm 2$ $10\% \pm 2$ $10\% \pm 2$ 16 $CH_3$ $10\% \pm 2$ 16 $CH_3$ $10\% \pm 2$ 17 $117$ $10\% \pm 2$ <td><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></td> <td>11 CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> CH<sub>3</sub>CH(CH<sub>3</sub>)<sub>1</sub> H 172-174 benzene <math>f</math> C<sub>12</sub>H<sub>6</sub>N<sub>4</sub>O<sub>4</sub> C<sub>5</sub> H 26% ± 2 40% ± 1 12 CH<sub>2</sub>CO<sub>5</sub>CH<sub>3</sub> CH<sub>5</sub>CH<sub>5</sub>OH H 22 C<sub>6</sub>H<sub>6</sub>N<sub>5</sub>O<sub>5</sub> C<sub>5</sub> H 30% ± 1 23% ± 2 33% ± 2 13 CH<sub>3</sub> CH<sub>5</sub>CH<sub>5</sub>OH H 22 C<sub>6</sub>H<sub>10</sub>N<sub>5</sub>O<sub>5</sub> C<sub>5</sub> H 30% ± 1 23% ± 5 13 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 56 ± 5 16 CH<sub>3</sub> CH<sub>3</sub>CH<sub>5</sub>CH(CH<sub>3</sub>)<sub>2</sub> CH<sub>5</sub>CH<sub>2</sub>OCOCH<sub>3</sub> H 22 C<sub>6</sub>H<sub>10</sub>N<sub>5</sub>O<sub>5</sub> C<sub>5</sub> H 23% ± 5 15 13 CH<sub>3</sub> CH<sub>3</sub>CH<sub>5</sub>CH(CH<sub>3</sub>)<sub>2</sub> CH<sub>5</sub>CH<sub>5</sub>CHCOCH H 2215 EtOH <math>g</math> C<sub>6</sub>H<sub>11</sub>N<sub>4</sub>O<sub>1</sub> C<sub>1</sub> H 25 ± 3 36 ± 3 15 CH<sub>3</sub> CH<sub>3</sub>CH<sub>5</sub>CH(CH<sub>3</sub>)<sub>2</sub> CH<sub>5</sub>CH<sub>5</sub>CH<sub>2</sub> CH<sub>3</sub> H 2002 CH<sub>3</sub> H 2002 C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>O<sub>1</sub> C<sub>1</sub> H 25 ± 2 17 (1-methyl-3-isobutyl*anthine)<sup>k</sup> 10 ± 3 215-2 17 (1-methyl-3-isobutyl*anthine)<sup>k</sup> 105 ± 2 100% ± 1 MIX (1-methyl-3-isobutyl*anthine)<sup>k</sup> 105 ± 2 17 (1-methyl-3-isobutyl*anthine)<sup>k</sup> 105 ± 2 100% ± 1 MIX (1-methyl-3-isobutyl*anthine)<sup>k</sup> 105 ± 2 100% ± 1 15 ± 2 10% ± 1 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 0 100 ± 1</td> <td>10</td> <td>CH<sub>2</sub>CO<sub>2</sub>H</td> <td>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub></td> <td>H</td> <td>308 dec</td> <td>EtOH</td> <td>65</td> <td>C, H, N, O</td> <td>C, H</td> <td><math>2.4\% \pm 2</math></td> <td><math>1.9\% \pm 1</math></td>	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	11 CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> CH <sub>3</sub> CH(CH <sub>3</sub> ) <sub>1</sub> H 172-174 benzene $f$ C <sub>12</sub> H <sub>6</sub> N <sub>4</sub> O <sub>4</sub> C <sub>5</sub> H 26% ± 2 40% ± 1 12 CH <sub>2</sub> CO <sub>5</sub> CH <sub>3</sub> CH <sub>5</sub> CH <sub>5</sub> OH H 22 C <sub>6</sub> H <sub>6</sub> N <sub>5</sub> O <sub>5</sub> C <sub>5</sub> H 30% ± 1 23% ± 2 33% ± 2 13 CH <sub>3</sub> CH <sub>5</sub> CH <sub>5</sub> OH H 22 C <sub>6</sub> H <sub>10</sub> N <sub>5</sub> O <sub>5</sub> C <sub>5</sub> H 30% ± 1 23% ± 5 13 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 56 ± 5 16 CH <sub>3</sub> CH <sub>3</sub> CH <sub>5</sub> CH(CH <sub>3</sub> ) <sub>2</sub> CH <sub>5</sub> CH <sub>2</sub> OCOCH <sub>3</sub> H 22 C <sub>6</sub> H <sub>10</sub> N <sub>5</sub> O <sub>5</sub> C <sub>5</sub> H 23% ± 5 15 13 CH <sub>3</sub> CH <sub>3</sub> CH <sub>5</sub> CH(CH <sub>3</sub> ) <sub>2</sub> CH <sub>5</sub> CH <sub>5</sub> CHCOCH H 2215 EtOH $g$ C <sub>6</sub> H <sub>11</sub> N <sub>4</sub> O <sub>1</sub> C <sub>1</sub> H 25 ± 3 36 ± 3 15 CH <sub>3</sub> CH <sub>3</sub> CH <sub>5</sub> CH(CH <sub>3</sub> ) <sub>2</sub> CH <sub>5</sub> CH <sub>5</sub> CH <sub>2</sub> CH <sub>3</sub> H 2002 CH <sub>3</sub> H 2002 C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>1</sub> C <sub>1</sub> H 25 ± 2 17 (1-methyl-3-isobutyl*anthine) <sup>k</sup> 10 ± 3 215-2 17 (1-methyl-3-isobutyl*anthine) <sup>k</sup> 105 ± 2 100% ± 1 MIX (1-methyl-3-isobutyl*anthine) <sup>k</sup> 105 ± 2 17 (1-methyl-3-isobutyl*anthine) <sup>k</sup> 105 ± 2 100% ± 1 MIX (1-methyl-3-isobutyl*anthine) <sup>k</sup> 105 ± 2 100% ± 1 15 ± 2 10% ± 1 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 0 100 ± 1	10	CH <sub>2</sub> CO <sub>2</sub> H	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	308 dec	EtOH	65	C, H, N, O	C, H	$2.4\% \pm 2$	$1.9\% \pm 1$
12 $CH_3$ $CH_2CH_2OH$ $H$ $268  dec$ $EtOH$ $22$ $C_6H_{10}N_0$ $C_7$ $H$ $30\% \pm 1$ $23\% \pm 5$ 13 $CH_3$ $CH_2CH_2OH$ $H$ $197-198$ $EtOH$ $g$ $C_{0}H_{10}N_0$ $C_7$ $H$ $33\% \pm 5$ $27\% \pm 5$ 14 $CH_3$ $CH_2CH_2OH_3$ $H$ $197-198$ $EtOH$ $g$ $C_0H_1N_0$ $C_7$ $H$ $43\% \pm 5$ $27\% \pm 5$ $10\% \pm 1$ $28\% \pm 3$ $10\% \pm 1$ $28\% \pm 2$ $10\% \pm 1$ $10$	12CH3CH2CH3CH2CH2H268 decEtOH22C6H330% ± 123% ± 513CH3CH3CH3CH3CH4N40C, H43% ± 527% ± 514CH3CH3CH4CH2CH4H23% ± 527% ± 527% ± 515CH3CH4H197-198EtOH73C, H43% ± 527% ± 515CH3CH4H210-211EtOH73C, H25 ± 352 ± 352 ± 315CH3CH4H213-215EtOH73C, H225 ± 336 ± 336 ± 316CH3HCH4CH473C, H338% ± 442% ± 210% ± 117I1(1-methyl-3-isobutyl-8-azaxanthine)153-154H272C, H1335% ± 511.0% ± 1MIX (1-methyl-3-isobutyl-8-azaxanthine)MIX (1-methyl-3-isobutyl-8-azaxanthine)6.3 ± 115 ± 2MIX (1-methyl-3-isobutyl-8-isobutyl-8-isobutyl-8-isobutyl-8-isobutyl-8-azaxanthine)86 ± 5177 ± 3MIX (1-methyl-3-isobutyl-8-is	12       CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> OH       H       268 dec       EtOH       22       C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub> C, H       30% ± 1       23% ± 5         13       CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> OCOCH, H       H       197-198       EtOH       g       C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> C, H       43% ± 5       27% ± 5         14       CH <sub>3</sub> CH <sub>3</sub> CH <sub>2</sub> OCOCH, H       H       210-211       EtOH       g       C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> C, H       43% ± 5       27% ± 5       27% ± 5         15       CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> O       C, H       23% ± 4       25 ± 3       36 ± 3       36 ± 3         16       CH <sub>3</sub> CH <sub>3</sub> OLOCH, H       H       210-211       EtOH       69       C <sub>10</sub> H <sub>13</sub> N <sub>4</sub> O <sub>3</sub> C, H       23% ± 5       10% ± 1       36 ± 3       36 ± 3       36 ± 3       10% ± 1       11% (1-nethyl-3-isobutyl-3-isob	12       CH3       CH2CH_0H       H       268 dec       EtOH       22 $C_{9}H_{10}N_{0}O_{1}^{3}$ C, H       30% ± 1       23% ± 5       27% ± 5         13       CH3       CH2CH_0COCH3       H       197-198       EtOH $z_{1}^{2}$ $C_{9}H_{10}N_{0}O_{1}^{3}$ C, H       30% ± 1       23% ± 5       27% ± 5       10% ± 1       28% ± 4       42% ± 2       10% ± 1       28% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 5       10% ± 1       25% ± 1       25% ± 1       25% ± 1	11	CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Н	172-174	benzene	f	C12H,NO4	C, H	$26\% \pm 2$	$40\% \pm 1$
13       CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>4</sub> 43% ± 5 $27\% \pm 5$ $27\% \pm 5$ 14       CH <sub>3</sub> CH <sub>3</sub> CH <sub>4</sub> CH <sub>3</sub> CH       43% ± 5 $27\% \pm 5$ $52 \pm 3$ $56 \pm 3$ $52 \pm 3$ $56 \pm 3$ $36 \pm 3$ $16 + 10^{12}$ $16 + 10^{12}$ $10^{12}$ $210 \pm 3$ $36 \pm 3$ $36 \pm 3$ $36 \pm 3$ $10\% \pm 1$	13 $CH_3$ $CH_2CH_2OCCH_3$ H $197-198$ $EtOH$ $g$ $C_{i0}H_{12}N_4O_4$ $C, H$ $43\% \pm 5$ $27\% \pm 5$ 14 $CH_3$ $CH_2CH_2CH_2$ H $210-211$ $EtOH$ $73$ $C_3H_{10}N_2O_2$ $C, H$ $25\pm 3$ $52\pm 3$ $10\% \pm 1$ $11\% \pm 1$ $11\% \pm 2$ $117$ $117\pm 3$ $117\pm 3$ $117\pm 3$ $117\pm 3$ $110\pm 3$ $110\pm 3$ $117\pm 3$ $117\pm 3$ $1$	13       CH3       CH3       CH3       CH4       197-198       BtOH $g$ C <sub>10</sub> H <sub>1</sub> N <sub>1</sub> O <sub>1</sub> C, H       43% ± 5       27% ± 5         14       CH3       CH3       C, H <sub>1</sub> O <sub>1</sub> O <sub>1</sub> C, H       25 ± 3       52 ± 3       52 ± 3       52 ± 3       55 ± 3       56 ± 3       55 ± 3       56 ± 3       10% ± 1 <td>13 CH<sub>3</sub> CH<sub>3</sub> CH<sub>2</sub>CH<sub>2</sub>OCOCH<sub>3</sub> H 197-198 EtOH <i>g</i> C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub> C, H 43% ± 5 27% ± 5 27% ± 5 14 CH<sub>3</sub> CH<sub>3</sub>CH<sub>2</sub>CH<sub>4</sub>CH<sub>4</sub>CH<sub>4</sub>CH<sub>4</sub> H 25 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 16 CH<sub>3</sub>CH<sub>2</sub>CH(CH<sub>3</sub>) CH<sub>3</sub>C(CH<sub>3</sub>)=CH<sub>4</sub> H 200 ± 0 C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub> C, H 205 ± 100 ± 3 36 ± 3 15 (1-methyl-3-isobutyl*8-azaxanthine) H 26 20 <math>C_{10}H_{13}N_{3}O_{3}</math> C, H, N 35% ± 4 <math>42\%</math> ± 2 10% ± 1 <math>17</math> (1-methyl-3-isobutyl*8-azaxanthine) H 25 213-215 H 1<sub>2</sub>O 72 C<sub>9</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 1X (1-methyl-3-isobutyl*8-azaxanthine) H 153-154 H<sub>2</sub>O 72 C<sub>9</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 1X (1-methyl-3-isobutyl*8-azaxanthine) H 100 ± 9 190 ± 6 <math>C_{14}H_{20}N_{13}N_{5}O_{3}</math> C, H, N 35% ± 5 1.0% ± 1 <math>17 \pm 3</math> theophylline <math>TX</math> (1-methyl-3-isobutyl*8-bromoxanthine) H 17 (1-methyl-3-isobutyl*8-azaxanthine) H 100 ± 9 190 ± 6 <math>C_{14}H_{20}N_{13}N_{5}O_{3}</math> C, H, N 35% ± 5 1.0% ± 1 <math>15\%</math> gield from 1-methyl-3-isobutyl*8-bromoxanthine) H 100 ± 9 190 ± 6 <math>C_{14}H_{20}N_{13}N_{5}O_{3}</math> C, H, N 35% ± 5 1.0% ± 1 <math>15\%</math> gield from 1-methyl-3-isobutyl*8-bromoxanthine<sup>3</sup> in 57% yield. <sup><i>A</i></sup> Prepared from 1-methyl+3-isobutyl*8-bromoxanthine<sup>3</sup> in 57% yield. <sup><i>A</i></sup> Prepared from 1-methyl-3-isobutyl*8-bromoxanthine<sup>3</sup> in 57% yield. <sup><i>A</i></sup> Prepared from 1-methyl-3-isobutyl*8-bromoxanthine<sup>3</sup> in 57% yield. <sup><i>A</i></sup> Prepared from 1-methyl-3-isobutyl*8-bromoxanthine<sup>3</sup> in 57% yield. <sup><i>A</i></sup> Prepared from 1-methyl-3-isobutyl*8-bromoxanthine yield (<i>A</i> Prepared</td> <td>12</td> <td>CH</td> <td>CH<sub>3</sub>CH<sub>3</sub>OH</td> <td>Н</td> <td>268 dec</td> <td>EtOH</td> <td>22</td> <td>C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub></td> <td>C, H</td> <td><math>30\% \pm 1</math></td> <td><math>23\% \pm 2</math></td>	13 CH <sub>3</sub> CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub> H 197-198 EtOH <i>g</i> C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub> C, H 43% ± 5 27% ± 5 27% ± 5 14 CH <sub>3</sub> CH <sub>3</sub> CH <sub>2</sub> CH <sub>4</sub> CH <sub>4</sub> CH <sub>4</sub> CH <sub>4</sub> H 25 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 52 ± 3 16 CH <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) CH <sub>3</sub> C(CH <sub>3</sub> )=CH <sub>4</sub> H 200 ± 0 C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> C, H 205 ± 100 ± 3 36 ± 3 15 (1-methyl-3-isobutyl*8-azaxanthine) H 26 20 $C_{10}H_{13}N_{3}O_{3}$ C, H, N 35% ± 4 $42\%$ ± 2 10% ± 1 $17$ (1-methyl-3-isobutyl*8-azaxanthine) H 25 213-215 H 1 <sub>2</sub> O 72 C <sub>9</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 1X (1-methyl-3-isobutyl*8-azaxanthine) H 153-154 H <sub>2</sub> O 72 C <sub>9</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 1X (1-methyl-3-isobutyl*8-azaxanthine) H 100 ± 9 190 ± 6 $C_{14}H_{20}N_{13}N_{5}O_{3}$ C, H, N 35% ± 5 1.0% ± 1 $17 \pm 3$ theophylline $TX$ (1-methyl-3-isobutyl*8-bromoxanthine) H 17 (1-methyl-3-isobutyl*8-azaxanthine) H 100 ± 9 190 ± 6 $C_{14}H_{20}N_{13}N_{5}O_{3}$ C, H, N 35% ± 5 1.0% ± 1 $15\%$ gield from 1-methyl-3-isobutyl*8-bromoxanthine) H 100 ± 9 190 ± 6 $C_{14}H_{20}N_{13}N_{5}O_{3}$ C, H, N 35% ± 5 1.0% ± 1 $15\%$ gield from 1-methyl-3-isobutyl*8-bromoxanthine <sup>3</sup> in 57% yield. <sup><i>A</i></sup> Prepared from 1-methyl+3-isobutyl*8-bromoxanthine <sup>3</sup> in 57% yield. <sup><i>A</i></sup> Prepared from 1-methyl-3-isobutyl*8-bromoxanthine yield ( <i>A</i> Prepared	12	CH	CH <sub>3</sub> CH <sub>3</sub> OH	Н	268 dec	EtOH	22	C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub>	C, H	$30\% \pm 1$	$23\% \pm 2$
14       CH <sub>3</sub> CH <sub>2</sub> CH=CH <sub>2</sub> H $210-211$ EtOH       73 $C_{3}H_{10}N_{2}O_{3}$ C, H $25\pm3$ $52\pm3$ $52\pm3$ $52\pm3$ $55\pm3$ $56\pm3$ $36\pm3$ $36\pm3$ $36\pm3$ $36\pm3$ $36\pm3$ $16$ $C_{10}H_{12}N_{0}O_{2}$ $h$ $10\pm3$ $36\pm3$ $36\pm3$ $10\pm3$ $10\pm3$ $36\pm3$ $10\pm3$ $36\pm3$ $10\pm3$ $10\pm3$ $36\pm3$ $10\pm3$ $10\pm4$ $10\pm3$ $10\pm3$ $10\pm4$ $10\pm3$ $10\pm4$ $10\pm3$ $10\pm4$ $10\pm3$ $10\pm4$ $10\pm3$ $10\pm3$ $10\pm3$ $10\pm4$ $10\pm3$ $10\pm3$ $10\pm3$ $10\pm2$ $10\pm3$ $10\pm4$ $10\pm3$ $10\pm4$ $10\pm4$ $10\pm4$ $10\pm4$ $10\pm4$ $10\pm4$	14       CH <sub>3</sub> CH <sub>1</sub> CH <sub>2</sub> CH <sub>2</sub> H       210-211       BtOH       73       C <sub>3</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> C, H       25 ± 3       52 ± 3       36 ± 3       10% ± 1       36% ± 1 <td< td=""><td>14       CH<sub>3</sub>       CH<sub>2</sub>CH=CH<sub>2</sub>       H       210-211       BtOH       73       <math>C_{9}H_{10}N_{2}O_{2}</math>       C, H       25 ± 3       52 ± 3       52 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       10 ± 3       10 ± 3       10 ± 4       10 ±</td><td>14<math>CH_3</math><math>CH_2CH=CH_2</math><math>H</math><math>210-211</math><math>BtOH</math><math>73</math><math>C_9H_{10}N_0O_3</math><math>C_1</math><math>25 \pm 3</math><math>52 \pm 3</math><math>52 \pm 3</math>15<math>CH_3</math><math>CH_3</math><math>CH_3</math><math>CH_3</math><math>CH_3</math><math>H_4</math><math>213-215</math><math>BtOH</math><math>69</math><math>C_{10}H_{12}N_0O_3</math><math>h</math><math>100 \pm 3</math><math>36 \pm 3</math>16<math>CH_3</math><math>CH_3</math><math>CH_3</math><math>CH_3</math><math>CH_3</math><math>CH_3</math><math>100 \pm 3</math><math>36 \pm 3</math><math>36 \pm 3</math>16<math>CH_3</math><math>CH_3</math><math>CH_3</math><math>CH_3</math><math>CH_3</math><math>100 \pm 3</math><math>100 \pm 3</math><math>100 \pm 3</math>17<math>(1-methyl-3-isobutyl-8-azarathine)^R</math><math>I_3</math><math>I_3</math><math>I_4</math><math>I_2</math><math>I_2</math><math>I_2</math><math>IIX</math><math>(1-methyl-3-isobutyl-8-azarathine)^R</math><math>I_3</math><math>I_3</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>IIX</math><math>(1-methyl-3-isobutyl-8-azarathine)^R</math><math>I_3</math><math>I_3</math><math>I_4</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math><math>I_2</math></td><td>13</td><td>CH<sub>3</sub></td><td>CH,CH,OCOCH,</td><td>Н</td><td>197-198</td><td>EtOH</td><td>00</td><td>C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub></td><td>C, H</td><td><math>43\% \pm 5</math></td><td><math>27\% \pm 5</math></td></td<>	14       CH <sub>3</sub> CH <sub>2</sub> CH=CH <sub>2</sub> H       210-211       BtOH       73 $C_{9}H_{10}N_{2}O_{2}$ C, H       25 ± 3       52 ± 3       52 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       55 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       36 ± 3       10 ± 3       10 ± 3       10 ± 3       10 ± 4       10 ±	14 $CH_3$ $CH_2CH=CH_2$ $H$ $210-211$ $BtOH$ $73$ $C_9H_{10}N_0O_3$ $C_1$ $25 \pm 3$ $52 \pm 3$ $52 \pm 3$ 15 $CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$ $H_4$ $213-215$ $BtOH$ $69$ $C_{10}H_{12}N_0O_3$ $h$ $100 \pm 3$ $36 \pm 3$ 16 $CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$ $100 \pm 3$ $36 \pm 3$ $36 \pm 3$ 16 $CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$ $100 \pm 3$ $100 \pm 3$ $100 \pm 3$ 17 $(1-methyl-3-isobutyl-8-azarathine)^R$ $I_3$ $I_3$ $I_4$ $I_2$ $I_2$ $I_2$ $IIX$ $(1-methyl-3-isobutyl-8-azarathine)^R$ $I_3$ $I_3$ $I_2$ $I_2$ $I_2$ $I_2$ $I_2$ $IIX$ $(1-methyl-3-isobutyl-8-azarathine)^R$ $I_3$ $I_3$ $I_4$ $I_2$	13	CH <sub>3</sub>	CH,CH,OCOCH,	Н	197-198	EtOH	00	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub>	C, H	$43\% \pm 5$	$27\% \pm 5$
15       CH <sub>3</sub> CH <sub>3</sub> CH <sub>2</sub> C(CH <sub>3</sub> )=CH <sub>1</sub> H       213-215       EtOH       69 $C_{10}H_{13}N_{0}O_{1}$ h       10±3       36±3       36±3         16       CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>1</sub> CH <sub>2</sub> C(CH <sub>3</sub> )=CH <sub>1</sub> H       213-215       EtOH       69 $C_{10}H_{13}N_{0}O_{1}$ h       10±3       36±3       42%±2         17       (1-methyl-3-isobutyl-8-azaxanthine) <sup>k</sup> H       153-154       H <sub>2</sub> O       72 $C_{9}H_{13}N_{5}O_{2}$ C       H       85%±5       1.0%±1         MIX (1-methyl-3-isobutylxanthine) <sup>k</sup> IS3-154       H <sub>2</sub> O       72 $C_{9}H_{13}N_{5}O_{2}$ C       H, N       35%±5       1.1%±2         MIX (1-methyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> II       I53-154       H <sub>2</sub> O       72       C <sub>9</sub> H_{13}N_{5}O_{2}       C       H, N       35%±5       II       15±2         MIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> III       III </td <td>15       CH3       CH3       CH4C(CH3)       CCH2       H       213-215       EtOH       69       Cu<sub>0</sub>H<sub>13</sub>N<sub>4</sub>O2       h       10±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±2       36±2       36±3       36±3       36±3       36±2       10±3       36±2       10±3       36±2       10±3       36±2       10±3       36±5       110±3       36±5       110±3       36±5       110±4       35±2       10±5±2       20±2       10±3       36±5       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       31±2       35±2       31±2       35±2       31±2       31±2       35±2       31±2       31±2       31±2       35±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2</td> <td>15 CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> H 213-215 EtOH 69 C<sub>10</sub>H<sub>13</sub>N<sub>4</sub>O<sub>3</sub> h 10 ± 3 36 ± 3 16 ± 3 16 CH<sub>3</sub>CH<sub>3</sub>)= CH<sub>3</sub> H 2CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> CH<sub>3</sub>CH<sub>3</sub> H 2S ± 4 42% ± 2 17 (1-methyl-3-isobutyl-8-azaranthine)<sup>k</sup> 1.0% ± 1 153-154 H<sub>2</sub>O 72 C<sub>3</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub> C, H, N 35% ± 5 1.15% ± 1 15 ± 2 MIX (1-isoantyl-3-isobutylxanthine)<sup>k</sup> 1.0% ± 1 153-154 H<sub>2</sub>O 72 C<sub>3</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub> C, H, N 35% ± 5 1.15 ± 2 17 ± 3 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 10 thethyl-3-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl</td> <td>15 CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> CH<sub>4</sub> C(CH<sub>3</sub>)=CH<sub>2</sub> H 213-215 EtOH 69 C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub> h 10±3 36±3 36±3 169-170 benzene 40 C<sub>14</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub> i 38% ± 4 42% ± 2 1.0% ± 1 15 ± 2 17 (1-methyl-3-isobutyl-8-azaranthine)<sup>k</sup> H 153-154 H<sub>2</sub>O 72 C<sub>9</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 11X (1-isobutyl-8-isobutyl-8-azaranthine)<sup>k</sup> 1.0% ± 1 153-154 H<sub>2</sub>O 72 C<sub>9</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 11X (1-isobutyl-8-isobutyl-8-azaranthine)<sup>k</sup> 1.0% ± 1 153-154 H<sub>2</sub>O 72 C<sub>9</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 155 ± 2 11X (1-isobutyl-8-isobutyl-8-isobutyl-8-azaranthine)<sup>k</sup> a theophyline are staticated from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Mat interval to the oncentrations of 1-methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 50% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 50% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine<sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation</td> <td>14</td> <td>CH<sub>3</sub></td> <td>CH<sub>2</sub>CH=CH<sub>2</sub></td> <td>Н</td> <td>210-211</td> <td>EtOH</td> <td>73</td> <td><math>C_{9}H_{10}N_{2}O_{2}</math></td> <td>C, H</td> <td><math>25 \pm 3</math></td> <td><math>52 \pm 3</math></td>	15       CH3       CH3       CH4C(CH3)       CCH2       H       213-215       EtOH       69       Cu <sub>0</sub> H <sub>13</sub> N <sub>4</sub> O2       h       10±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±3       36±2       36±2       36±3       36±3       36±3       36±2       10±3       36±2       10±3       36±2       10±3       36±2       10±3       36±5       110±3       36±5       110±3       36±5       110±4       35±2       10±5±2       20±2       10±3       36±5       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       117±3       35±2       31±2       35±2       31±2       35±2       31±2       31±2       35±2       31±2       31±2       31±2       35±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2       31±2	15 CH <sub>3</sub> H 213-215 EtOH 69 C <sub>10</sub> H <sub>13</sub> N <sub>4</sub> O <sub>3</sub> h 10 ± 3 36 ± 3 16 ± 3 16 CH <sub>3</sub> CH <sub>3</sub> )= CH <sub>3</sub> H 2CH <sub>3</sub> CH <sub>3</sub> H 2S ± 4 42% ± 2 17 (1-methyl-3-isobutyl-8-azaranthine) <sup>k</sup> 1.0% ± 1 153-154 H <sub>2</sub> O 72 C <sub>3</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> C, H, N 35% ± 5 1.15% ± 1 15 ± 2 MIX (1-isoantyl-3-isobutylxanthine) <sup>k</sup> 1.0% ± 1 153-154 H <sub>2</sub> O 72 C <sub>3</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> C, H, N 35% ± 5 1.15 ± 2 17 ± 3 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 9 100 ± 10 thethyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl	15 CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>4</sub> C(CH <sub>3</sub> )=CH <sub>2</sub> H 213-215 EtOH 69 C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> h 10±3 36±3 36±3 169-170 benzene 40 C <sub>14</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> i 38% ± 4 42% ± 2 1.0% ± 1 15 ± 2 17 (1-methyl-3-isobutyl-8-azaranthine) <sup>k</sup> H 153-154 H <sub>2</sub> O 72 C <sub>9</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 11X (1-isobutyl-8-isobutyl-8-azaranthine) <sup>k</sup> 1.0% ± 1 153-154 H <sub>2</sub> O 72 C <sub>9</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 15 ± 2 11X (1-isobutyl-8-isobutyl-8-azaranthine) <sup>k</sup> 1.0% ± 1 153-154 H <sub>2</sub> O 72 C <sub>9</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> C, H, N 35% ± 5 1.0% ± 1 155 ± 2 11X (1-isobutyl-8-isobutyl-8-isobutyl-8-azaranthine) <sup>k</sup> a theophyline are staticated from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Mat interval to the oncentrations of 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation to 1-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>h</sup> Structure stabilished by hydrogenation	14	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	Н	210-211	EtOH	73	$C_{9}H_{10}N_{2}O_{2}$	C, H	$25 \pm 3$	$52 \pm 3$
16 $CH_{5}CH_{5}CH_{5}(CH_{3})_{1}$ $CH_{2}C(CH_{3})_{1}$ $CH_{2}C(CH_{3})_{1}$ $38\% \pm 4$ $42\% \pm 2$ 17 $(1 - methy) - 3 - isobuty) - 8 - azaxanthine)^{k}$ $153 - 154$ $H_{2}O$ $72$ $C_{9}H_{13}N_{5}O_{1}$ $C, H, N$ $35\% \pm 5$ $1.0\% \pm 1$ $MIX$ (1-methy) - 3 - isobuty) ranthine)^{k} $153 - 154$ $H_{2}O$ $72$ $C_{9}H_{13}N_{5}O_{1}$ $C, H, N$ $35\% \pm 5$ $1.0\% \pm 1$ $MIX$ (1-methy) - 3 - isobuty) ranthine)^{k} $1.53 - 154$ $H_{2}O$ $72$ $C_{9}H_{13}N_{5}O_{1}$ $C, H, N$ $35\% \pm 5$ $1.0\% \pm 1$ $MIX$ (1-methy) - 3 - isobuty) ranthine)^{k} $1.53 - 154$ $H_{2}O$ $72$ $C_{9}H_{13}N_{5}O_{1}$ $C, H, N$ $35\% \pm 5$ $1.0\% \pm 2$ $MIX$ (1-isoamy) - 3 - isobuty) ranthine)^{k} $1.73 \pm 3$ $1.73 \pm 3$ $1.73 \pm 3$ $1.00 \pm 9$ $190 \pm 6$	16 $CH_3CH_3CH(CH_3)$ , $CH_3C(CH_3)=CH_2$ H 169-170 benzene 40 $C_{i4}H_{20}N_4O_2$ i 38% ± 4 42% ± 2 17.0% ± 1 MIX (1-methyl-3-isobutyl*anthine) <sup>k</sup> MIX (1-methyl-3-isobutyl*anthine) <sup>k</sup> MIX (1-methyl-3-isobutyl*anthine) <sup>k</sup> MIX (1-methyl-3-isobutyl*anthine) <sup>k</sup> MIX (1-methyl-3-isobutyl*anthine) <sup>k</sup> $17 \pm 3$ $100 \pm 9$ $100 \pm 9$ $100 \pm 6$ $17 \pm 3$ $100 \pm 6$ $100 \pm 6$	16 $CH_{3}(H_{3}(CH_{3})_{1}$ $CH_{2}(CH_{3})_{2}$ $CH_{2}(CH_{3})_{2}$ $CH_{3}(CH_{3})_{3}$ $CH_{3}(CH_{3})_{4}$ $CH_{3}(CH_{3})_{3}$ $CH_{3}(CH_{3})_{4}$ $CH_{3}(CH_{3})_{3}$ $CH_{3}(CH_{3})_{3}$ $CH_{3}(CH_{3})_{3}$ $CH_{3}(H_{3}N_{3}O_{3}$ $CH_{3}(H_{3}N_{3}O_{3})_{3}$ $CH_{3}(H_{3}N_{3})_{3}$ $CH_{3}(H_{3}N_{3})_{$	16 $CH_{3}(H_{3}CH_{3}(CH_{3})_{2}$ $CH_{2}(CH_{3})_{2}$ $CH_{2}(CH_{3})_{2}$ $CH_{2}(CH_{3})_{4}$ $CH_{3}(CH_{3})_{4}$ $CH_{3}(H_{3}N_{3}O_{3}$ $CH_{3}(H_{3}N_{3}O_{3})_{4}$	15	CH,	$CH_{2}C(CH_{3})=CH_{2}$	Н	213-215	EtOH	69	$C_{10}H_{12}N_4O_2$	Ч	$10 \pm 3$	$36 \pm 3$
17 (1-methyl-3-isobutyl-8-azaxanthine)153-154 $H_2O$ 72 $C_9H_{13}N_sO_2$ $C, H, N$ $35\% \pm 5$ $1.0\% \pm 1$ MIX (1-methyl-3-isobutylxanthine) $k$ $153-154$ $H_2O$ $72$ $C_9H_{13}N_sO_2$ $C, H, N$ $35\% \pm 5$ $11.0\% \pm 1$ IIX (1-isoamyl-3-isobutylxanthine) $k$ $17 \pm 3$ $17 \pm 3$ $17 \pm 3$ $100 \pm 9$ $190 \pm 6$	17 (1-methyl-3-isobutyl-8-azaxanthine)153-154H <sub>2</sub> O72C <sub>9</sub> H <sub>13</sub> N <sub>5</sub> O <sub>2</sub> C, H, N35% ± 51.0% ± 1MIX (1-methyl-3-isobutylxanthine)6.3 ± 115 ± 2 $1.0\% \pm 1$ $15 \pm 2$ $1.7 \pm 3$ IIX (1-isoanyl-3-isobutylxanthine)6.3 ± 1 $1.5 \pm 2$ $1.0\% \pm 1$ $1.7 \pm 3$ IIX (1-isoanyl-3-isobutylxanthine)6.3 ± 1 $1.7 \pm 3$ $1.7 \pm 3$ IIX (1-isoanyl-3-isobutylxanthine)6.3 ± 1 $1.7 \pm 3$ $1.00 \pm 9$ $190 \pm 6$ $^{a}$ Vield from 1, 3-disubstituted 5-nitroso-6-aminouracil $^{b}$ Prepared from 3 in 67% yield. $^{c}$ Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. $^{d}$ Prepared	17 (1-methyl-3-isobutyl-8-azaxanthine)153-154 $H_2O$ 72 $C_9H_{13}N_5O_2$ $C, H, N$ $35\% \pm 5$ $1.0\% \pm 1$ MIX (1-methyl-3-isobutylxanthine) <sup>k</sup> $1.0\% \pm 1$ $1.0\% \pm 1$ $1.0\% \pm 1$ $1.0\% \pm 1$ MIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> $1.0\% \pm 1$ $1.0\% \pm 1$ $1.0\% \pm 1$ IX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> $1.0\% \pm 1$ $1.0\% \pm 1$ $1.0\% \pm 1$ IX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> $1.0\% \pm 1$ $1.0\% \pm 1$ $1.\% \pm 3$ IA (1-isoamyl-3-isobutyl-3-isobutyl-3-isobutyl-8-bromozanthine <sup>3</sup> in 50\% yield. $e$ Prepared from 1methyl-3-isobutyl-8-bromozanthine <sup>3</sup> in 50\% yield. $e$ Prepared from 1.0 in 68\% yield. $e$ Prepared from 1methyl-3-isobutyl-8-bromozanthine <sup>3</sup> in 50\% yield. $h$ Structureat Null-3-isobutyl-8-bromozanthine <sup>3</sup> in 50\% yield. $e$ Prepared from 1.0 in 68\% yield. $e$ Prepared from 1.0 in 68\% yield. $e$ Prepared from 1.0 in 68\% yield. $h$ Structure	17 (1-methyl-3-isobutyl-8-azaxanthine) 17 (1-methyl-3-isobutyl-8-azaxanthine) MIX (1-methyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutyl-8-isobutyl-8-isobutyl-8-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1.4 isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1.4 isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>e</sup> Prepared from 1.5 isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>d</sup> Prepared from 1.6 isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>e</sup> Prepared from 1.5 isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>e</sup> Prepared from 1.5 isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>d</sup> Prepared from 1.6 in 68% yield. <sup>e</sup> Prepared from 1.4 in 7 in 78% yield. <sup>f</sup> Prepared from 1.0 in 68% yield. <sup>e</sup> Prepared from 1.8 in 50% yield. <sup>h</sup> Structure is the concentrations of 1.4 in 9 in 61% yield. <sup>f</sup> Prepared from 1.0 in 68% yield. <sup>e</sup> Prepared from 1.4 in 7 in 78% yield. <sup>h</sup> Structure is the concentrations of 1.4 in 9 in 61% yield. <sup>f</sup> Prepared from 1.0 in 68% yield. <sup>e</sup> Prepared from 1.6 in 1.8 in 51% yield. <sup>h</sup> Structure is the concentrations of 1.4 in 9 in 1.6 in 1.5 in 9.5 in 9	16	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	$CH_{2}C(CH_{3}) = CH_{2}$	Н	169 - 170	benzene	40	C <sub>14</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub>	•••	$38\% \pm 4$	$\mathbf{42\%} \pm 2$
$\begin{array}{cccc} \text{MIX} (1-\text{methyl}-3-\text{isobutylxanthine})^k & \text{6.3 \pm 1} & 15 \pm 2 \\ \text{6.3 \pm 1} & 17 \pm 3 \\ \text{86 \pm 5} & 17 \pm 3 \\ \text{100 \pm 9} & 190 \pm 6 \\ \text{100 \pm 9} & 190 \pm 6 \end{array}$	MIX (1-methyl-3-isobutylxanthine) <sup>k</sup> IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> $86 \pm 5$ $17 \pm 3$ $100 \pm 9$ $100 \pm 9$ $100 \pm 6$ a Yield from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared	MIX (1-methyl-3-isobutylxanthine) <sup>k</sup> IX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> IX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> theophylline <sup>a</sup> Yield from 1,3-disubstituted 5-nitroso-6-aminouracil. <sup>b</sup> Prepared from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 10 in 68% yield. <sup>e</sup> Prepared from 12 in 83% yield. <sup>d</sup> Structure at Nuclear theorem of MIX <sup>i</sup> Structure of MIX <sup>i</sup> S	<ul> <li>MIX (1-methyl-3-isobutylxanthine)<sup>k</sup></li> <li>MIX (1-isoamyl-3-isobutylxanthine)<sup>k</sup></li> <li>IX (1-isoamyl-3-isobutylxanthine)<sup>k</sup></li> <li>IX (1-isoamyl-3-isobutyl-3-i</li></ul>	17 (1	-methyl-3-isobutyl-8	3-azaxanthine)		153 - 154	$H_2O$	72	C <sub>0</sub> H <sub>13</sub> N <sub>5</sub> O <sub>2</sub>	C, H, N	$35\% \pm 5$	$1.0\% \pm 1$
IIX $(1-isoamy -3-isobuty xanthine)^k$ theophylline $100 \pm 9$ $190 \pm 6$	IIX (1-isoamyl-3-isobutylxanthine) <sup>#</sup> theophylline <sup>a</sup> Yield from 1,3-disubstituted 5-nitroso-6-aminouracil. <sup>b</sup> Prepared from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared	<ul> <li>IIX (1-isoamyl-3-isobutylxanthine)<sup>k</sup></li> <li>190 ± 5</li> <li>190 ± 6</li> <li>100 ± 9</li> <li>1</li></ul>	IIX (1-isoamyl-3-isobutylxanthine) <sup>k</sup> 86 ± 5 17 ± 3 theophylline <sup>86</sup> ± 5 17 ± 3 190 ± 6 190 ± 6 theophylline <sup>a</sup> Yield from 1,3-disubstituted 5-nitroso-6-aminouracil. <sup>b</sup> Prepared from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>d</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>d</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>h</sup> Structure isstablished by hydrosoff from 1. <sup>d</sup> Antholusi from 1. <sup>d</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 1. <sup>h</sup> Structure isstablished by hydrosoff from 1. <sup>h</sup> Antholusi from 1. <sup>h</sup> A	MIX	(1-methyl-3-isobuty)	lxanthine) <sup>k</sup>			I		1		$6.3 \pm 1$	$15 \pm 2$
the ophylline $100 \pm 9$ $190 \pm 6$	the ophylline $a$ Yield from 1,3-disubstituted 5-nitroso-6-aminouracil. <sup>b</sup> Prepared from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared	theophylline $100 \pm 9$ $100 \pm 10$ $100 \pm 100$ $1000 \pm 100$ $1000 \pm 1000$ $1000 \pm 1000$ $1000 \pm 1000$ $1000 \pm 1000$ $10000 \pm 10000$ $10000000$ $10000000000000000000$	theophylline $190 \pm 6$ $190 \pm 10$ $100 \pm 100$ $10$	IIX (C	l-isoamyl-3-isobutyl	txanthine) <sup>k</sup>							86 ± 5	$17 \pm 3$
	<sup>a</sup> Yield from 1,3-disubstituted 5-nitroso-6-aminouracil. <sup>b</sup> Prepared from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared	<sup>a</sup> Yield from 1,3-disubstituted 5-nitroso-6-aminouracil. <sup>b</sup> Prepared from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1 -methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>e</sup> Prepared from 7 in 78% yield. <sup>f</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 12 in 83% yield. <sup>h</sup> Structure from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>h</sup> Structure from 10 in 68% yield. <sup>g</sup> Prepared from 7 in 78% yield. <sup>f</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 12 in 83% yield. <sup>h</sup> Structure from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>h</sup> Structure from 10 in 68% yield. <sup>g</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 12 in 83% yield. <sup>h</sup> Structure from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>h</sup> Structure from 10 in 68% yield. <sup>g</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 1-methyle from 12 in 83% yield. <sup>h</sup> Structure from 1-methyle from 10 in 68% yield. <sup>g</sup> Prepared from 1-methyle from 1-me	<sup>a</sup> Yield from 1,3-disubstituted 5-nitroso-6-aminouracil. <sup>b</sup> Prepared from 3 in 67% yield. <sup>c</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 57% yield. <sup>d</sup> Prepared from 1-methyl-3-isobutyl-8-bromoxanthine <sup>3</sup> in 50% yield. <sup>e</sup> Prepared from 7 in 78% yield. <sup>f</sup> Prepared from 10 in 68% yield. <sup>g</sup> Prepared from 12 in 83% yield. <sup>h</sup> Structure stabilished by hydrogenation to MIX. <sup>i</sup> Structure established by hydrogenation to 1-isoamyl-3-isobutyl*anthine. <sup>j</sup> $I_{so}$ values are the concentrations of inhibitor ( $\mu$ M) that in the hydrodenation to MIX. <sup>i</sup> Structure established by hydrogenation to 1-isoamyl-3-isobutyl*anthine. <sup>j</sup> $I_{so}$ values are the concentrations of inhibitor ( $\mu$ M) that interval of the hydrodenation to MIX. <sup>i</sup> Structure established by hydrogenation to 1-isoamyl-3-isobutyl*anthine. <sup>j</sup> $I_{so}$ values are the concentrations of inhibitor ( $\mu$ M) that interval of the hydrodenation to MIX. <sup>i</sup> Structure established by hydrogenation to 1-isoamyl-3-isobutyl*anthine. <sup>j</sup> $I_{so}$ values are the concentrations of inhibitor ( $\mu$ M) that interval of the hydrodenation to MIX.	theor	hylline								$100 \pm 9$	$190 \pm 6$



**Figure 1.** Hypothetical topographical map of the active sites of calmodulin-sensitive (peak I, left panel) and "cyclic AMP specific" (peak II, right panel) forms of phosphodiesterase. The upper panels represent the binding of the high-affinity substrates to the respective active sites, while the lower panels represent binding of a generalized xanthine to the active sites.

phosphodiesterase. If this is true, information concerning the nature of the active sites can be drawn both from a knowledge of the substrates and from the SAR of the inhibitors. Energy calculations indicate that the "syn" conformation of cyclic GMP is strongly preferred, while the "anti" conformation is somewhat preferred by cyclic AMP.<sup>5</sup> To help account for the specificity of the two enzymes, it is assumed that the active sites accomodate their high-affinity substrate in its "preferred" conformation. Inspection of molecular models of the cyclic nucleotides in their "preferred" conformations will reveal that the ribose phosphate moiety which lies perpendicular to the plane of the purine ring is bisected by that plane into two very dissimilar sides. One side contains the 2' and 3'carbons, the charged phosphate moiety, and the 2'hydroxyl and, thus, presents a relatively hydrophilic surface. The other side, however, contains only the 1', 4', and  $5^\prime$  carbons, the ether oxygen, and the  $5^\prime\text{-ester}$  oxygen and is relatively nonpolar. It is assumed that the catalytic sites of both peak I and peak I type phosphodiesterases bind to this more nonpolar portion of the ribose moieties of cyclic GMP and cyclic AMP, respectively. Some support for this assumption is found in a report that replacement of the charged phosphate group by an uncharged sulfate does not appreciably reduce the affinity of cyclic AMP for the catalytic site of phosphodiesterase.<sup>6</sup> A further suggestion that the polar portion of the ribose-phosphate moiety is not required for binding to the catalytic sites is found in the high apparent affinity of some inhibitors for these sites. Papaverine, which lacks polar substituents, inhibits peak II hydrolysis of 1 µM cyclic AMP by 50% at 3  $\mu$ M,<sup>7</sup> and MIX, also lacking polar substituents, inhibits by 50% the hydrolysis of 1  $\mu$ M cyclic GMP by peak I at 6.3  $\mu$ M. Thus, the affinity of these inhibitors apparently approaches that of the high-affinity substrates. Replacement of the 3-methyl group of theophylline with larger and

more lipophillic groups (i.e., isobutyl to give MIX) dramatically increases the potency of the xanthine to inhibit both forms of phosphodiesterase. It seems reasonable to assume that, since both enzyme forms are involved in the hydrolysis of an essentially identical 3',5'-ribose cyclic phosphate, the ribose binding areas would be similar, perhaps having been conserved during evolution. Since variation of substituents at the 3 position of xanthine has similar effects on the potencies against both enzyme forms while variation of other positions has different effects, it is assumed that the 3-substituent of the xanthine is bound at the ribose binding sites. As shown in the upper panels of Figure 1, we envision this site as accommodating the nonpolar portion of the ribose phosphate while excluding the polar phosphate and hydroxyl groups of the cyclic nucleotides. Evidence indicates that the hydrolytic sites of peak I and peak II differ from each other essentially in the manner in which they accommodate the purine moiety of the cyclic nucleotides. These sites also differ in the manner in which they bind the xanthine ring of the inhibitors. The maps shown in Figure 1 account for these differences in part by reversing the orientation of the bicyclic ring binding sites. It is clear from the data in Table I and ref 3 that changes in the electronic properties of the xanthine ring have profound effects on inhibitory potencies against both peak I and peak II phosphodiesterases. The data do not indicate how these electronic effects are expressed. We have, therefore, depicted this binding in Figure 1 by labeling the sites as "pyrimidine" and "imidazole", simply to indicate the asymmetric nature of these interactions and the essentially reversed orientations in the peak I and peak II active sites. The sterically hindered sites to the left of the ring binding sites in Figure 1 account for the reduced affinity of xanthines with large 1-substituents for peak I and for the reduced affinity of xanthines with 7- or 8-substituents for peak II. The areas with bulk tolerance indicated to the right of the ring binding sites account for the ability of peak I to accommodate 7- or 8-substituted xanthines and for the ability of peak II to accommodate xanthines with 1-substitutents larger than methyl.

Based upon this model, it would be predicted that increased alkyl bulk near the 6 position of the papaverine

<sup>(5)</sup> Yathindra, N.; Sundaralingam, M. Biochem. Biophys. Res. Commun. 1974, 56, 119.

<sup>(6)</sup> Severin, E. S.; Tkachuk, V. A.; Gulyaev, N. N. Biokhimiya 1976, 41(2), 384.

<sup>(7)</sup> Wells, J. N.; Wu, Y. J.; Baird, C. E.; Hardman, J. G. Mol. Pharmacol. 1975, 11, 775.

nucleus would lead to increased selectivity toward inhibition of peak II phosphodiesterase activity. The simple modification of replacing the 6-methoxyl with an isopropoxyl group does increase selectivity toward inhibition of peak II. This isopropoxyl analogue is one-half as potent as papaverine as an inhibitor of peak I activity but is 3-fold more potent than papaverine as an inhibitor of peak II activity (data not shown). Thus, while this working model of the topographical map of the two active sites is highly speculative, it does give some rational direction to the design of new phosphodiesterase inhibitors.

## **Experimental Section**

Melting points were determined in open glass capillary tubes using a Laboratory Devices Mel-Temp and are reported uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 257 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a JOEL Model JNM-MH-100 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Gailbraith Laboratories, Inc., Knoxville, TN. In all cases, spectral data were consistent with the proposed structures and elemental analyses were within  $\pm 0.4\%$ of the calculated values.

Phosphodiesterase Assay. The compounds were assayed for inhibitory activity against the separated forms of phosphodiesterase from pig coronary arteries (peaks I and II). Enzyme preparation and assay procedures have been reported.<sup>2,3,8</sup> Assays were performed with 1 µM substrate at 30 °C for 30 min at enzyme dilutions that gave 10-20% hydrolysis of substrate in the absence of inhibitor. MIX  $(10^{-5} \text{ and } 10^{-4} \text{ M})$  was included in each experiment to assure that the enzyme preparation was responding in a normal manner. The compounds were dissolved in 30%  $Me_2SO$ , and then 25  $\mu$ L of this solution was added to the assay tube (final volume was  $250 \,\mu$ L). All activities (including control and no-enzyme blank) were measured in the presence of 3% Me<sub>2</sub>SO. Product accumulation was linear for at least 30 min under the conditions of the assay. Compounds that were sufficiently soluble in aqueous buffer were also tested in the absence of Me<sub>2</sub>SO. The presence or absence of Me<sub>2</sub>SO had no effect on the potency of the xanthines as phosphodiesterase inhibitors (data not shown). None of the compounds altered the efficacy of the nucleotidase step or subsequent steps in the assay. Concentrations of the compounds that inhibited by 50% the hydrolysis of 1  $\mu$ M substrate  $(I_{50})$  were determined from concentration-percent inhibition curves, utilizing concentrations of the compounds from  $10^{-7}$  to  $10^{-4}$  M (or  $10^{-7}$  to  $10^{-3}$  M if the compound was sufficiently soluble). The more potent xanthines were competitive inhibitors of peak I phosphodiesterase, but  $K_i$  values are not reported, since the purpose of this study was to compare inhibition of the separated forms, and the apparently negatively cooperative behavior of peak II complicated the determination of  $K_i$  values with this enzyme. The presence or absence of calmodulin and/or calcium ion did not affect the activity of the compounds studied.

General Synthesis of Xanthines. The appropriate 1-substituted 6-aminouracil was prepared and alkylated following the procedure of Papesch and Schroeder<sup>9</sup> to give the 1,3-disubstituted 6-aminouracil. The crude aminouracil (5–10 mmol) was suspended or dissolved by warming in 20% HOAC (25 mL). Sodium nitrite

(15 mmol) in H<sub>2</sub>O was added dropwise to give the 5-nitroso-6aminouracil as a red or purple precipitate. The crude 5nitroso-6-aminouracil was dried in vaccuo. The dry 5-nitroso-6-aminouracil was suspended in methanol and hydrogenated over PtO2 at 50 psi of hydrogen in a Parr hydrogenator until the uptake of hydrogen had ceased. The catalyst was removed by filtration. and the volatiles were removed in vaccuo. The allyl- and methallylnitrosouracils were reduced to the diamines and isolated according to the method of Kramer et al.<sup>3</sup> The crude diaminouracil was dissolved in pyridine when reacted with about 1.5 equiv of an acid chloride or anhydride, but was reacted neat with excess hydroxyacetic acid, butyrolactone, or 97% formic acid. The mixture was heated to about 100 °C for 20 min. After the reaction was completed, the volatiles were removed and the residue was dissolved by heating under reflux in 10% sodium hydroxide for 20 min. The solution was cooled, extracted with benzene and/or methylene chloride to remove colored impurities, and then neutralized with HCl. The resulting precipitate was recrystallized from water or ethanol and water (Table I).

1-Methyl-3-isobutyl-8-azaxanthine (17). 3-Methyl-1-isobutyl-5,6-diaminouracil (2.1 g, 10 mmol) was dissolved in 20 mL of 1 N HCl, and then 2 equiv of NaNO<sub>2</sub> in 15 mL of H<sub>2</sub>O was added. The red precipitate that formed was collected by filtration and recrystallized from H<sub>2</sub>O.

1-Methyl-3-isobutyl-8-(chloromethyl)xanthine (4). 1-Methyl-3-isobutyl-8-(hydroxymethyl)xanthine (3; 800 mg, 3.2 mmol) was heated at 100 °C with 10 mL of  $POCl_3$  for 2.5 h. The volatiles were removed in vaccuo. The residue was recrystallized from ethanol.

1-Methyl-3-isobutyl-8-(methylamino)xanthine (5). 1-Methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> (1 g, 3.3 mmol) and 3 mL of 40% aqueous methylamine were dissolved in 3 mL of ethanol. The solution was heated at 130 °C for 12 h in a pressure tube. The volatiles were removed in vaccuo and the residue was extracted with 10% sodium hydroxide. The basic solution was decolorized by treatment with charcoal and then acidified with HOAc. The resulting solid was recrystallized from ethanol.

1-Methyl-3-isobutyl-8-(dimethylamino)xanthine (6). 1-Methyl-3-isobutyl-8-bromoxanthine<sup>3</sup> (1 g, 3.3 mmol) was heated in a pressure vessel with 8 mL of 25% aqueous dimethylamine at 130 °C for 12 h. The resulting crystals were collected and recrystallized from ethanol.

1-Methyl-3-isobutyl-8-(carbomethoxyethyl)xanthine (8). 1-Methyl-3-isobutyl-8-(carboxyethyl)xanthine (7; 586 mg, 2 mmol) was dissolved in 200 mL of dry methanol, and 1 drop of concentrated  $H_2SO_4$  was added. The solution was heated under reflux for 72 h. The volatiles were removed in vaccuo to give a white residue that was recrystallized from methanol.

1-(Carbomethoxymethyl)-3-isobutylxanthine (11). 1-(Carboxymethyl)-3-isobutylxanthine (10) was esterified as described for 8 and recrystallized from benzene.

1-Methyl-3-(2-acetoxyethyl)xanthine (13). 1-Methyl-3-(2hydroxyethyl)xanthine (12; 1 g, 4.8 mmol) was heated with 5 mL of acetyl chloride until most of the acetyl chloride had evaporated (about 1 h).  $H_2O$  (10 mL) was added, and the resulting precipitate was collected by filtration and recrystallized from ethanol.

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<sup>(8)</sup> Keravis, T. M.; Wells, J. N.; Hardman, J. G. Biochim. Biophys. Acta 1980, 613, 116.

<sup>(9)</sup> Papesch, V.; Schroeder, E. F. J. Org. Chem. 1953, 16, 1879.